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Preparation of a chloride salt of covalently modified isoniazid

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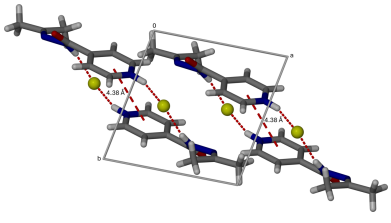
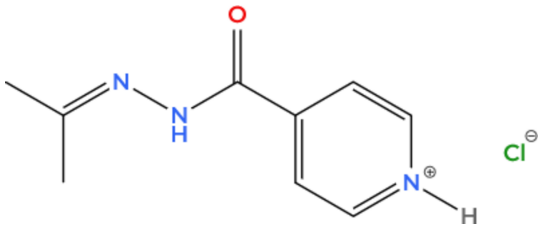
A novel covalently modified isoniazid salt {4-[*N*′-(propan-2-ylidene)-hydrazinecarbonyl]pyridin-1-ium chloride}, $C_9H_{12}N_3O^+\cdot Cl^-$, was synthesized using a slow diffusion layering technique under ambient conditions. Single-crystal X-ray diffraction (SC-XRD) analysis revealed that the compound crystallizes in the triclinic space group $P\overline{1}$. The crystal structure features prominent N—H···Cl hydrogen bonds, indicating strong intermolecular interactions between the chloride ion and the modified isoniazid framework.

1. Chemical context

Isoniazid (pyridine-4-carboxylic acid hydrazide) is a well-established first-line antitubercular drug that remains a cornerstone of combination therapy for tuberculosis worldwide (Hegde *et al.*, 2021). Owing to its clinical significance, isoniazid has been the subject of extensive structural modification efforts aimed at improving its physicochemical and pharmacological properties (Setshedi *et al.*, 2022; Smith & Lemmerer, 2018). One such strategy involves condensation of the hydrazide moiety with a carbonyl compound, yielding a hydrazone derivative while preserving the integrity of the pyridine ring (Lemmerer, 2012). This covalent transformation introduces an imine C═N double bond adjacent to the aromatic system, enhancing molecular rigidity and modulating the electronic environment of the hydrazide functionality (Lemmerer, 2012). Although the pyridine nitrogen remains chemically unaltered, it frequently participates in strong hydrogen bonding, which plays a critical role in stabilizing the crystal structure (Aakeröy *et al.*, 2007; Setshedi *et al.*, 2021). These directional interactions often organize the molecular components into extended supramolecular chains or layered assemblies, defining the overall packing architecture. The neutral hydrazone compound was first synthesized by Wang *et al.* (2008), and then by Lemmerer (2012); however, its isolation and crystallographic characterization as a salt have not previously been reported. Covalent modification of isoniazid derivatives often leads to improved activity against multi-drug resistant tuberculosis (Hearn *et al.*, 2004; Setshedi & Smith, 2021) and their crystal structures provide valuable insights into the role of ionic interactions and hydrogen-bonding networks in consolidating the solid state (Scheepers & Lemmerer, 2023).





2. Structural commentary

The asymmetric unit of the title compound comprises one molecule of the covalently modified isoniazid hydrazone, namely *N*′-(2-propanylidene)isonicotinohydrazide and one chloride ion (Fig. 1). The hydrazone moiety adopts an extended conformation, with the imine C=N double bond in the (*E*)-configuration, consistent with previously reported structures of neutral analogues. The chloride ion is located in close proximity to the hydrazide N—H donor, forming a strong N—H···Cl hydrogen bond that anchors the ionic framework (Table 1). All bond lengths and angles fall within expected ranges for hydrazone derivatives. The C=N bond measures 1.2835 (15) Å, confirming its double-bond character, while the N—N and C=O distances are consistent with typical hydrazide geometry.

In the free base, *N*′-(2-propanylidene)isonicotinohydrazide, the crystal structure is consolidated by hydrogen bonding between the carbonyl oxygen acceptor and the amide hydrogen donor (Lemmerer, 2012; Fig. 2). In contrast, in the chloride salt reported in this study, the amide hydrogen donor interacts with a chloride ion, forming a chloride bridge. The chloride ion is further hydrogen bonded to the protonated (aminium) nitrogen of the pyridine ring, resulting in a four-membered hydrogen-bonded ring motif (Fig. 3).

3. Supramolecular features

The packing arrangement of the title compound is illustrated in Fig. 4. In the crystal, the chloride anion forms a strong, directional N—H···Cl hydrogen bond with the hydrazide N—H donor, with an H···Cl distance of 2.1 Å and an N—H···Cl angle of 175° (Table 1). These interactions link cations and anions into one-dimensional chains along the *c*-axis direction, which are further connected into two-dimensional layers through weaker C—H···Cl interactions (Table 1) and van der Waals contacts. Adjacent pyridine rings are approximately parallel, with a centroid–centroid distance of 4.3823 (7) Å, indicative of weak long-range π–π interactions that may contribute subtly to the packing cohesion, also seen in Fig. 4. Overall, the supramolecular assembly is dominated by the strong N—H···Cl hydrogen bonding, with secondary interactions supporting the layered crystal architecture.

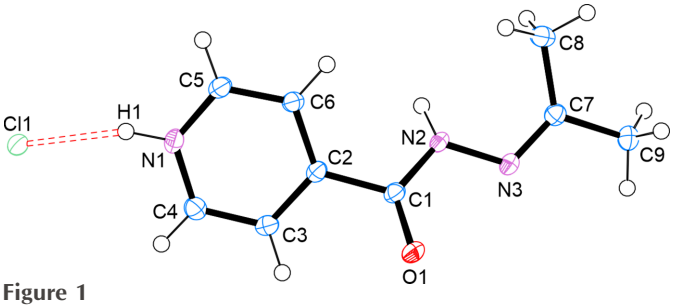


Figure 1
The asymmetric unit of the chloride salt of covalently modified isoniazid with displacement ellipsoids drawn at the 50% probability level.

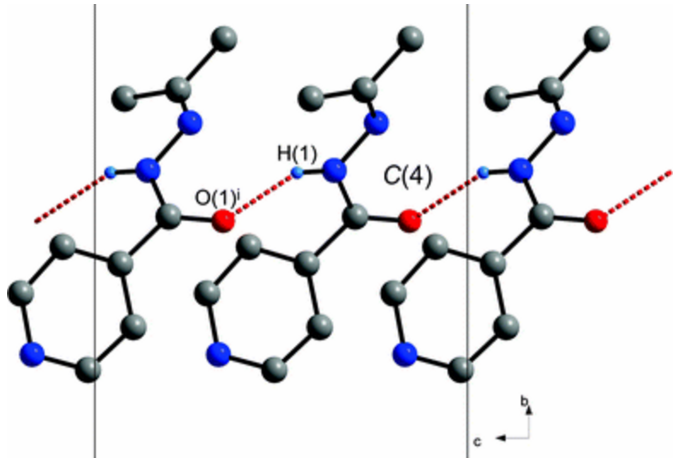


Figure 2
The crystal structure of *N*′-(2-propanylidene)isonicotinohydrazide. Reproduced directly from Lemmerer (2012).

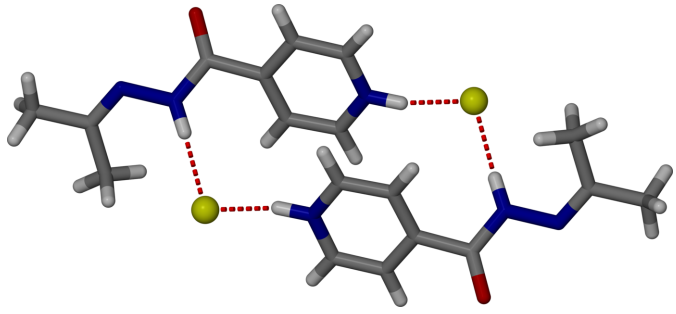


Figure 3
The four-membered hydrogen-bonded ring motif of the chloride salt.

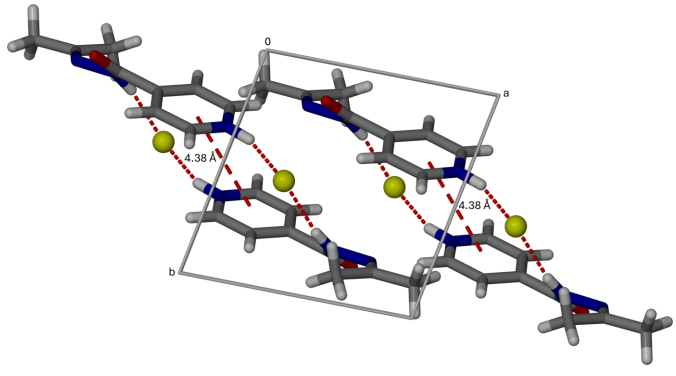


Figure 4
Crystal packing diagram of the chloride salt of covalently modified isoniazid, viewed along the *c*-axis, highlighting π–π stacking interactions between adjacent pyridine rings.

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···Cl1	0.920 (16)	2.137 (16)	3.0120 (10)	158.8 (14)
N2—H2···Cl1^{i}	0.897 (15)	2.314 (16)	3.2012 (10)	170.1 (14)
C3—H3···Cl1^{ii}	0.95	2.75	3.6711 (12)	163
C4—H4···Cl1^{iii}	0.95	2.74	3.5670 (12)	146
C5—H5···O1^{iv}	0.95	2.45	3.1487 (15)	131
C5—H5···N3^{iv}	0.95	2.38	3.2936 (15)	161

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

4. Database survey

In this paper, we report the chloride salt of *N*′-(2-propanylidene)isonicotinohydrazide, obtained via reaction with isopropanol. A search of the Cambridge Structural Database (CSD, Version 2025.1; Groom *et al.*, 2016) identified 15 crystal structures of *N*′-(2-propanylidene)isonicotinohydrazide. The structure of the free base has previously been published by Wang *et al.* (2008, refcode ROFCIZ) and Lemmerer *et al.* (2012, refcode ROFCIZ01). Notably, all 15 covalently modified structures were prepared from the reaction of isoniazid with acetone. In contrast, the salt presented here was obtained from isoniazid and isopropanol in the presence of an iron catalyst. Interestingly, aside from the two free-base structures mentioned above and a hydrate reported by Álvarez-Vidaurre *et al.* (2021, refcode UQEJEI), all acetone-derived isoniazid derivatives crystallized as co-crystals. By contrast, synthesis from isopropanol, as reported here, yielded a salt.

5. Synthesis and crystallization

All reagents were commercially sourced and used without further purification. To synthesize the title compound, $FeCl_3$ (162.21 mg, 1.00 mmol) was dissolved in 3 ml of DMSO by stirring at room temperature for 10 minutes. Once fully dissolved, isoniazid (INH) (137.1 mg, 1.00 mmol) was added with continuous stirring, followed by the addition of three drops of concentrated hydrochloric acid. The reaction mixture was stirred for a further 20 minutes. The resulting solution was carefully layered with 4 ml of isopropanol and left undisturbed at room temperature (±298.15 K) for two weeks. This procedure yielded two distinct crystalline forms: green crystals of the iron complex and colourless crystals of the corresponding salt.

6. Refinement

Crystal data, data collection, and structure refinement details are summarized in Table 2. Carbon-bound hydrogen atoms were first located in the difference Fourier map, then positioned geometrically and refined using a riding model, with isotropic displacement parameters set to 1.2 times those of their parent carbon atoms. The coordinates of the nitrogen-bound hydrogen atom involved in hydrogen bonding interactions were refined freely, with isotropic displacement parameters set to 1.5 times those of the parent nitrogen atom.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_9H_{12}N_3O^+\cdot Cl^-$
M_r	213.67
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	100
a, b, c (Å)	7.6446 (2), 7.8650 (3), 8.7236 (3)
α, β, γ (°)	100.488 (1), 91.053 (1), 100.038 (1)
V (Å^3)	507.17 (3)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.35
Crystal size (mm)	0.58 × 0.30 × 0.17
Data collection	
Diffractometer	Bruker APEXII CCD
Absorption correction	–
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	28203, 2332, 2258
R_{int}	0.029
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.650
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.026, 0.076, 1.11
No. of reflections	2324
No. of parameters	135
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.38, −0.21

Computer programs: *APEX3*, *SAINT-Plus* and *XPREP* (Bruker 2016), *OLEX2* (Dolomanov *et al.*, 2019), *SHELXT2014* (Sheldrick, 2015*a*), *SHELXL2014/7* (Sheldrick, 2015*b*), *ORTEP-3 for Windows* and *WinGX* publication routines (Farrugia, 2012), *Mercury* (Macrae *et al.*, 2020) and *PLATON* (Spek, 2020).

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Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Conflict of interest

The authors declare no conflicts of interest regarding this article.

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Computing details

4-[*N*′-(Propan-2-ylidene)hydrazinecarbonyl]pyridin-1-ium chloride

Crystal data

$C_9H_{12}N_3O^+\cdot Cl^-$
$M_r = 213.67$
Triclinic, $P\overline{1}$
$a = 7.6446$ (2) Å
$b = 7.8650$ (3) Å
$c = 8.7236$ (3) Å
$\alpha = 100.488$ (1)°
$\beta = 91.053$ (1)°
$\gamma = 100.038$ (1)°
$V = 507.17$ (3) Å^3
$Z = 2$
$F(000) = 224$
$D_x = 1.399$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 9473 reflections
$\theta = 2.4$–27.5°
$\mu = 0.35$ mm^{-1}
$T = 100$ K
Block, colourless
0.57 × 0.30 × 0.17 mm

Data collection

Bruker APEXII CCD diffractometer
φ and ω scans
28203 measured reflections
2332 independent reflections
2258 reflections with $I > 2\sigma(I)$
$R_{int} = 0.029$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.4°$
$h = -9\rightarrow9$
$k = -10\rightarrow10$
$l = -11\rightarrow11$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.026$
$wR(F^2) = 0.076$
$S = 1.11$
2324 reflections
135 parameters
0 restraints
0 constraints
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0365P)^2 + 0.2176P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.38$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. The crystal structure was solved with *OLEX2* (Dolomanov *et al.*, 2019) by direct methods using SHELXT (Sheldrick, 2015). Non-hydrogen atoms were initially refined isotropically, followed by anisotropic refinement using full-matrix least-squares calculations based on F^2 with *SHELXL*.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.55980 (15)	0.78876 (14)	0.54588 (13)	0.0168 (2)
C3	0.35037 (15)	0.65162 (15)	0.72127 (13)	0.0179 (2)
H3	0.449994	0.624807	0.772559	0.022*
C4	0.18139 (16)	0.60644 (15)	0.77089 (13)	0.0193 (2)
H4	0.163402	0.546093	0.855847	0.023*
C8	0.62897 (16)	0.87847 (17)	0.10016 (14)	0.0227 (2)
H8A	0.569495	0.768289	0.034188	0.034*
H8B	0.683094	0.959495	0.034062	0.034*
H8C	0.541702	0.931803	0.164363	0.034*
C9	0.95546 (16)	0.85452 (17)	0.14704 (14)	0.0224 (2)
H9A	1.006503	0.978093	0.148385	0.034*
H9B	0.951451	0.787694	0.040233	0.034*
H9C	1.029234	0.806303	0.215253	0.034*
C6	0.22523 (15)	0.77914 (15)	0.52266 (13)	0.0169 (2)
H6	0.239081	0.838311	0.436726	0.02*
C2	0.37274 (14)	0.73748 (14)	0.59433 (12)	0.0156 (2)
C5	0.05897 (15)	0.73335 (15)	0.57808 (13)	0.0184 (2)
H5	−0.042623	0.761916	0.531327	0.022*
C7	0.77068 (15)	0.84150 (14)	0.20401 (13)	0.0176 (2)
N2	0.57561 (12)	0.78193 (13)	0.39063 (11)	0.0170 (2)
H2	0.485 (2)	0.724 (2)	0.3240 (18)	0.02*
N1	0.04194 (13)	0.64795 (13)	0.69882 (11)	0.0182 (2)
H1	−0.069 (2)	0.613 (2)	0.7336 (18)	0.022*
N3	0.75011 (12)	0.80011 (13)	0.33906 (11)	0.0180 (2)
O1	0.68331 (11)	0.83507 (12)	0.64431 (10)	0.02301 (19)
Cl1	−0.27331 (3)	0.46775 (3)	0.84678 (3)	0.01841 (10)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0136 (5)	0.0184 (5)	0.0191 (5)	0.0041 (4)	−0.0001 (4)	0.0044 (4)
C3	0.0169 (5)	0.0193 (5)	0.0177 (5)	0.0048 (4)	−0.0017 (4)	0.0027 (4)
C4	0.0206 (6)	0.0202 (5)	0.0172 (5)	0.0034 (4)	0.0014 (4)	0.0037 (4)
C8	0.0226 (6)	0.0286 (6)	0.0193 (5)	0.0075 (5)	−0.0001 (4)	0.0077 (5)
C9	0.0183 (6)	0.0281 (6)	0.0211 (5)	0.0035 (5)	0.0040 (4)	0.0060 (5)
C6	0.0155 (5)	0.0193 (5)	0.0160 (5)	0.0040 (4)	−0.0004 (4)	0.0033 (4)
C2	0.0132 (5)	0.0166 (5)	0.0160 (5)	0.0026 (4)	0.0001 (4)	0.0004 (4)
C5	0.0151 (5)	0.0217 (5)	0.0179 (5)	0.0048 (4)	−0.0012 (4)	0.0012 (4)
C7	0.0169 (5)	0.0177 (5)	0.0176 (5)	0.0031 (4)	0.0006 (4)	0.0021 (4)
N2	0.0105 (4)	0.0229 (5)	0.0175 (5)	0.0025 (4)	0.0001 (3)	0.0038 (4)
N1	0.0137 (5)	0.0207 (5)	0.0186 (5)	0.0014 (4)	0.0029 (4)	0.0011 (4)
N3	0.0124 (4)	0.0224 (5)	0.0195 (5)	0.0034 (4)	0.0015 (3)	0.0046 (4)
O1	0.0136 (4)	0.0350 (5)	0.0193 (4)	0.0012 (3)	−0.0022 (3)	0.0054 (3)
Cl1	0.01409 (14)	0.02298 (15)	0.01776 (15)	0.00193 (10)	0.00002 (9)	0.00423 (10)

Geometric parameters (Å, º)

C1—C2	1.5065 (15)	C9—H9B	0.98
C1—N2	1.3541 (15)	C9—H9C	0.98
C1—O1	1.2239 (14)	C9—C7	1.4989 (16)
C3—H3	0.95	C6—H6	0.95
C3—C4	1.3780 (16)	C6—C2	1.3954 (15)
C3—C2	1.3966 (16)	C6—C5	1.3804 (16)
C4—H4	0.95	C5—H5	0.95
C4—N1	1.3453 (15)	C5—N1	1.3452 (15)
C8—H8A	0.98	C7—N3	1.2835 (15)
C8—H8B	0.98	N2—H2	0.896 (16)
C8—H8C	0.98	N2—N3	1.4076 (13)
C8—C7	1.4995 (16)	N1—H1	0.918 (16)
C9—H9A	0.98		
N2—C1—C2	114.95 (9)	C7—C9—H9C	109.5
O1—C1—C2	120.18 (10)	C2—C6—H6	120.4
O1—C1—N2	124.87 (10)	C5—C6—H6	120.4
C4—C3—H3	120.6	C5—C6—C2	119.22 (10)
C4—C3—C2	118.90 (10)	C3—C2—C1	117.40 (10)
C2—C3—H3	120.6	C6—C2—C1	122.83 (10)
C3—C4—H4	120.1	C6—C2—C3	119.70 (10)
N1—C4—C3	119.88 (11)	C6—C5—H5	120.3
N1—C4—H4	120.1	N1—C5—C6	119.47 (10)
H8A—C8—H8B	109.5	N1—C5—H5	120.3
H8A—C8—H8C	109.5	C9—C7—C8	117.72 (10)
H8B—C8—H8C	109.5	N3—C7—C8	126.34 (10)
C7—C8—H8A	109.5	N3—C7—C9	115.94 (10)
C7—C8—H8B	109.5	C1—N2—H2	119.5 (10)
C7—C8—H8C	109.5	C1—N2—N3	116.06 (9)
H9A—C9—H9B	109.5	N3—N2—H2	119.3 (10)
H9A—C9—H9C	109.5	C4—N1—H1	117.2 (10)
H9B—C9—H9C	109.5	C5—N1—C4	122.81 (10)
C7—C9—H9A	109.5	C5—N1—H1	120.0 (10)
C7—C9—H9B	109.5	C7—N3—N2	116.08 (9)
C1—N2—N3—C7	−161.70 (10)	C2—C6—C5—N1	−0.70 (16)
C3—C4—N1—C5	−0.05 (17)	C5—C6—C2—C1	−177.47 (10)
C4—C3—C2—C1	178.54 (10)	C5—C6—C2—C3	−0.47 (16)
C4—C3—C2—C6	1.38 (16)	N2—C1—C2—C3	146.32 (10)
C8—C7—N3—N2	2.47 (17)	N2—C1—C2—C6	−36.62 (15)
C9—C7—N3—N2	−177.92 (9)	O1—C1—C2—C3	−34.86 (15)
C6—C5—N1—C4	0.99 (17)	O1—C1—C2—C6	142.20 (12)
C2—C1—N2—N3	−169.69 (9)	O1—C1—N2—N3	11.56 (17)
C2—C3—C4—N1	−1.14 (17)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···Cl1	0.920 (16)	2.137 (16)	3.0120 (10)	158.8 (14)
N2—H2···Cl1^{i}	0.897 (15)	2.314 (16)	3.2012 (10)	170.1 (14)
C3—H3···Cl1^{ii}	0.95	2.75	3.6711 (12)	163
C4—H4···Cl1^{iii}	0.95	2.74	3.5670 (12)	146
C5—H5···O1^{iv}	0.95	2.45	3.1487 (15)	131
C5—H5···N3^{iv}	0.95	2.38	3.2936 (15)	161

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