2-[4-(Het)aryl-2-oxopyrrolidin-1-yl]acetohydrazides: synthesis, structures, and reactions with carbonyl compounds

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2-[4-(Het)aryl-2-oxopyrrolidin-1-yl]acetohydrazides, structural analogs of piracetam, were synthesized by the condensation of 2-[4-(het)aryl-2-oxopyrrolidin-1-yl]acetates with hydrazine hydrate and phenylhydrazine. New [*N′*-alkyl(hetaryl)idene]-4-(het)aryl-2-oxopyrrolidin-1-ylacetohydrazides were synthesized by the reaction of 2-[4-(het)aryl-2-oxopyrrolidin-1-yl]-acetohydrazides with aromatic aldehydes, acetone, and acetophenone.

Key words: racetams, 2-pyrrolidone, 2-pyrrolidonecarbohydrazides, hydrazides, hydrazones, rotamers, molecular structure, X-ray diffraction.

1-Carbamoylmethyl-2-pyrrolidone (piracetam) and its structural analogs, which are active substances of racetams marketed as nootropic drugs, are the most well-known 2-pyrrolidone derivatives.[1—4]

Pharmacological properties and applications of more than a dozen piracetam-like racetams containing an acetamide moiety, *e.g.*, phenotropil (phenylpiracetam, carphedon), oxiracetam, levetiracetam, *etc.*, were studied in detail. It is worth noting that the nature of substituents in the acetamide moiety has a great effect on the character and degree of the pharmacological activity of these compounds.[5] For example, piracetam is used as a nootropic drug; its analog levetiracetam [(*S*)-(2-oxopyrrolidin-1-yl)butanamide] is an antiepileptic drug;[6,7] the replacement of the amide group in the carphedon molecule (the phenyl analog of piracetam) by the carbazoyl group results in the appearance of strong antidepressant and anxiolytic activity, apart from nootropic properties.[8]

Active substances of a number of pain-relieving, antipyretic, antibacterial, and other medications contain, apart from heterocycles, hydrazide functions or alkyl(hetaryl)idene moieties. For example, isonicotinic acid hydrazide (isoniazid) and its derivatives (phthivazid, saluzid) are known antituberculosis drugs.[2,9,10]

Therefore, the synthesis of analogs of piracetam-like racetams, which are promising biologically active substances containing carbohydrazide functions or alkyl(aryl)idene moieties, apart from hetaryl substituents on the lactam ring, is of great interest. 1-Alkoxycarbonylmethyl-4-(het)aryl-2-pyrrolidones are convenient precursors in the synthesis of these compounds because their hydrazinolysis and reactions of acetohydrazides with carbonyl compounds provide an approach to the synthesis of new piracetam analogs, [4-(het)aryl-2-oxopyrrolidin-1-yl]-acetohydrazides and *N′*-alkyl(hetaryl)idene carbohydrazides. An analysis of the literature[11—14] shows that the data on the methods for the synthesis and properties of (2-oxopyrrolidin-1-yl)acetohydrazides are scarce and mainly concern the procedures for the preparation of new piracetam derivatives.

This study is a continuation of our research on the development of efficient methods for the synthesis of new pharmacologically active substances of a series of structurally modified piracetam analogs containing both the lactam ring and carbohydrazide moieties.[15,16] Here we studied the reactions of ethyl 2-[4-(het)aryl-2-oxopyrrolidin-1-yl]acetates **1a—i** with hydrazine hydrate and phenylhydrazine. Compounds **1a—i** were synthesized by a procedure reported previously.[17]

It was shown that the reactions of esters **1a—i** with hydrazine hydrate under rather mild conditions (the storage of the reaction mixture at 18—20 °C for 20 h) proceed smoothly to produce the corresponding carbohydrazides **2a—i** in good yields (40—90%); hydrazide **2a** was characterized previously[8,11] (Scheme 1).

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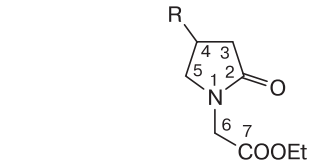
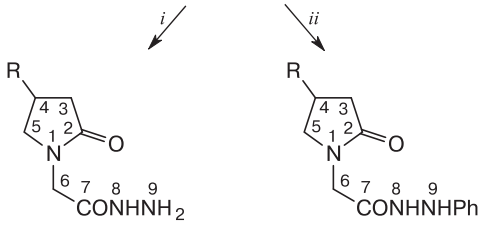
Scheme 1



1a—i



2a—i **3a—c**

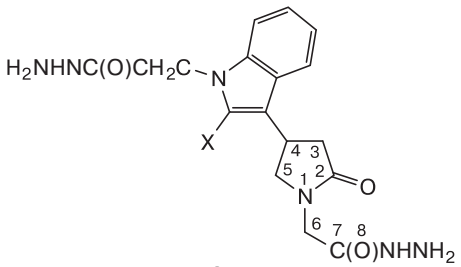
1, **2**	R	**1**, **2**	R
a	Ph	**f**	1-Bn-indol-3-yl
b	4-MeC_6H_4	**g**	1,2-$(Me)_2$-indol-3-yl
c	4-ClC_6H_4	**h**	1- R′C(O)CH_2-indol-3-yl
d	4-$MeOC_6H_4$	**i**	1-R′C(O)CH_2-2-Me-indol-3-yl
e	1-Me-indol-3-yl		

R′ = EtO (**1h,i**), H_2NNH (**2h,i**)

3: R = 4-MeC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**)

Reagents: *i*. $H_2NNH_2 \cdot H_2O$; *ii*. H_2NNHPh.

It should be noted that both ester groups of compounds **1h,i** underwent hydrazinolysis giving dihydrazides **2h,i** in yields of up to 48%.



2h,i

X = H (**h**), Me (**i**)

The reactions of esters **1b—d** with phenylhydrazine were accomplished under similar conditions to prepare phenylhydrazides **3a—c**. The reactions of indole-containing esters **1e—i** with phenylhydrazine under these and more severe conditions (heating at 170 °C for 10 min, heating under reflux for 4 h in *p*-xylene) did not bring the success, as the expected phenylhydrazides were not produced.

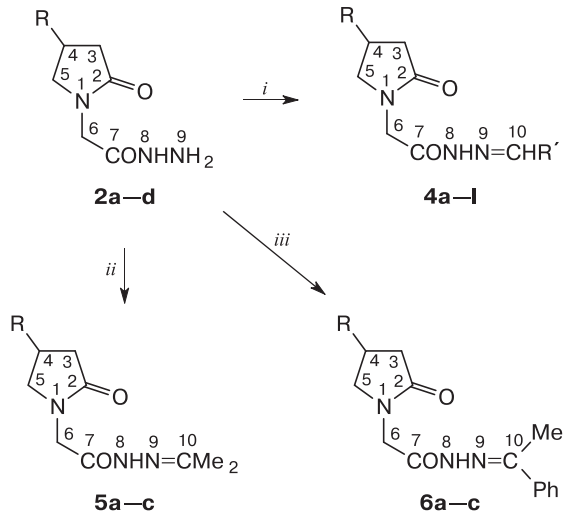
Compounds **2a—i** and **3a—c** are of interest as potential biologically active compounds. Besides, hydrazides **2a—i** can be used in reactions with carbonyl compounds to synthesize new piracetam analogs, [*N*′-alkyl(hetaryl)-idene]-4-(het)aryl-2-oxopyrrolidin-1-ylacetohydrazides.

Thus, the reactions of compounds **2a,c,d** with 3-pyridinecarbaldehyde, benzaldehyde and its 4-chloro- and 4-methoxy-substituted derivatives performed on heating under reflux in ethanol over 10 min produced the corresponding *N*′-(het)arylmethylideneacetohydrazides **4a—l** in good yields (up to 89%). Meanwhile, the reactions of compounds **2a,c,d** with acetone required more severe conditions. The reactions of these compounds were carried out under reflux in an excess of acetone (1 : 30) for 1 h to prepare *N*′-isopropylideneacetohydrazides **5a—c** in yields of up to 85%.

The reactions of hydrazides **2a,c,d** with acetophenone were investigated to optimize the reaction conditions. The heating of carbohydrazides **2a,c,d** with an equimolar amount of acetophenone in ethanol under reflux for 3 h resulted in the formation of [*N*′-(1-phenylethylidene)]-acetohydrazides **6a,b** in 69—71% yields only in the reactions with carbohydrazides **2a,c**, respectively (method **A**). The reaction of hydrazide **2d** with acetophenone required an increase in the time of refluxing up to 9 h (method **B**) and produced compound **6c** in 65% yield (Scheme 2).

All synthesized compounds **2—6** are stable colorless crystalline solids with distinct melting points. Their structures were confirmed by IR spectroscopy, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy, $^1H—^{13}C$ HMQC, $^1H—^{13}C$ HMBC, and $^1H—^1H$ NOESY experiments, and X-ray diffraction.

Scheme 2



2a—d **4a—l** **5a—c** **6a—c**

R = Ph (**2a**, **5a**, **6a**), 4-ClC_6H_4 (**2c**, **5b**, **6b**), 4-$MeOC_6H_4$ (**2d**, **5c**, **6c**)

4	R	R′	**4**	R	R′
a	Ph	Ph	**g**	4-ClC_6H_4	4-$MeOC_6H_4$
b	Ph	4-ClC_6H_4	**h**	4-ClC_6H_4	3-C_5H_4N
c	Ph	4-$MeOC_6H_4$	**i**	4-$MeOC_6H_4$	Ph
d	Ph	3-C_5H_4N	**j**	4-$MeOC_6H_4$	4-ClC_6H_4
e	4-ClC_6H_4	Ph	**k**	4-$MeOC_6H_4$	4-$MeOC_6H_4$
f	4-ClC_6H_4	4-ClC_6H_4	l	4-$MeOC_6H_4$	3-C_5H_4N

Reagents: *i*. R′CHO, EtOH; *ii*. MeCOMe; *iii*. MeCOPh, EtOH.

Table 1. IR spectra* of compounds **2a—i** and **3a—c**

Compound	IR, ν/cm^{-1}
2a	3305 (NH); 3200 (NH_2); 1670 br (C=O);
2b	3320 (NH); 3209 (NH_2); 1680, 1651 (C=O)
2c	3316 (NH); 3207 (NH_2); 1680, 1647 (C=O)
2d	3325 (NH); 3208 (NH_2); 1680, 1652 (C=O)
2e	3335 (NH); 3221 (NH_2); 1709, 1647 (C=O);
2f	3339 (NH); 3263 (NH_2); 1672, 1655 (C=O)
2g	3302 (NH); 3278 (NH_2); 1688, 1666 (C=O)
2h	3301 (NH); 3119 (NH_2); 1701, 1658 (C=O)
2i	3384 (NH); 3210 (NH_2); 1671, 1627 (C=O)
3a	3232 (NH); 1684, 1662 (C=O)
3b	3230 (NH); 1686, 1665 (C=O)
3c	3300, 3244 (NH); 1689, 1665 (C=O)

* The IR spectra were recorded as KBr pellets.

The IR spectra of hydrazides **2a—i**, phenylhydrazides **3a—c**, and *N′*-alkyl(hetaryl)ideneacetohydrazides **4a—l**, **5a—c**, and **6a—c** show stretching bands of all functional groups (Tables 1 and 2). These characteristics have similar values and are in good agreement with each other (see Tables 1 and 2).

The ^{1}H and ^{13}C{^{1}H} NMR spectra of hydrazides **2a—i** contain one set of proton signals of all structural units, which indicates that they are diastereomerically pure compounds (Tables 3 and 4). The ^{1}H NMR spectra of compounds **2a—i** show proton signals of the pyrrolidone ring, (het)aryl substituents, and the side chain along with proton signals of the hydrazide moiety (see Table 3). It is known that substituted amides can exist as (*E′*) or (*Z′*) conformers due to hindered rotation about the (O)C—NH bond. Generally, the conformation of these compounds is determined from the chemical shifts of C=O carbon atoms: $\delta_C \approx 168$ for the (*Z′*) conformer and $\delta_C \approx 173$ for the (*E′*) conformer.[15,18,19]

The fact that the carbonyl carbon atom C(7) of hydrazides **2a—i** gives signals at δ 167.44—167.63 is indicative of the (*Z′*) conformation, *i.e.*, the C=O oxygen atom and the NH_2 group are *cis* to the C—N bond.

The assignment of the carbon signals of C(2)=O groups of the lactam ring and the hydrazide function at the C(7) atom of compounds **2a—i** and the signals of hydrazide NH protons was confirmed by ^{1}H—^{13}C HMBC experiments for compounds **2a,c,d,f**. Thus, the ^{1}H—^{13}C HMBC NMR spectrum of compound **2d** shows cross-peaks between the C(3)H_2 protons (δ_H 2.32, δ_H 2.61) and the C(4) (δ_C 36.50) and C(2) atoms (δ_C 173.95), between the C(6)H_2 (δ_H 3.78, δ_H 3.83) and H(8) protons (δ_H 9.15) and the C(7) atom (δ_C 167.48). Similar correlations are observed for the whole series of compounds **2a,c,f**. Since the ^{1}H and ^{13}C{^{1}H} NMR spectra of compounds **2a,c,d,f** are in good agreement with those of hydrazides **2a—i,** it can be assumed with a high degree of certainty that all these compounds exist as (*Z′*) conformers in a solution in DMSO-d_6.

It should be noted that there are differences in the appearance the proton and carbon signals in the ^{1}H and ^{13}C{^{1}H} NMR spectra of compounds **3—6**. Thus, the ^{1}H and ^{13}C{^{1}H} NMR spectra of compounds **3—6** (see

Table 2. IR spectra* of compounds **4a—l**, **5a—c**, and **6a—c**

Compound	IR, ν/cm^{-1}	Compound	IR, ν/cm^{-1}	Compound	IR, ν/cm^{-1}
4a	3205, 3112 (NH); 1698, 1661 br (C=O, C=N**)	**4g**	3201, 3101 (NH); 1697, 1662 br (C=O, C=N**)	**5a**	3332, 3209, 3062 (NH); 1700, 1675 br (C=O, C=N**)
4b	3213, 3129 (NH); 1698, 1659 br (C=O, C=N**)	**4h**	3468, 3212, 3128 (NH); 1701 br (C=O, C=N**)	**5b**	3433, 3213, 3051 (NH); 1697, 1674 br (C=O, C=N**)
4c	3198, 3132 (NH); 1694, 1675 br (C=O, C=N**)	**4i**	3180, 3060 (NH); 1693, 1672 br (C=O, C=N**)	**5c**	3437, 3208, 3108 (NH); 1689, 1672 br (C=O, C=N**)
4d	3205, 3090 (NH); 1699, 1666 (C=O); 1647 (C=N)	**4j**	3443, 3214, 3152 (NH); 1698, 1667 (C=O); 1658 (C=N)	**6a**	3446, 3194, 3086 (NH); 1692, 1674 br (C=O, C=N**)
4e	3205, 3105 (NH); 1697, 1666 br (C=O, C=N**)	**4k**	3205, 3119 (NH); 1696, 1666 (C=O); 1649 (C=N)	**6b**	3436, 3190, 3085 (NH); 1690, 1672 br (C=O, C=N**)
4f	3213, 3105 (NH); 1701, 1662 br (C=O, C=N**)	**4l**	3189, 3062 (NH); 1689, 1675 br (C=O, C=N**)	**6c**	3436, 3211, 3087 (NH); 1695 br (C=O, C=N**)

* The IR spectra were recorded as KBr pellets.

** In the IR spectra of compounds **4a—c**, **4e—i**, **4l**, **5a—c**, and **6a—c**, a broadened absorption band with a maximum at 1701—1655 cm^{-1} is due to overlapping of absorption bands of the lactam carbonyl group and the C=N bond.

Table 3. ^{1}H NMR spectra* of compounds **2a—i** and **3a—c**

Compound	δ (*J*/Hz)					
	R; [Ph]	H′(3) (dd), H″(3) (dd)	H(4) (m)	H′(5) (m), H″(5) (m)	H′(6) (d), H″(6) (d) [NCH_2]	H(8) (s) [H(9) (s)]
2a	7.20—7.30 (m)	2.36 (1 H, *J* = 8.7, *J* = 16.4); 2.66 (1 H, *J* = 9.0, *J* = 16.4)	3.50—3.56	3.36, 3.70	3.79 (1 H, *J* = 16.2); 3.84 (1 H, *J* = 16.2)	9.15 [4.22]
2b	7.07—7.19 (m); 2.23 (s, 3 H, Me)	2.33 (1 H, *J* = 8.7, *J* = 16.4); 2.62 (1 H, *J* = 8.9, *J* = 16.4)	3.48—3.55	3.32, 3.67	3.78 (1 H, *J* = 16.3); 3.83 (1 H, *J* = 16.3)	9.13 [4.21]
2c	7.26—7.39 (m)	2.34 (1 H, *J* = 8.5, *J* = 16.5); 2.66 (1 H, *J* = 8.9, *J* = 16.5)	3.55—3.62	3.34, 3.70	3.78 (1 H, *J* = 16.2); 3.84 (1 H, *J* = 16.2)	9.15 [4.22]
2d	6.82—7.24 (m); 3.68 (s, 3 H, OMe)	2.32 (1 H, *J* = 8.9, *J* = 16.4); 2.61 (1 H, *J* = 9.0, *J* = 16.4)	3.48—3.55	3.31, 3.69	3.78 (1 H, *J* = 16.2); 3.83 (1 H, *J* = 16.2)	9.15 [4.23]
2e	6.94—7.57 (m); 3.69 (s, 3 H, NMe)	2.43 (1 H, *J* = 8.0, *J* = 16.2); 2.70 (1 H, *J* = 8.2, *J* = 16.2)	3.73—3.80	3.45, 3.78	3.81—3.88 (m, 2 H)	9.13 [4.21]
2f	6.95—7.59 (m); 5.30 (d, 1 H, *J* = 16.3); 5.34 (d, 1 H, *J* = 16.3), [7.14—7.30 (m)]	2.47 (1H, *J* = 8.0, *J* = 16.3); 2.72 (1 H, *J* = 8.4, *J* = 16.3)	3.77—3.82	3.48, 3.79	3.83 (1 H, *J* = 16.0); 3.87 (1 H, *J* = 16.0); 5.30 (1 H, *J* = 16.5); 5.35 (1 H, *J* = 16.5)	9.14 [4.24]
2g	6.90—7.53 (m); 3.59 (s, 3 H, NMe); 2.33 (s, 3 H, 2-Me)	2.50—2.58 (m, 2 H)	3.62—3.69	3.56, 3.84	3.82 (1 H, *J* = 16.3); 3.92 (1 H, *J* = 16.3)	9.14 [4.23]
2h	6.95—7.56 (m)	2.44 (1 H, *J* = 8.2, *J* = 16.3); 2.71 (1 H, *J* = 8.2, *J* = 16.3)	3.43—3.50	3.72—3.81	3.81 (1 H, *J* = 16.2); 3.86 (1 H, *J* = 16.2) [4.66 (s, 2 H)]	9.14, 9.35 [4.25 (4 H)]
2i	6.87—7.60 (m); 2.32 (s, 3 H, 2-Me)	2.50—2.62 (m, 2 H)	3.87—3.95	3.57—3.68	3.77—3.98 (m, 2 H) [4.66 (s, 2 H)]	9.15, 9.38 [4.25 (4 H)]
3a	7.05—7.21 (m); 2.23 (s, 3 H, Me); [6.63—7.21 (m)]	2.26—2.40 (m, 2 H); 2.59—2.70 (m, 2 H)	3.46—3.60	3.29—3.43, 3.63—3.78	3.90—4.10	*E′*: 9.26, [7.93] *Z′*: 9.79 (d, 1 H, *J* = 2.4); [7.73 (d, 1 H, *J* = 2.4)]
3b	7.30—7.38 (m); [6.63—7.21 (m)]	2.25—2.40 (m, 2 H); 2.62—2.73 (m, 2 H)	3.52—3.66	3.28—3.43, 3.68—3.80	3.89—4.10	*E′*: 9.26, [7.93] *Z′*: 9.80 (d, 1 H, *J* = 2.4); [7.73 (d, 1 H, *J* = 2.4)]
3c	6.82—7.25 (m), 3.68 (s, 3 H, OMe) [6.63—7.25 (m)]	2.23—2.38 (m, 2 H), 2.57—2.68 (m, 2 H)	3.46—3.58	3.30—3.40, 3.64—3.75	3.88—4.09	*E′*: 9.25, [7.93] *Z′*: 9.79 (d, 1 H, *J* = 2.4); [7.73 (d, 1 H, *J* = 2.4)]

* The ^{1}H NMR spectra were recorded in DMSO-d_6 (isomer ratio (*Z′*) : (*E′*) = 5 : 1 (**3a—c**)).

Tables 3—7) show double sets of proton and carbon signals of all structural units, which attests to the existence of these compounds as a mixture of (*E′*) and (*Z′*) conformers (with respect to the (O)C—NH bond) in DMSO-d_6.

For example, the $^{13}C\{^1H\}$ NMR spectrum of compound **3c** contains carbon signals of C=O groups at δ_C 172.65 and 168.19, which should be assigned to the C(7) atoms of the (*E′*) and (*Z′*) conformers, respectively. This

Table 4. $^{13}C\{^1H\}$ NMR spectra* of compounds **2a—i**

Compound	δ							
	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(Me)	C(R) [C(Ph)]
2a	173.83	38.69	37.14	54.82	44.35	167.46	—	127.17, 127.49, 129.11, 143.43
2b	173.87	38.73	36.80	54.90	44.35	167.46	21.13	127.36, 129.64, 136.18, 140.35
2c	173.66	38.57	36.53	54.63	44.33	167.44	–	129.02, 129.48, 131.73, 142.52
2d	173.95	38.88	36.50	55.07	44.33	167.48	55.59	114.45, 128.53, 135.22, 158.50
2e	174.35	37.74	28.90	53.87	44.28	167.51	30.05	110.73, 116.05, 119.27, 119.46, 121.98, 127.17, 127.52, 136.82
2f	174.17	37.81	29.17	54.15	44.37	167.56	—	110.85, 116.15, 119.31, 119.54, 122.04, 127.24, 127.59, 136.95 [49.52, 126.08, 127.86, 129.06, 138.80]
2g	174.45	37.57	28.51	53.51	44.25	167.63	10.56, 29.85	109.89, 110.65, 118.78, 119.00, 120.75, 125.71, 134.16, 137.16
2h	174.18	37.79	29.10	54.05	44.36	167.55	—	47.86, 110.59, 115.87, 119.37, 121.97, 126.64, 127.11, 137.40, 167.28
2i	174.42	37.46	28.49	53.40	44.25	167.62	10.62	44.83, 110.00, 111.07, 118.82, 119.29, 120.87, 125.96, 134.45, 137.28, 167.55

* The $^{13}C\{^1H\}$ NMR spectra were recorded in DMSO-d_6.

Table 5. $^{13}C\{^1H\}$ NMR spectra* of compounds **3a—c**

Compound	δ								
	E′/Z′	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(Me)	C(R)
3a	*Z′*	174.03	38.73	36.86	55.07	44.43	168.17	21.15	112.58—149.66
	E′	173.95	38.84	36.73	54.84	43.10	172.63	21.15	112.58—149.66
3b	*Z′*	173.80	38.58	36.56	54.79	44.41	168.15	—	112.57—149.64
	E′	173.70	38.67	36.42	54.54	43.10	172.61	—	112.57—149.64
3c	*Z′*	174.06	38.86	36.54	55.23	44.41	168.19	55.57	112.57—158.52
	E′	173.99	38.96	36.40	54.99	43.06	172.65	55.57	112.57—158.52

* The $^{13}C\{^1H\}$ NMR spectra were recorded in DMSO-d_6.

Table 6. ^1H NMR spectra* of compounds **4a—l**, **5a—c**, and **6a—c**

Compound	*E/Z*	δ (*J*/Hz)						
		R; [R′]	H′(3) (dd), H″(3) (dd)	H(4) (m)	H′(5) (m), H″(5) (m)	H′(6) (d), H″(6) (d)	H(8) (s)	H(10) (s) [Me (s)]
4a	*E′E*	7.17—7.34 (m); [7.37—7.67 (m)]	2.37 (2 H, *J* = 8.4, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.42—3.47, 3.76—3.83	4.39 (1 H, *J* = 17.6); 4.45 (1 H, *J* = 17.6)	11.55	7.97
	Z′E	7.17—7.34 (m); [7.37—7.67 (m)]	2.37 (2 H, *J* = 8.4, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.42—3.47, 3.76—3.83	3.99 (1 H, *J* = 16.5); 4.04 (1 H, *J* = 16.5)	11.55	8.18
4b	*E′E*	7.18—7.36 (m); [7.43—7.70 (m)]	2.36 (2 H, *J* = 8.2, *J* = 16.6); 2.71 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.38—3.45, 3.76—3.82	4.38 (1 H, *J* = 17.7); 4.44 (1 H, *J* = 17.7)	11.59	7.95
	Z′E	7.18—7.36 (m); [7.43—7.70 (m)]	2.36 (2 H, *J* = 8.2, *J* = 16.6); 2.71 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.38—3.45, 3.76—3.82	3.98 (1H, *J* = 16.5); 4.03 (1 H, *J* = 16.5)	11.59	8.17
4c	*E′E*	7.16—7.36 (m); [6.93—7.61 (m); 3.79 (s, 3 H OMe)]	2.37 (2 H, *J* = 8.4, *J* = 16.6); 2.71 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.40—3.47, 3.76—3.83	4.36 (1 H, *J* = 17.7); 4.42 (1H, *J* = 17.7)	11.39	7.90

(*to be continued*)

Table 6 (*continued*)

Compound	*E*/*Z*	δ (*J*/Hz)						
		R; [R′]	H′(3) (dd), H″(3) (dd)	H(4) (m)	H′(5) (m), H″(5) (m)	H′(6) (d), H″(6) (d)	H(8) (s)	H(10) (s) [Me (s)]
4c	*Z′E*	7.16—7.36 (m); [6.95—7.64 (m); 3.76 (s, 3 H OMe)]	2.37 (2 H, *J* = 8.4, *J* = 16.6); 2.71 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.40—3.47, 3.76—3.83	3.95 (1 H, *J* = 16.4); 4.00 (1 H, *J* = 16.4)	11.37	8.11
4d	*E′E*	7.15—7.36 (m); [7.39—8.82 (m)]	2.37 (2 H, *J* = 8.4, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.40—3.47, 3.76—3.83	4.41 (1 H, *J* = 17.7); 4.46 (1 H, *J* = 17.7)	11.69	7.99
	Z′E	7.15—7.36 (m); [7.39—8.82 (m)]	2.37 (2 H, *J* = 8.4, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.64	3.40—3.47, 3.76—3.83	4.00 (1 H, *J* = 16.3); 4.06 (1 H, *J* = 16.3)	11.69	8.24
4e	*E′E*	7.30—7.38 (m); [7.36—7.67 (m)]	2.35 (2 H, *J* = 8.0, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.55—3.65	3.38—3.43, 3.75—3.82	4.39 (1 H, *J* = 17.7); 4.45 (1 H, *J* = 17.7)	11.54	7.97
	Z′E	7.30—7.38 (m); [7.36—7.67 (m)]	2.35 (2 H, *J* = 8.0, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.55—3.65	3.38—3.43, 3.75—3.82	3.98 (1 H, *J* = 16.5); 4.04 (1 H, *J* = 16.5)	11.54	8.18
4f	*E′E*	7.31—7.38 (m); [7.43—7.69 (m)]	2.34 (2 H, *J* = 8.1, *J* = 16.6); 2.72 (2 H, *J* = 9.1, *J* = 16.6)	3.56—3.66	3.37—3.44, 3.76—3.83	4.38 (1 H, *J* = 17.7); 4.44 (1 H, *J* = 17.7)	11.59	7.95
	Z′E	7.31—7.38 (m); [7.43—7.69 (m)]	2.34 (2 H, *J* = 8.1, *J* = 16.6); 2.72 (2 H, *J* = 9.1, *J* = 16.6)	3.56—3.66	3.37—3.44, 3.76—3.83	3.97 (1 H, *J* = 16.7); 4.02 (1 H, *J* = 16.7)	11.59	8.17
4g	*E′E*	7.31—7.38 (m); [6.93—7.61 (m); 3.78 (s, 3 H OMe)]	2.34 (2 H, *J* = 8.1, *J* = 16.6); 2.72 (2 H, *J* = 9.1, *J* = 16.6)	3.55—3.66	3.37—3.43, 3.76—3.83	4.35(1 H, *J* = 17.6); 4.41 (1 H, *J* = 17.6)	11.40	7.90
	Z′E	7.31—7.38 (m); [6.95—7.63 (m); 3.75 (s, 3 H OMe)]	2.34 (2 H, *J* = 8.1, *J* = 16.6); 2.72 (2 H, *J* = 9.1, *J* = 16.6)	3.55—3.66	3.37—3.43, 3.76—3.83	3.95 (1 H, *J* = 16.3); 4.01 (1 H, *J* = 16.3)	11.40	8.11
4h	*E′E*	7.32—7.38 (m); [7.40—8.82 (m)]	2.35 (2 H, *J* = 8.1, *J* = 16.7); 2.72 (2 H, *J* = 9.1, *J* = 16.7)	3.56—3.66	3.37—3.44, 3.76—3.82	4.40 (1 H, *J* = 17.7); 4.46 (1 H, *J* = 17.7)	11.69	8.00
	Z′E	7.32—7.38 (m); [7.40—8.82 (m)]	2.35 (2 H, *J* = 8.1, *J* = 16.7); 2.72 (2 H, *J* = 9.1, *J* = 16.7)	3.56—3.66	3.37—3.44, 3.76—3.82	3.98 (1 H, *J* = 16.5); 4.04 (1 H, *J* = 16.5)	11.69	8.23
4i	*E′E*	6.84—7.24 (m); 3.69 (s, 3 H OMe) [7.36—7.68 (m)]	2.33 (2 H, *J* = 8.5, *J* = 16.6); 2.67 (2 H, *J* = 9.0, *J* = 16.6)	3.45—3.58	3.36—3.42, 3.71—3.78	4.38 (1 H, *J* = 17.7); 4.44 (1 H, *J* = 17.7)	11.54	7.97
	Z′E	6.81—7.19 (all m); 3.68 (s, 3 H OMe) [7.36— 7.68 (all m)]	2.33 (2 H, *J* = 8.5, *J* = 16.6); 2.67 (2 H, *J* = 9.0, *J* = 16.6)	3.45—3.58	3.36—3.42, 3.71—3.78	3.98 (1 H, *J* = 16.5); 4.03 (1 H, *J* = 16.5)	11.53	8.19

(*to be continued*)

Table 6 (*continued*)

Compound	*E*/*Z*	δ (*J*/Hz)						
		R; [R′]	H′(3) (dd), H″(3) (dd)	H(4) (m)	H′(5) (m), H″(5) (m)	H′(6) (d), H″(6) (d)	H(8) (s)	H(10) (s) [Me (s)]
4j	*E′E*	6.83—7.25 (m); 3.69 (s, 3 H OMe) [7.43—7.70 (m)]	2.33 (2 H, *J* = 8.5, *J* = 16.6), 2.67 (2 H, *J* = 9.0, *J* = 16.6)	3.47—3.58	3.35—3.42, 3.70—3.77	4.38 (1 H, *J* = 17.7); 4.43 (1 H, *J* = 17.7)	11.59	7.95
	Z′E	6.83—7.25 (m); 3.69 (s, 3 H OMe) [7.43—7.70 (m)]	2.33 (2 H, *J* = 8.5, *J* = 16.6), 2.67 (2 H, *J* = 9.0, *J* = 16.6)	3.47—3.58	3.35—3.42, 3.70—3.77	3.97 (1 H, *J* = 16.6); 4.02 (1 H, *J* = 16.6)	11.59	8.17
4k	*E′E*	6.83—7.24 (m); 3.68 (s, 3 H OMe) [6.93—7.61 (m); 3.78 (s, 3 H OMe)]	2.33 (2 H, *J* = 8.5, *J* = 16.7); 2.67 (2 H, *J* = 9.0, *J* = 16.7)	3.47—3.58	3.35—3.41, 3.70—3.77	4.35 (1 H, *J* = 17.7); 4.41 (1 H, *J* = 17.7)	11.40	7.90
	Z′E	6.83—7.24 (m); 3.68 (s, 3 H OMe) [6.93—7.61 (m); 3.75 (s, 3 H OMe)]				3.95 (1 H, *J* = 16.4); 3.99 (1 H, *J* = 16.4)	11.38	8.12
4l	*E′E*	6.83—7.24 (m); 3.69 (s, 3 H OMe) [7.40—8.82 (all m)]	2.33 (2 H, *J* = 8.5, *J* = 16.5); 2.67 (2 H, *J* = 9.0, *J* = 16.5)	3.46—3.58	3.35—3.42, 3.70—3.77	4.39 (1 H, *J* = 17.7); 4.44 (1 H, *J* = 17.7)	11.70	7.99
	Z′E	6.83—7.24 (m); 3.68 (s, 3 H OMe) [7.40—8.82 (m)]				3.98 (1 H, *J* = 16.6); 4.03 (1 H, *J* = 16.6)		8.23
5a	*E′*	7.16—7.33 (m)	2.35(2 H, *J* = 8.4, *J* = 16.5); 2.70 (2 H, *J* = 9.1, *J* = 16.5)	3.51—3.63	3.36—3.45, 3.71—3.80	4.23 (1 H, *J* = 18.4); 4.29 (1 H, *J* = 18.4)	10.30	[1.82, 1.88]
	Z′					3.95 (1 H, *J* = 16.4); 4.03 (1 H, *J* = 16.4)	10.15	[1.82, 1.89]
5b	*E′*	7.27—7.40 (m)	2.32 (2 H, *J* = 8.1, *J* = 16.5); 2.69 (2 H, *J* = 9.2, *J* = 16.5)	3.52—3.64	3.32—3.42, 3.70—3.79	4.21 (1 H, *J* = 18.6); 4.26 (1 H, *J* = 18.6)	10.29	[1.81, 1.88]
	Z′					3.93 (1 H, *J* = 16.2); 4.01 (1 H, *J* = 16.2)	10.13	
5c	*E′*	6.77—730 (m); 3.69 (s, 3 H OMe)	2.32 (2 H, *J* = 8.6, *J* = 16.4); 2.65 (2 H, *J* = 8.9, *J* = 16.4)	3.45—3.58	3.31—3.41, 3.65—3.76	4.16—4.31 (m, 2 H)	10.30	[1.82, 1.88]
	Z′					3.94 (1 H, *J* = 16.4); 4.02 (1 H, *J* = 16.4)	10.15	[1.82, 1.89]
6a	*E′E*	7.18—7.35 (m); [7.34—7.79 (m)]	2.38 (2 H, *J* = 8.3, *J* = 16.6); 2.72 (2 H, *J* = 9.0, *J* = 16.6)	3.54—3.65	3.40—3.47, 3.77—3.84	4.41—4.48 (m, 2 H)	10.79	[2.22]
	Z′E		2.37 (2 H, *J* = 8.6, *J* = 16.5); 2.72 (2 H, *J* = 9.0, *J* = 16.5)			4.07 (1 H, *J* = 16.5); 4.16 (1 H, *J* = 16.5)	10.55	[2.25]

(*to be continued*)

Table 6 (*continued*)

Compound	*E*/*Z*	δ (*J*/Hz)						
		R; [R′]	H′(3) (dd), H″(3) (dd)	H(4) (m)	H′(5) (m), H″(5) (m)	H′(6) (d), H″(6) (d)	H(8) (s)	H(10) (s) [Me (s)]
6b	*E′E*	7.32—7.45 (m); [7.32—7.90 (m)]	2.35 (2 H, *J* = 8.0, *J* = 16.6); 2.73 (2 H, *J* = 9.1, *J* = 16.6)	3.55—3.66	3.37—3.42, 3.77—3.84	4.40—4.48 (m, 2 H)	10.77	[2.21]
	Z′E					4.07 (1 H, *J* = 16.5); 4.16 (1 H, *J* = 16.5)	10.54	[2.24]
6c	*E′E*	6.82—7.26 (m); 3.69 (s, 3 H OMe) [7.33—7.91 (m)]	2.34 (2 H, *J* = 8.5, *J* = 16.5); 2.68 (2 H, *J* = 9.0, *J* = 16.5)	3.47—3.58	3.37—3.43, 3.74—3.80	4.40—4.49 (m, 2 H)	10.78	[2.22]
	Z′E					4.07 (1 H, *J* = 16.8); 4.16 (1 H, *J* = 16.8)	10.54	[2.25]

* The ^{1}H NMR spectra were recorded in DMSO-d_6 (isomer ratio (*Z′E*) : (*E′E*) = 1 : 3 (**4a—l**); (*Z′*) : (*E′*) = 1 : 2 (**5a—c**); (*Z′E*) : (*E′E*) = = 1 : 3 (**6a—c**)).

Table 7. $^{13}C\{^1H\}$ NMR spectra* of compounds **4a—l**, **5a—c**, and **6a—c**

Compound	*E*/*Z*	δ								
		C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(10)	C(Me)	C(R, R′)
4a	*E′E*	174.06	38.77	37.18	54.96	44.07	169.71	144.22	—	127.19, 127.35, 127.46, 127.61, 129.14, 129.35,
	Z′E	174.02	38.69	37.12	54.96	44.68	164.83	147.52	—	130.45, 130.63, 134.53, 134.67, 143.53, 143.61
4b	*E′E*	174.03	38.74	37.15	54.93	44.05	169.77	142.91	—	127.18, 127.45, 129.00, 129.13, 129.23, 129.43,
	Z′E	174.03	38.66	37.15	54.93	44.67	164.91	146.20	—	130.56, 133.50, 133.63, 134.87, 135.07, 143.52, 143.62
4c	*E′E*	173.99	38.77	37.17	54.94	44.04	169.43	144.09	55.83	114.84, 114.93, 127.17, 127.46, 128.93, 129.14,
	Z′E	173.97	38.69	37.11	55.92	44.66	164.51	147.43	—	129.19, 143.56, 143.63, 161.02, 161.22
4d	*E′E*	174.06	38.74	37.17	54.94	44.09	169.87	141.45	—	124.44, 124.48, 127.18, 127.44, 129.13, 130.48,
	Z′E	174.06	38.66	37.17	54.94	44.69	165.04	144.86	—	130.61, 133.88, 133.97, 143.51, 143.60, 148.99, 149.28, 151.04, 151.25
4e	*E′E*	173.87	38.65	36.53	54.74	44.05	169.68	144.25	—	127.35, 127.60, 129.04, 129.33, 129.40, 130.45,
	Z′E	173.84	38.56	36.53	54.74	44.66	164.81	147.54	—	130.63, 131.76, 134.53, 134.66, 142.61, 142.70
4f	*E′E*	173.86	38.63	36.51	54.73	44.04	169.75	142.95	—	129.04, 129.23, 129.40, 129.61, 130.55, 131.75,
	Z′E	173.83	38.54	36.51	54.73	44.65	164.89	146.23	—	133.49, 133.64, 134.89, 135.07, 142.61, 142.72
4g	*E′E*	173.83	38.66	36.52	54.74	44.02	169.41	144.13	55.82	114.84, 114.93, 127.14, 127.19, 129.04, 129.19,
	Z′E	173.80	38.58	36.47	54.70	44.64	164.50	147.44	55.91	129.40, 130.51, 131.73, 142.64, 142.73, 161.23, 161.38

(*to be continued*)

Table 7 (*continued*)

Compound	*E*/*Z*	δ								
		C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(10)	C(Me)	C(R, R′)
4h	*E′E*	173.88	38.62	36.51	54.74	44.06	169.85	141.48	—	124.46, 124.51, 129.05, 129.42, 130.47, 130.60,
	Z′E	173.88	38.54	36.51	54.74	44.64	164.99	144.85	—	131.75, 133.91, 133.98, 142.62, 142.72, 148.98, 149.27, 151.05, 151.26
4i	*E′E*	174.13	38.94	36.52	55.19	44.04	169.72	144.20	55.56	114.41, 114.49, 127.35, 127.61, 128.47, 128.91,
	Z′E	174.10	38.86	36.47	55.19	44.67	164.84	147.51	55.56	129.35, 129.44, 130.45, 130.63, 134.55, 135.13, 135.32, 135.39, 158.49, 158.52
4j	*E′E*	174.13	38.92	36.50	55.18	44.03	169.79	142.90	55.57	114.49, 128.47, 129.00, 129.23, 129.42, 130.55,
	Z′E	174.09	38.85	36.47	55.18	44.64	164.88	146.19	55.57	133.50, 133.62, 134.86, 135.05, 135.30, 135.39, 158.52
4k	*E′E*	174.09	38.94	36.51	55.19	44.01	169.45	144.07	55.57, 55.89	114.49, 114.84, 114.91, 127.10, 128.47, 128.93,
	Z′E	174.06	38.88	36.45	55.19	44.64	164.53	147.40	55.57, 55.82	129.19, 130.51, 135.33, 135.40, 158.52, 161.04, 161.21
4l	*E′E*	174.15	38.90	36.50	55.19	44.05	169.88	141.43	55.57	114.42, 114.49, 124.47, 128.47, 130.49, 133.89,
	Z′E	174.15	38.85	36.50	55.19	44.64	165.04	144.81	55.57	133.98, 135.30, 135.39, 148.99, 149.27, 151.05, 151.26, 158.52
5a	*E′*	173.95	38.77	37.17	54.90	44.26	169.72	151.74	17.52, 25.69	127.16, 127.46, 129.12, 143.63
	Z′	173.89	38.77	37.07	54.90	44.40	164.52	156.53	18.12, 25.46	127.16, 127.46, 129.12, 143.63
5b	*E′*	173.74	38.67	36.48	54.69	44.24	169.69	151.79	17.54, 25.68	129.02, 129.43, 131.71,
	Z′	173.69	38.62	36.42	54.69	44.36	164.47	156.58	18.12, 25.47	142.77
5c	*E′*	174.04	38.94	36.50	55.15	44.22	169.73	151.74	17.54, 25.69, 55.55	114.46, 128.48, 135.40, 158.50
	Z′	173.98	38.94	36.40	55.15	44.35	164.53	156.49	18.12, 25.48, 55.55	
6a	*E′E*	174.04	38.79	37.16	54.95	44.55	170.54	148.70	14.04	126.58, 126.85, 127.18, 127.48, 128.86, 128.92,
	Z′E	174.04	38.79	37.16	54.95	44.55	165.31	152.55	14.74	129.14, 129.68, 138.50, 143.66
6b	*E′E*	173.85	38.68	36.50	54.74	44.53	170.51	148.75	14.03	126.58, 126.85, 128.91, 129.04, 129.42, 129.67,
	Z′E	173.85	38.68	36.50	54.74	44.53	165.28	152.61	14.73	131.73, 138.50, 142.79
6c	*E′E*	174.12	38.96	36.52	55.19	44.53	170.54	148.68	14.02, 55.57	114.49, 126.57, 126.85, 128.48, 128.85, 128.91,
	Z′E	174.12	38.96	36.52	55.19	44.53	165.32	152.53	14.72, 55.57	129.66, 135.44, 138.51, 158.52

* The $^{13}C\{^1H\}$ NMR spectra were recorded in DMSO-d_6.
** The signals of both isomers coincide with each other.

is in good agreement with the values for related structures published in the literature.[15,18] The $^{13}C\{^1H\}$ NMR spectra of all compounds **3—6** show similar patterns of signals for the C(7) atoms.

The ^1H NMR spectra of compounds **3—6** existing as (*Z′*) and (*E′*) conformers contain signals of hydrazide NH protons, apart from signals of H(3), H(4), and H(5) of the pyrrolidone ring and the side-chain H(6) atom (see Tables 3

and 6). The ^{1}H NMR spectra of compounds **4a—l** show proton signals of the lactam ring, the side chain, and NH groups along with singlets of H(10) of the arylidene moiety (see Table 6).

It should be noted that a comparison of the integrated intensities of proton signals in the ^{1}H NMR spectra of compounds **3—6** allowed the determination of the (*Z′*) to (*E′*) isomer ratio in a mixture in DMSO-d_6 as (*Z′*) : (*E′*) = = 5 : 1 (**3a—c**), 1 : 3 (**4a—l**, **6a—c**), and 1 : 2 (**5a—c**).

The validity of the interpretation of the ^{1}H and ^{13}C{^{1}H} NMR spectra of compounds **3—6** was confirmed by ^{1}H—^{13}C HMQC, ^{1}H—^{13}C HMBC, and ^{1}H—^{1}H NOESY experiments for compounds **3c**, **4a—l**, **5a**, **5b**, **6a**, and **6c**. An analysis of the ^{1}H—^{13}C HMQC and ^{1}H—^{13}C HMBC spectra made it possible to reliably assign the hydrazide NH protons, the H(3), H(4), and H(5) protons of the pyrrolidone ring, and the side-chain C(6)H_2 proton to the carbons atoms C(3), C(4), C(5), and C(6) and also the signals of the carbon atoms C(7) and C(2) of C=O groups and the C(10) atoms of the azomethine moiety for all compounds **3—6**.

The ^{1}H—^{1}H NOESY spectra of compounds **4d** and **6d** have nuclear Overhauser effect cross-peaks between the azomethine protons H(8) and H(10) (compound **4d**) and between the H(8) proton and the CH_3 protons (compound **6d**) of the (*Z′*) and (*E′*) conformers. This is indicative of the close spatial proximity of these protons and is indirect evidence of their *E* configuration (with respect to the C=N(9) bond). Similar correlations are observed in the ^{1}H—^{1}H NOESY spectra of compounds **4a—c**, **4e—i**, and **6a—c**.

Apparently, carbohydrazides **4** and **6** exist as a mixture of (*Z′ E*) and (*E′ E*) isomers in different ratios in a solution in DMSO-d_6. Meanwhile, the presence of two identical substituents at the C=N bond in compounds **5a—c** excludes the possibility of the formation of geometric isomers. Hence, these compounds exist as a mixture of (*Z′*) and (*E′*) conformers in DMSO-d_6.

The structure of one of the synthesized compounds (compound **4d**) was determined by X-ray diffraction (Fig. 1).

According to the X-ray diffraction data, compound **4d** crystallizes as a crystal hydrate (the **4d** : water ratio is 4 : 1). The asymmetric unit of the crystal structure comprises two independent molecules (**A** and **B**) and a water molecule, which occupies a special position on a twofold axis. The molecule **B** is disordered over two positions. The C(12)B, N(1)B, C(3)B÷C(11)B atoms were refined with an occupancy of 0.587; the C(12)C, N(1)C, C(3)C÷C(11) C atoms, with an occupancy of 0.413. The relative configurations of the chiral centers C(4) in the molecules **A** and **B** is *S**, and the configuration is *R** in the disordered fragment **C**, but the crystal hydrate is a racemate (true racemate) since the crystal is centrosymmetric. The five-membered rings of the independent molecules **A** and **B**, including the disordered fragment **C**, adopt the C(4)-envelope conformation, with the C(4) atom deviating from the C(3)C(2)N(1)C(5) plane. The geometric parameters of these rings are equal within experimental error. In the disordered molecules **B** and **C**, the C(4) atom deviates from the C(3)C(2)N(1)C(5) plane in opposite directions (by 0.8 and 0.7 Å in the molecules **B** and **C**), which corresponds to the *S** and *R** configurations of the chiral centers C(4) in the molecules **B** and **C**, respectively.

In all three molecules (**A**, **B**, and **C**), the hydrazide moieties have a planar zigzag *Z′ E* conformation.

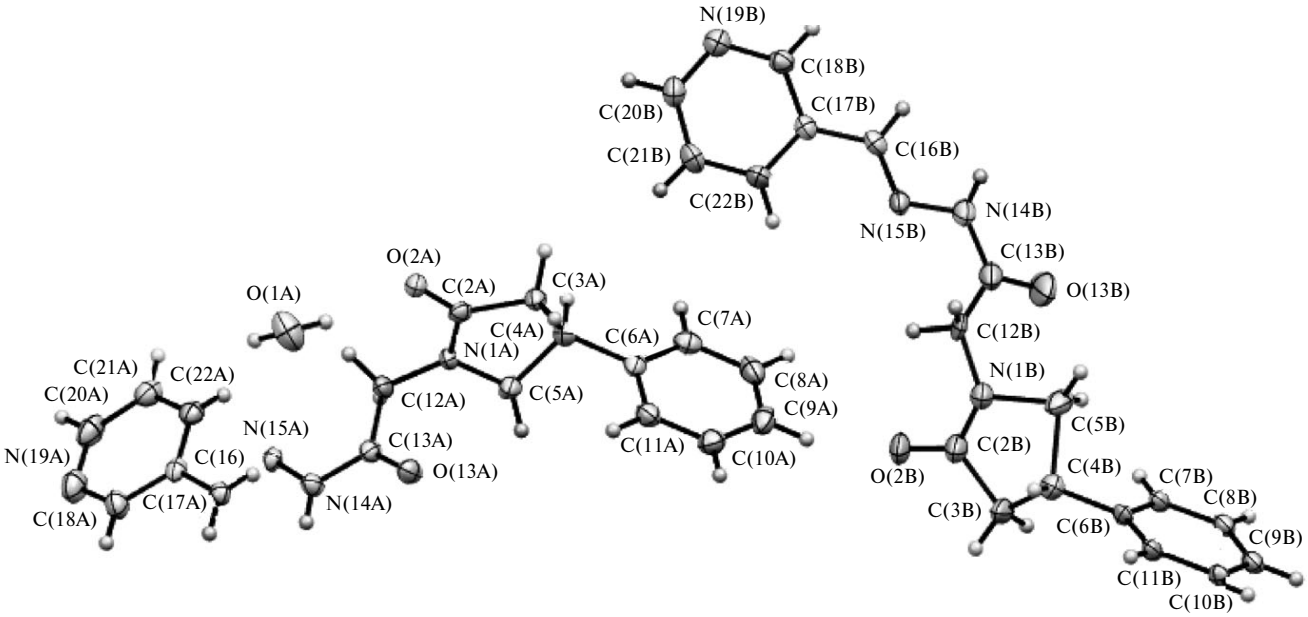


Fig. 1. Geometry of the molecules in the asymmetric unit of the crystal structure of **4d**. The disordered atoms of the molecule **B** (fragment **C**) are omitted for clarity. Thermal displacement ellipsoids are drawn at the 50% probability level.

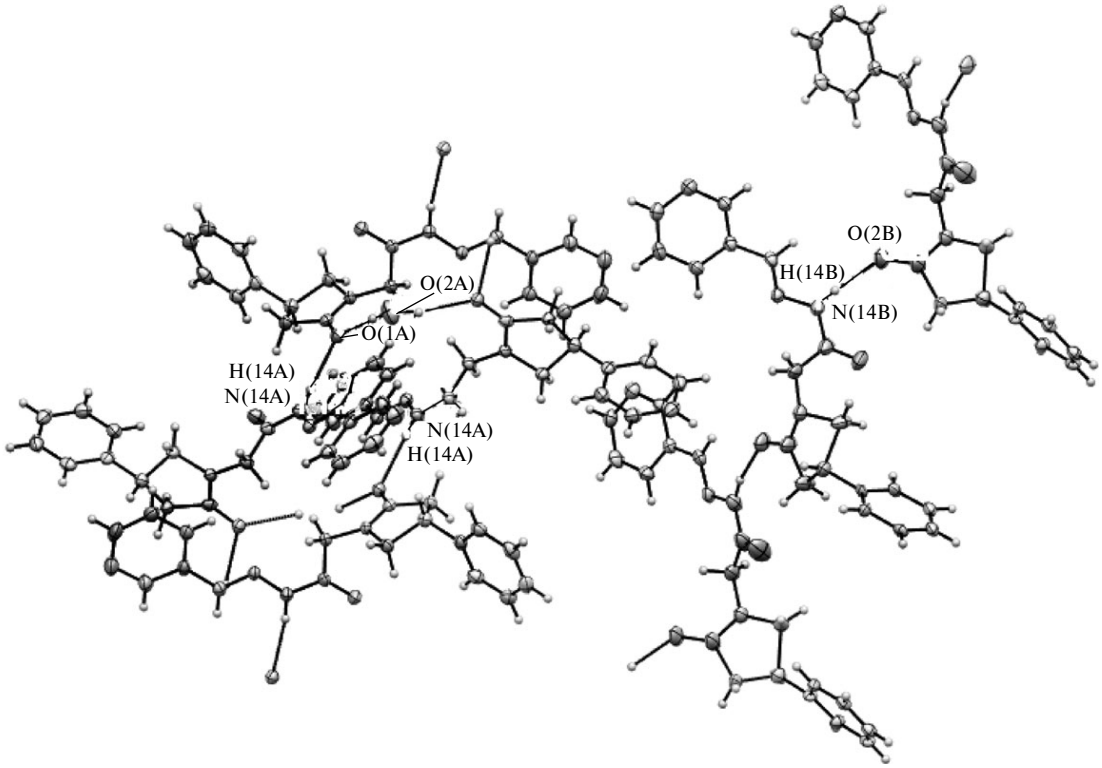


Fig. 2. Hydrogen bond network in the crystal of **4d**. Independent molecules **A** form hydrogen bonds only with the molecules **A** through water molecules; the molecules **B** form hydrogen bonds only with the molecules **B** and **C** (the disordered fragment **C** is omitted for clarity).

The crystal structure of compound **4d** is stabilized by classical hydrogen bonds. In the crystal of compound **4d**, the molecules **A** form hydrogen bonds only with the molecules **A** and water molecules of crystallization (double zigzag chains), while the molecules **B** form hydrogen bonds only with the molecule **B** (simple chains) (Fig. 2).

It should be noted that both the double zigzag chains, composed of the molecules **A** and water molecules, and the simple chains, which include the enantiomeric molecules **B** and **C**, are heterochiral.

In conclusion, we synthesized new representatives of the modified piracetam molecule, namely, 2-[4-(het)aryl-2-oxopyrrolidin-1-yl]acetohydrazides. Preparatively convenient methods were developed for the synthesis of *N′*-alkyl(hetaryl)idene-2-[4-(het)aryl-2-oxopyrrolidin-1-yl]-acetohydrazides based on these acetohydrazides.

The structures of the new compounds were characterized and established by IR spectroscopy, ^{1}H and ^{13}C{^{1}H} NMR spectroscopy (using ^{1}H—^{13}C HMQC, ^{1}H—^{13}C HMBC, and ^{1}H—^{1}H NOESY experiments), and X-ray diffraction. It was shown that the comparative chemical shifts of the C=O carbon atoms of the carbohydrazide moiety can be used as an analytical criterion to decide whether substituted hydrazides have the (*E′*) or (*Z′*) conformation. Compounds **2—6** can be used to synthesize new 2-pyrrolidone derivatives. They are also of interest as promising biologically active compounds.

Experimental

The spectroscopic and elemental analysis data for the synthesized products were obtained using equipment of the Center for Collective Use at the Faculty of Chemistry of the Herzen State Pedagogical University of Russia.

The ^{1}H, ^{13}C{^{1}H}, ^{1}H—^{13}C HMQC, ^{1}H—^{13}C HMBC, ^{1}H—^{1}H NOESY NMR spectra were measured on a JEOL ECX400A spectrometer operating at 399.78 (^{1}H) and 100.525 MHz (^{13}C) in DMSO-d_6 using residual signals of the nondeuterated solvent as the internal standard. The IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer as KBr pellets. Elemental analysis was performed on a EuroVector EA 3000 analyzer (CHN Dual mode). The melting points were measured on a PTP (M) melting-point apparatus.

Starting ethyl 2-[4-(het)aryl-2-oxopyrrolidin-1-yl]acetates **1a—i** were synthesized by a known procedure.[17]

2-(4-Phenyl-2-oxopyrrolidin-1-yl)acetohydrazide (2a). Hydrazine hydrate (4.86 mL, 0.1 mol) was added portionwise with vigorous stirring to ethyl 2-[4-phenyl-2-oxopyrrolidin-1-yl]-acetate (**1a**) (2.47 g, 0.01 mol), the temperature being maintained at 0—5 °C. The reaction mixture was vigorously stirred for 20 h at 18—20 °C. The crystalline product was filtered off. Yield 1.82 g (78%), m.p. 152—154 °C (propan-2-ol). Found (%): C, 61.97; H, 6.50; N, 18.02. $C_{12}H_{15}N_3O_2$. Calculated (%): C, 61.80; H, 6.44; N, 18.03.

Compounds **2b—i** were synthesized in a similar way.

2-[4-(4-Methylphenyl)-2-oxopyrrolidin-1-yl]acetohydrazide (2b) was synthesized from ester **1b**. Yield 61%, m.p. 97—99 °C (propan-2-ol). Found (%): C, 63.26; H, 6.71; N, 17.05. $C_{13}H_{17}N_3O_2$. Calculated (%): C, 63.14; H, 6.93; N, 16.99.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]acetohydrazide (2c) was synthesized from ester **1c**. Yield 70%, m.p. 102—104 °C (propan-2-ol). Found (%): C, 50.89; H, 4.81; N, 15.42. $C_{12}H_{14}N_3O_2Cl$. Calculated (%): C, 50.84; H, 5.27; N, 15.70.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]acetohydrazide (2d) was synthesized from ester **1d**. Yield 76%, m.p. 123—125 °C (propan-2-ol). Found (%): C, 59.33; H, 6.47; N, 16.03. $C_{13}H_{17}N_3O_3$. Calculated (%): C, 59.31; H, 6.46; N, 15.97.

2-[4-(1-Methylindol-3-yl)-2-oxopyrrolidin-1-yl]acetohydrazide (2e) was synthesized from ester **1e**. Yield 40%, m.p. 105—107 °C (propan-2-ol). Found (%): N, 19.18. $C_{15}H_{18}N_4O_2$. Calculated (%): N, 19.57.

2-[4-(1-Benzylindol-3-yl)-2-oxopyrrolidin-1-yl]acetohydrazide (2f) was synthesized from ester **1f**. Yield 66%, m.p. 132—135 °C (propan-2-ol). Found (%): C, 69.55; H, 5.94; N, 15.44. $C_{21}H_{22}N_4O_2$. Calculated (%): C, 69.59; H, 6.12; N, 15.46.

2-[4-(1,2-Dimethylindol-3-yl)-2-oxopyrrolidin-1-yl]acetohydrazide (2g) was synthesized from ester **1g**. Yield 45%, m.p. 194—196 °C (propan-2-ol). Found (%): C, 63.87; H, 6.53; N, 18.89. $C_{16}H_{20}N_4O_2$. Calculated (%): C, 63.98; H, 6.71; N, 18.65.

2-{4-[1-(2-Hydrazino-2-oxoethyl)indol-3-yl]-2-oxopyrrolidin-1-yl}acetohydrazide (2h) was synthesized from diester **1h**. Yield 41%, m.p. 201—203°C (propan-2-ol). Found (%): C, 54.95; H, 5.64; N, 24.28. $C_{16}H_{20}N_6O_3$. Calculated (%): C, 55.80; H, 5.85; N, 24.40.

2-{4-[1-(2-Hydrazino-2-oxoethyl)-2-methylindol-3-yl]-2-oxopyrrolidin-1-yl}acetohydrazide (2i) was synthesized from diester **1i**. Yield 48%, m.p. 150—152°C (propan-2-ol). Found (%): N, 23.87. $C_{17}H_{22}N_6O_3$. Calculated (%): N, 23.45.

2-[4-(4-Methylphenyl)-2-oxopyrrolidin-1-yl]-*N*′-phenylacetohydrazide (3a). A mixture of ethyl 2-[4-(4-methylphenyl)-2-oxopyrrolidin-1-yl]acetate (**1b**) (1.57 g, 0.006 mol) and freshly distilled phenylhydrazine (1.77 mL, 0.018 mol) was vigorously stirred for 20 h. The crystalline product was filtered off. Yield 1.00 g (52%), m.p. 182—184 °C (propan-2-ol). Found (%): C, 70.64; H, 6.38; N, 13.08. $C_{19}H_{21}N_3O_2$. Calculated (%): C, 70.57; H, 6.55; N, 12.99.

Compounds **3b** and **3c** were synthesized in a similar way.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-phenylacetohydrazide (3b) was synthesized from ester **1c**. Yield 50%, m.p. 172—174 °C (propan-2-ol). Found (%): C, 62.84; H, 5.25; N, 12.10. $C_{18}H_{18}ClN_3O_2$. Calculated (%): C, 62.88; H, 5.28; N, 12.22.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-*N*′-phenylacetohydrazide (3c) was synthesized from ester **1d**. Yield 61%, m.p. 170—172 °C (propan-2-ol). Found (%): C, 67.14; H, 6.20; N, 12.34. $C_{19}H_{21}N_3O_3$. Calculated (%): C, 67.24, H, 6.24; N, 12.38.

2-(4-Phenyl-2-oxopyrrolidin-1-yl)-*N*′-[(*E*)-phenylmethylidene]acetohydrazide (4a). A mixture of 2-[4-phenyl-2-oxopyrrolidin-1-yl]acetohydrazide (**2a**) (0.58 g, 0.0025 mol) and benzaldehyde (0.38 mL, 0.0037 mol) in ethanol (8 mL) was refluxed for 10 min and then cooled to room temperature. The crystalline product was filtered off. Yield 0.65 g (81%), m.p. 160—162 °C (methanol). Found (%): N, 12.73. $C_{19}H_{19}N_3O_2$. Calculated (%): N, 13.08.

Compounds **4b—l** were synthesized in a similar way.

***N*′-[(*E*)-(4-Chlorophenyl)methylidene]-2-(4-phenyl-2-oxopyrrolidin-1-yl)acetohydrazide (4b)** was synthesized from hydrazide **2a** and 4-chlorobenzaldehyde. Yield 89%, m.p. 163—165 °C (methanol). Found (%): N, 11.43. $C_{19}H_{18}N_3O_2Cl$. Calculated (%): N, 11.81.

***N*′-[(*E*)-(4-Methoxyphenyl)methylidene]-2-(4-phenyl-2-oxopyrrolidin-1-yl)acetohydrazide (4c)** was synthesized from hydrazide **2a** and 4-methoxybenzaldehyde. Yield 71%, m.p. 154—156 °C (methanol). Found (%): N, 12.19. $C_{20}H_{21}N_3O_3$. Calculated (%): N, 11.96.

2-(4-Phenyl-2-oxopyrrolidin-1-yl)-*N*′-[(*E*)-(pyridin-3-yl)methylidene]acetohydrazide (4d) was synthesized from hydrazide **2a** and 3-pyridinecarbaldehyde. Yield 62%, m.p. 157—159 °C (methanol). Found (%): N, 17.07. $C_{18}H_{18}N_4O_2$. Calculated (%): N, 17.38.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-phenylmethylidene]acetohydrazide (4e) was synthesized from hydrazide **2c** and benzaldehyde. Yield 75%, m.p. 153—155 °C (methanol). Found (%): N, 11.58. $C_{19}H_{18}N_3O_2Cl$. Calculated (%): N, 11.81.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-(4-chlorophenyl)methylidene]acetohydrazide (4f) was synthesized from hydrazide **2c** and 4-chlorobenzaldehyde. Yield 78%, m.p. 147—149 °C (methanol). Found (%): N, 10.37. $C_{19}H_{17}N_3O_2Cl_2$. Calculated (%): N, 10.77.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-(4-methoxyphenyl)methylidene]acetohydrazide (4g) was synthesized from hydrazide **2c** and 4-methoxybenzaldehyde. Yield 84%, m.p. 144—146 °C (methanol). Found (%): C, 62.54; H, 5.15; N, 10.58. $C_{20}H_{20}N_3O_3Cl$. Calculated (%): C, 62.26; H, 5.22; N, 10.89.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-(pyridin-3-yl)methylidene]acetohydrazide (4h) was synthesized from hydrazide **2c** and 3-pyridinecarbaldehyde. Yield 68%, m.p. 83—85 °C (methanol). Found (%): N, 15.21. $C_{18}H_{17}N_4O_2Cl$. Calculated (%): N, 15.70.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-phenylmethylidene]acetohydrazide (4i) was synthesized from hydrazide **2d** and benzaldehyde. Yield 70%, m.p. 181—183 °C (methanol). Found (%): C, 68.28; H, 6.02; N, 11.91. $C_{20}H_{21}N_3O_3$. Calculated (%): C, 68.36; H, 6.02; N, 11.96.

***N*′-[(*E*)-(4-Chlorophenyl)methylidene]-2-[4-(4-methoxyphenyl)-2-oxopyrrolidin-1-yl]acetohydrazide (4j)** was synthesized from hydrazide **2d** and 4-chlorobenzaldehyde. Yield 76%, m.p. 146—148 °C (methanol). Found (%): N, 10.88. $C_{20}H_{20}N_3O_3Cl$. Calculated (%): N, 10.89.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-(4-methoxyphenyl)methylidene]acetohydrazide (4k) was synthesized from hydrazide **2d** and 4-methoxybenzaldehyde. Yield 86%, m.p. 162—164 °C (methanol). Found (%): C, 66.42; H, 5.97; N, 10.72. $C_{21}H_{23}N_3O_4$. Calculated (%): C, 66.13; H, 6.08; N, 11.02.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(*E*)-(pyridin-3-yl)methylidene]acetohydrazide (4l) was synthesized from hydrazide **2d** and 3-pyridinecarbaldehyde. Yield 76%, m.p. 144—146 °C (methanol). Found (%): N, 15.71. $C_{19}H_{20}N_4O_3$. Calculated (%): N, 15.91.

2-(4-Phenyl-2-oxopyrrolidin-1-yl)-*N*′-isopropylideneacetohydrazide (5a). A solution of 2-[4-phenyl-2-oxopyrrolidin-1-yl]acetohydrazide (**2a**) (1.17 g, 0.005 mol) in acetone (11 mL) was refluxed for 1 h and then cooled. The crystalline product was filtered off and dried in air. Yield 1.17 g (85%), m.p. 150—152 °C (methanol). Found (%): C, 65.43; H, 6.97; N, 15.63. $C_{15}H_{19}N_3O_2$. Calculated (%): C, 65.91; H, 7.01; N, 15.37.

Compounds **5b** and **5c** were synthesized in a similar way.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-isopropylideneacetohydrazide (5b) was synthesized from hydrazide **2c**. Yield 71%, m.p. 123—125 °C (acetone). Found (%): N, 13.22. $C_{15}H_{18}N_3O_2Cl$. Calculated (%): N, 13.65.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-*N*′-isopropylideacetohydrazide (5c) was synthesized from hydrazide **2d**. Yield 73%, m.p. 156—158 °C (methanol). Found (%): C, 63.18;

H, 6.97; N, 13.76. $C_{16}H_{21}N_3O_3$. Calculated (%): C, 63.35; H, 6.98; N, 13.85.

2-(4-Phenyl-2-oxopyrrolidin-1-yl)-*N*′-[(1*E*)-1-phenylethylidene]acetohydrazide (6a). A mixture of 2-[4-phenyl-2-oxopyrrolidin-1-yl]acetohydrazide (**2a**) (0.58 g, 0.0025 mol) and acetophenone (0.29 mL, 0.0025 mol) in ethanol (10 mL) was refluxed for 3 h. The crystalline product was filtered off and dried in air. Yield 0.58 g (69%), m.p. 193—195 °C (methanol). Found (%): C, 71.44; H, 6.39; N, 12.64. $C_{20}H_{21}N_3O_2$. Calculated (%): C, 71.62; H, 6.31; N, 12.53.

Compound **6b** was synthesized in a similar way.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(1*E*)-1-phenylethylidene]acetohydrazide (6b) was synthesized from hydrazide **2c**. Yield 71%, m.p. 165—166 °C (methanol). Found (%): C, 65.12; H, 5.51; N, 11.21. $C_{20}H_{20}N_3O_2Cl$. Calculated (%): C, 64.95; H, 5.45; N, 11.36.

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-*N*′-[(1*E*)-1-phenylethylidene]acetohydrazide (6c). A mixture of 2-[4-(4-methoxyphenyl)-2-oxopyrrolidin-1-yl]acetohydrazide (**2d**) (0.66 g, 0.0025 mol) and acetophenone (0.29 mL, 0.0025 mol) in ethanol (10 mL) was refluxed for 9 h. The crystalline product was filtered off and dried in air. Yield 0.59 g (65%), m.p. 158—160 °C (methanol). Found (%): N, 11.46. $C_{21}H_{23}N_3O_3$. Calculated (%): N, 11.50.

X-ray diffraction study of compound 4d. The X-ray diffraction data were collected on a Bruker Smart APEX II CCD diffractometer at the Department of X-ray Diffraction Research of the Multiple-Access Center on the basis of the Laboratory of Diffraction Research Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry within the framework of the state assignment to the Kazan Scientific Center of the Russian Academy of Sciences. The molecular and crystal structure was analyzed and discussed at the Kazan National Research Technological University named after A. N. Tupolev (KAI).

Crystals of compound **4d** suitable for X-ray diffraction were obtained by the crystallization from methanol. The crystals of compound **4d** (crystal hydrate) ($4(C_{18}H_{18}N_4O_2)\cdot H_2O$, M = 1307.47, one water molecule per four molecules **4d**) are colorless, prismatic, monoclinic, m.p. 157—159 °C, at 100 K a = 52.952(4) Å, b = 8.8432(6) Å, c = 14.3272(10) Å, β = 105.433(4)°, V = 6467.0(8) Å^3, Z = 2 (two independent molecules, **A** and **B**; a water molecule occupies a special position on a twofold axis), space group $C2/c$, d_{calc} = 1.343 g cm^{-3}, μ = 0.09 mm^{-1}, $F(000)$ = 2760, 2 θ_{max} < 56°. A total of 70439 measured reflections (R_{int} = 0.114), 7795 of which are unique; the number of observed reflections with $I > 2\sigma(I)$ is 4705. An absorption correction was applied with the SADABS program.[20]

The structure was solved by direct methods using the SHELXT-2018/2 program package[21] and refined by the full-matrix least-squares method based on F^2 using the SHELXL-2018/3 program package.[22] The disorder of the pyrrolidone ring with the attached phenyl substituent in the independent molecule **B** was revealed based on the sizes of the displacement ellipsoids and the presence of strong peaks in difference electron density maps. The refinement of the occupancies of the disordered fragments gave 0.587 for **B** and 0.413 for **C**. All calculations were performed using the WinGX-2014.1 program package.[23] Nonhydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms at the carbon atoms were positioned geometrically and refined isotropically using a riding model. The H(1) atoms at the nitrogen atoms N(1) and hydrogens of the water molecules were found in difference electron density maps and refined isotropically. The refinement converged to R = 0.1164, wR_2 = 0.1959 based on all reflections, R = 0.0631, wR_2 = 0.1619 based on unique reflections, GOOF = 0.969, 530 refined parameters.

Crystallographic data were deposited with the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk; CCDC 1957188).

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