Molecular recognition in β-lactams: the crystal packing in 4-sulfonyl β-lactams

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Single crystal X-ray structures of 4-phenyl sulfonyl 2-azetidinone **1**, a 1:2 conglomerate of the corresponding 3-methyl (trans) and 3,3-dimethyl derivatives **2A** and **2B/2C** respectively and 3-acetoxymethyl 1,4-diphenyl 2-azetidinone **3** revealed interesting variation in crystal packing dictated by H-bonding and hydrophobic interactions which may be responsible for molecular recognition in β-lactams.

Keywords: β-lactams, crystal packing

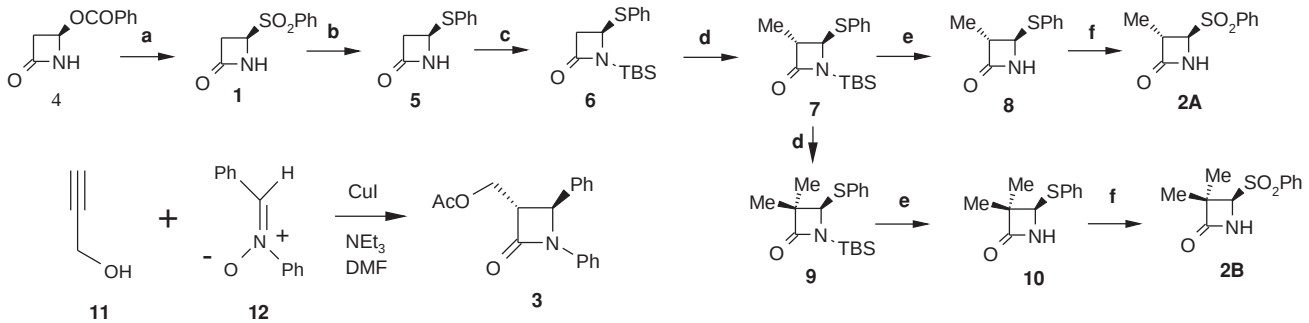
Although the chemistry of the β-lactams[1] is about one hundred years old, correlations between the biological activity and the 3D-structure of β-lactams remains elusive. The reactivity of this class of compounds is related to the pyramidalisation of the lactam nitrogen,[2] which is connected to the strain in the 4-membered ring. The high rate of acylation of the penicillin binding proteins by penicillins, the basis of their antibacterial activity,[3] has been attributed to the strain of the 4-membered ring usually induced by the fusion of 5- or 6-membered rings. The discovery of biologically active monocyclic β-lactams or monobactams,[4] which are reported to be planar, has cast serious doubts on the strain theory. The reactivity of a β-lactam may not be a measure of its activity towards transpeptidase or β-lactamase. The weak non-bonding interactions between the substrate and the enzyme provide molecular recognition and binding energy to lower the activation barrier for interaction with target enzymes.[5] Useful information may be obtained regarding the influence of weak interactions like H-bonds and hydrophobic interactions by studying the crystal structures of β-lactams. For example, in N-unsubstituted 4-phenylsulfonyl β-lactams, there is the possibility of intermolecular H-bonding between N–H and O=C, as well as N–H—O=S and intermolecular π-stacking interactions involving the phenyl rings. Consequently, it will be interesting to know what type of H-bonding is present in 4-phenylsulfonyl β-lactams and whether it is influenced by parameters like ring planarity, substitution pattern and hydrophobic interactions. It is also interesting to know the crystal packing in fully substituted 2-azetidinones where H-bonding is not possible.

Results and discussion

We synthesised four monocyclic β-lactams; 4-phenyl sulfonyl 2-azetidinone **1**, its 3-methyl and 3, 3-dimethyl derivatives **2A** and **2B** respectively and the azetidinone **3** (Scheme 1). Compound **1** was prepared according to the literature method[6-8] while compound **2A** was prepared by C-3 alkylation of N-TBS 4-thiophenyl azetidinone **6** with LDA and methyl iodide (1.2 equiv) followed by desilylation and oxidation with *m*-CPBA.[9] Further alkylation of N-TBS 3-methyl 4-thiophenyl azetidinone **7** with LDA and methyl iodide afforded the dimethyl azetidinone **2B** in a similar manner. These compounds were previously synthesised by Kaneko *et al*.[10] *via* a Pummerer rearrangement. The crystal structures of **1** and **3** were determined from single crystals. The individual crystal structure of β-lactams **2A** or **2B** could not be obtained because of lack of single crystal. Interestingly, single crystals with a composition of 1:2 were obtained from a hexane-ethyl acetate solution containing both **2A** and **2B/2C** (**2C** indicates the other molecule corresponding to **2B** present in the unit cell) and thus the crystal structure for the conglomerate was determined.

Analysis of the bonds connected to N1 shows normal (sp^2) C–N bond distance in all the β-lactams. However, there is some difference in the geometry of the lactam ring; it is not planar in all the cases. The planarity is governed by the nature of substitution in the ring. The deviation of planarity of the nitrogen atom from the plane of the other three atoms is highest in compound **3**. The β-lactam ring in **2A**, **2B** and **2C** is completely planar while it is slightly non planar in compound **1** (Table 2).

All the three molecules (**1, 2A, 2B** and **3**) are mainly packed by hydrophobic interactions (Figs. 1–3). However, in molecules **1–2**, hydrogen bonding also plays a crucial role in packing (Table 3). In molecule **3**, due to the lack of any hydrogen donor, the packing is stabilised by segregation of the hydrophobic and hydrophilic interactions along the *c* axis The aromatic rings are stacked along the *b* axis. The hydrogen bonding pattern in molecule **1** and in the



Scheme 1 (a) $PhSO_2Na$, H_2O,45 °C; (b) PhSH, (-)cinchonine, benzene, 45 °C; (c) TBSCl, NEt_3, DMF, r.t.; (d) BuLi, -78 °C, 30 min, then MeI (2.2 eq) at -78 °C for 1h, finally quenched with NH_4Cl; (e) 0.1(N)HCl, MeOH, r.t.; (f) m-CPBA,CH_2Cl_2, r.t.

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Table 1 Selected bond lengths (Å)

	1	2A	2B	2C	3A	3B
N1-C15	-	-	-	-	1.402(6)	1.399(7)
N1-C4	1.436(3)	1.440(5)	1.438(5)	1.436(6)	1.480(5)	1.486(6)
N1-C2	1.342(3)	1.339(7)	1.355(7)	1.348(8)	1.375(7)	1.365(7)
C2-O5	1.215(2)	1.212(6)	1.199(6)	1.193(8)	1.216(5)	1.215(6)

Table 2 Deviation of N from plane formed by atoms C2–C3–C4 of the β lactam ring

Molecule	Deviation (Å)
1	0.032(2)
2A	Planar
2B	Planar
2C	Planar
3A	0.073(4)
3B	0.040(4)

conglomerate of **2A** and **2B**/**2C** are quite different. In molecule **1**, the N–H…O (of CO) type of hydrogen bonding and in the conglomerate of **2A** and **2B/2C**, N–H…O (of SO_2) type H-bonding are predominant. In molecule **1**, segregation of the hydrophobic zones is observed along the *c* axis with the phenyl ring stacks along the *a* axis. In the crystal packing of conglomerate of **2A** and **2B/2C**, a hydrophobic core is formed and the hydrogen bonded chain proceeds along the *c* axis.

In conclusion molecular recognition of the β-lactam derivatives may involve hydrophobic interactions and hydrogen bonding such as N-H…O=C and N-H…O=S depending upon the orientation of the molecules in an assembly.

Experimental

*General***:** IR spectra were recorded on Perkin Elmer model 883 using KBr pellet for solids and neat for liquids. The characteristic peaks are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer. Melting points (m.p.) were recorded on a Toshniwal hot-coil stage melting point apparatus and are uncorrected. Mass spectra were obtained from CRIM (Clinical Research Institute of Montreal), Canada and Central Research Facility, IIT, Kharagpur. Columns were prepared with silica gel (60 to 120 mesh, S. D. Fine Chemicals). All the reactions were carried out under argon/nitrogen atmosphere.

Synthesis of trans-3-methyl-4-thiophenyl-2-azetidinone **(8):** To a solution of 4-thiophenyl-2-azetidinone[11] (**5**, 300 mg, 1.68 mmol) in DMF, triethylamine (257 μl, 1.85 mmol) was added followed by TBSCl (279 mg, 1.85 mmol). The solution was stirred at r.t. for 8 h. The precipitated solid was filtered off and the filtrate was partitioned between ethyl acetate and water. The ethyl acetate layer was washed several times with water, brine and then dried over anhydrous Na_2SO_4. Removal of solvent and purification by silica-gel column chromatography (hexane-ethyl acetate 15:1) afforded the N-TBS-4-thiophenyl-2-azetidinone (**6,** 468 mg, 95%) as greenish viscous oil.

n-BuLi (15% in hexane, 957 μl, 2.24 mmol) was added dropwise to a solution of N-protected azetidinone **6** (400 mg, 1.36 mmol) in dry THF at –78 °C, The solution was stirred at –78 °C for 30 min after which MeI (110 μl, 1.77 mmol) was added and the solution was stirred for 1 h at –78 °C. The reaction mixture was then quenched with saturated ammonium chloride solution and then allowed to warm upto 0 °C and finally partitioned between ethyl acetate and water. The ethyl acetate layer was washed with 5% $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4. Removal of solvent gave yellowish green oil from which the N-TBS-trans-3-Methyl-4-thiophenyl-2-azetidinone[12] (**7,** 230 mg, 55%) was isolated as a colourless oil by radial chromatography (hexane-ethyl acetate 7:1).

The N-TBS-*trans*-3-Methyl-4-thiophenyl-2-azetidinone (**7**, 200mg, 0.65 mmol) was dissolved in 0.1(N) methanolic HCl (3 ml) and stirred at room temperature for 8 h. The solution was diluted with ethyl acetate and washed successively with 5% $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and crystallisation from chloroform-hexane afforded **8** as a white solid[13] (120 mg, 95%); m.p. 98 °C; υ_{max} (KBr) 1768cm^{-1}; δ_H 7.46–7.30 (5H, complex, Ph), 6.4 (1H, bs, NH), 4.62 (1H, d, *J* =2 Hz, H-4β), 3.06 (1H, m, H-3), 1.35 (3H, d, *J* = 7.4 Hz, Me); δ_c 169.87, 133.26, 131.80, 128.49, 127.71, 61.95, 53.69, 12.47; Mass (CI) 194 (MH^+), 138; HRMS: calcd. for $C_{10}H_{12}NOS$ 194.0641 found 194.0644.

Synthesis of trans-3-methyl-4-phenylsulfonyl-2-azetidinone **(2A):** a solution of m-CPBA (197 mg, 1.14 mmol) in CH_2Cl_2 (5 ml) was added slowly over 10 min to a solution of the trans-3-Methyl-4-thiophenyl-2-azetidinone (**8**, 100 mg, 0.52 mmol) in CH_2Cl_2 at 0 °C under argon. The reaction mixture was allowed to warm upto room temperature over a period of 30 min. and stirred for further 4 h. It was washed successively with Na_2SO_3, saturated solution of $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. It was evaporated and chromatographed over silica gel. The desired compound **2A** was isolated from the hexane-ethyl acetate elutes (4:1) as white crystals (100 mg, 85%); m.p.134 °C; υ_{max} (KBr)1791cm^{-1}; δ_H 7.97-7.58

Table 3 Intermolecular hydrogen bonds.

Molecule	Donor (D)	Acceptor (A)	Distance (D–A) (Å)	Symmetry relation
1	N1	O5	3.052(3)	–x + 1, –y, –z
2	N1A	O8B	3.041(5)	x, y, z
2	N1B	O7C	3.077(6)	x-1, y, z+1
2	N1C	O7A	3.018(5)	x+1, y, z

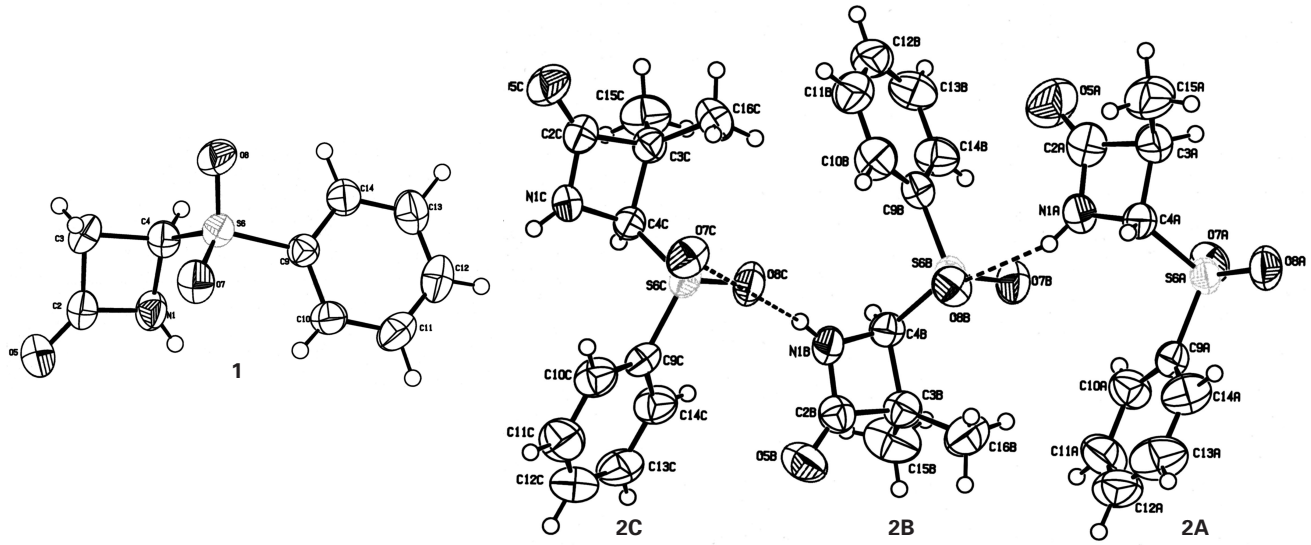

Fig. 1 ORTEP representations of the molecular structures **1** and conglomerate of **2A** and **2B/2C** in solid state. Thermal ellipsoids are shown to the 50% probability level.

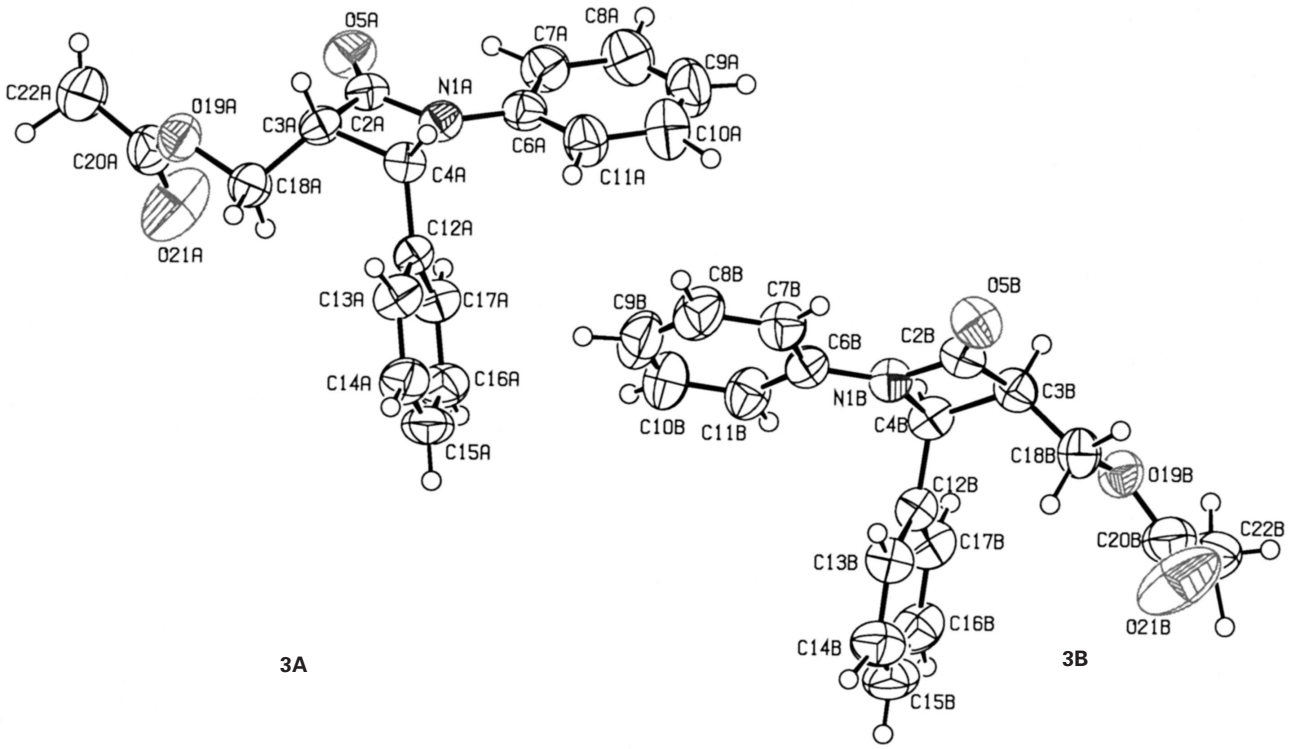

Fig. 2 ORTEP representations of the molecular structures **3A** and **3B** in solid state. Thermal ellipsoids are shown to the 50% probability level.

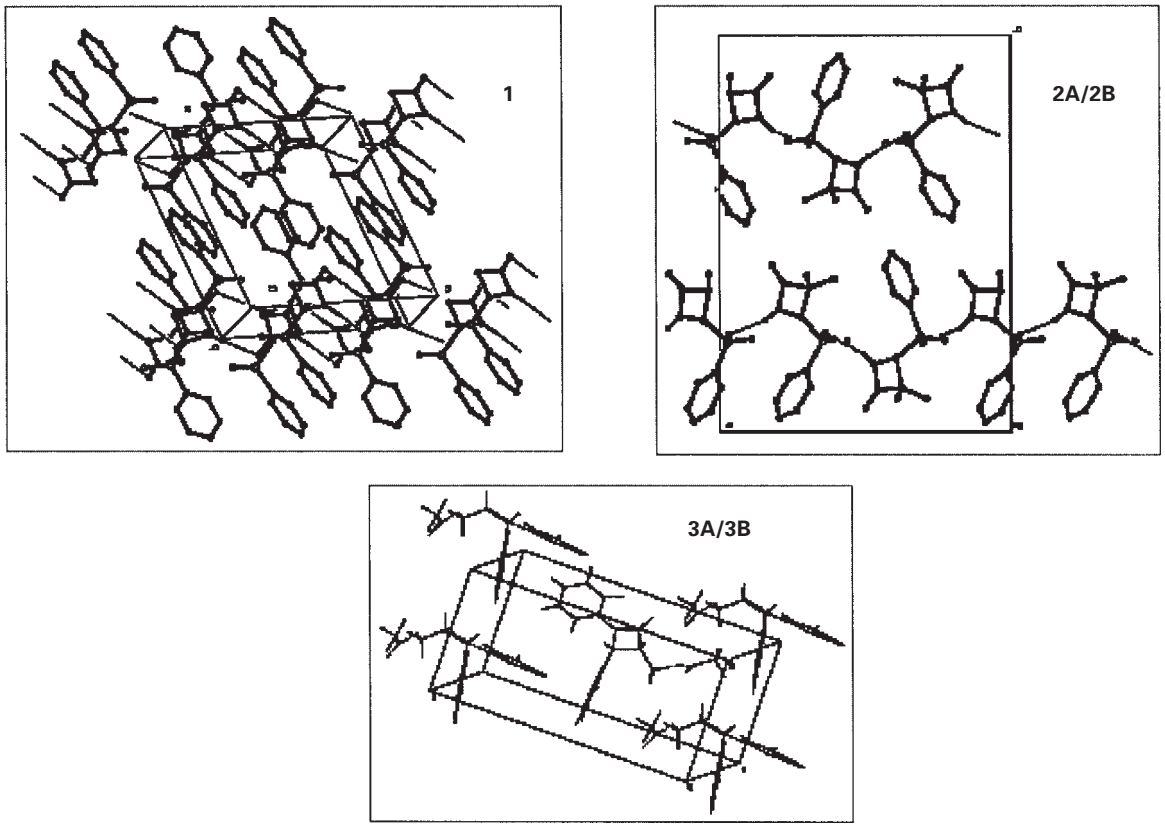

Fig. 3 View of the packing of the molecules.

(5H, m, Ar-H), 6.40 (1H, bs, NH), 4.36 (1H, d, J = 2 Hz, H-4), 3.47 (1H, m, H-3), 1.38 (3H, J = 7.5 Hz, Me); δ_c 169.40, 134.74, 129.66, 129.27, 71.92, 50.42, 12.46; Mass (CI) 226 (MH^+), 170; HRMS: calcd. for $C_{10}H_{12}NO_3S$ 226.0538 found 226.0542.

Synthesis of 3,3-dimethyl-4-thiophenyl-2-azetidinone **(10):** This was prepared as a colourless solid[14] from **7** following the same procedure as reported for the preparation of **8.** However, the yield was low (20%); δ_H 7.75 (5H, m, Ar-H), 6.39 (1H, bs, NH), 4.31 (1H, s, H-4), 1.50 (3H, s, CH_3), 1.50 (3H, s, CH_3); δ_C 167.73, 135.03, 134.74, 129.62, 129.43, 67.38, 44.37, 26.21, 16.77; Mass (CI) 208 (MH^+), 138; HRMS: calcd. for $C_{11}H_{14}NOS$ 208.0797 found 208.0799.

Synthesis of 3,3-dimethyl-4-phenylsulfonyl-2-azetidinone **(2B/2C):** This was prepared as a white solid from **10** by m-CPBA oxidation following the procedure as described for the preparation of **2A** (yield 80%); δ_H 7.75 (5H, m, Ar-H), 6.63 (1H, bs, NH), 4.75 (1H, s, H-4), 1.39 (3H, s, CH_3), 1.37 (3H, s, CH_3); δ_C169.86, 131.80, 126.71, 68.66, 21.87, 18.19; Mass (CI) 240 (MH^+), 170; HRMS: calcd. for $C_{11}H_{14}NO_3S$ 240.0695 found 240.0699.

Compound **3** was prepared according to our published procedure.[15]

Crystal data for **1/2/3:** $C_9H_9NO_3S$ / $C_{32}H_{37}N_3O_9S_3$ / $C_{18}H_{17}NO_3$; Z = 4 / 2 / 2; P21 / a / $P2_1$ / P1; a = 10.047(3) / 5.693(4) / 5.860(2) Å; b = 9.517(2) / 20.134(12) / 8.166(5) Å; c = 10.588(4) / 14.966(10) / 16.715(10) Å; α = 90.00 / 90.00 / 97.332(2) °; β = 110.317(12) / 98.233(3) / 97.876(3) °; λ = 90.00 / 90.00 / 91.229(3) °; M_r = 211.23 / 703.83 / 295.33; V = 949.36(5) / 1697.93(19) / 785.21(7) Å^3; μ = 0.319 / 0.275 / 0.085 mm^{-1}, F (000) = 440 / 740 / 312.

X-ray data were collected at room temperature on a Nonius Kappa CCD single crystal diffractometer with Mo-Kα radiation (λ= 0.71070 Å) and φ-ω scan. The structures were solved by direct methods with SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97.[16] All non-hydrogen atoms were refined anisotropically and the hydrogens were located from a difference Fourier map and geometrically. The final R-value was 0.0382 / 0.0503 / 0.0615 for 1900 / 3024 / 2851 Fo > 4α (Fo), wR2 = 0.1149 / 0.1191 / 0.1635, S = 1.024 / 1.101 / 1.133 using 163 / 440 / 530 parameters and no restraints. The weighting scheme, $w = 1 / [\sigma^2(F_o^2) + (0.0659 * P)^2 + 0.21 * P]$ / $w = 1 / [\sigma^2(F_o^2) + (0.0448 * P)^2 + 0.33 * P]$ / $w = 1 / [\sigma^2(F_o^2) + (0.0889 * P)^2 + 0.03 * P]$ where $P = (\text{Max} (F_o^2, 0) + 2 * F_c^2)/ 3$ gave satisfactory analysis of the variance. Data collection: COLLECT (Nonius, 1997);[17] cell refinement: DENZO-SMN (Otwinowski & Minor, 1997);[18] data reduction: DENZO-SMN; molecular graphics: PLATON (Spek, 1999).[19] The crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 215832 – 215834.

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