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Synthesis and Crystal Structure of Monofluorinated Iminosugar Derivative (*S*)-1-((3*R*,4*R*,5*S*)-1-benzyl-4-fluoro-5-((4-nitrobenzoyl)oxy)piperidin-3-yl)ethane-1,2-diyl *Bis*(4-nitrobenzoate)

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Monofluorinated iminosugar derivative (*S*)-1-((3*R*,4*R*,5*S*)-1-benzyl-4-fluoro-5-((4-nitrobenzoyl)oxy)piperidin-3-yl)ethane-1,2-diyl *bis*(4-nitrobenzoate) (**I**) has been synthesized from triol (**II**) *via* ester formation. Compound (**I**) was fully characterized by IR, MS and ^{1}H (^{13}C, ^{19}F) NMR spectra. In addition, the molecular structure of this compound was established by X-ray crystallography. The crystal of title compound crystallizes in monoclinic, spacegroup P21/n with a = 7.2630(14), b = 20.461(4), c = 11.456(2) Å, α = 90.00, β = 96.877(4), γ = 90°, V = 1690.3(6) Å^3, Z = 2, $C_{35}H_{29}FN_4O_{12}$, Mr = 716.62, Dc = 1.408 g/cm^3, F(000) = 744 and μ(MoKα) = 0.111 mm^{-1}. The final R = 0.0824 and wR = 0.2177 for 8897 observed reflections [I > 2σ(I)] and R = 0.1333 and wR = 0.2497 for all data. From the analysis of the crystal structure, it was observed that the piperidinyl ring adopted the chair form conformation with the equatorial location of the large group. The identified distortions of conjugated systems, orthogonal multipolar interactions and π binding forces were also discussed through the analysis of electrostatic interactions at their origin.

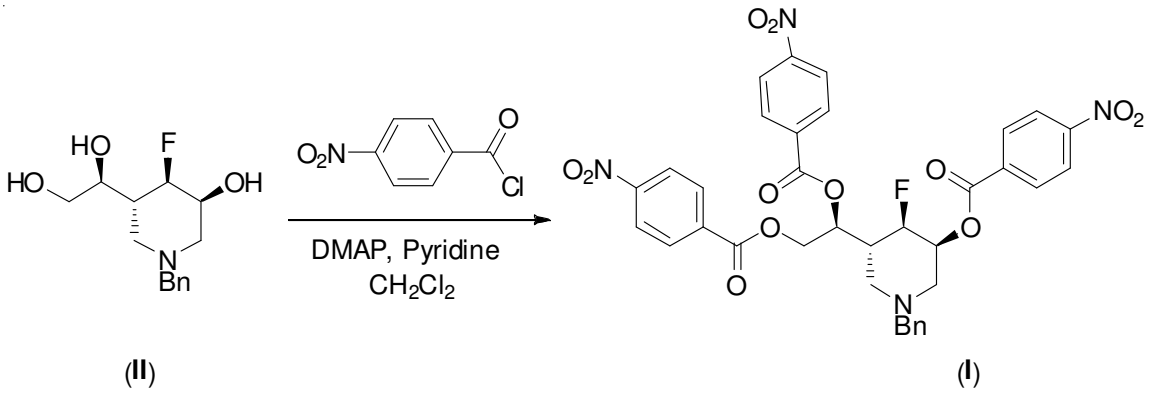
Keywords: Iminosugar, Piperidine, Fluorine, X-ray crystallography, Electrostatic interactions.

INTRODUCTION

Iminosugars have attracted much attention among synthetic chemists and biochemists in recent years because these compounds exhibit significant therapeutic potential for the treatment of metabolic diseases, inhibition of tumor metastasis and control of infections of fungi and viruses[1-5]. Structurally, iminosugars contain a basic nitrogen atom in place of the conventional carbohydrate endocyclic oxygen. Hence, they act as carbohydrate mimics for regulating the activities of a wide array of glycosidases and carbohydrate-recognising proteins[2-5]. Two iminosugar-based drugs have been successfully completed clinical trials: Glyset™ (N-hydroxyethyl-DNJ) in 1996 for treatment of complications associated with type II diabetes and Zavesca™ (N-butyl-1-DNJ) in 2003 as the first oral drug for Gaucher disease, a severe lysosomal storage disorder (Fig. 1). Although the initial potentials have been presented by these iminosugar molecules, the understanding of the relationships between the structures of iminosugars and their bioactivities and relevant pharmalogical mechanisms is still very empirical and unpenetrating[2,3,5]. It is evident that structural information is quite crucial for elucidating the binding affinity of these bioactive iminosugars and target proteins. Considering our continuing interest in the structural modification of iminosugar and structure-activity relationships studies[6-9], herein we report the synthesis and crystal structure of monofluorinated iminosugar derivative (*S*)-1-((3*R*,4*R*,5*S*)-1-benzyl-4-fluoro-5-((4-nitrobenzoyl)oxy)piperidin-3-yl)-ethane-1,2-diyl *bis*(4-nitrobenzoate) (**I**) and take systematic analysis of the crystal data in order for a better understanding of the substituent effect on the conformation of the piperidine ring[10-12] (**Scheme-I**).

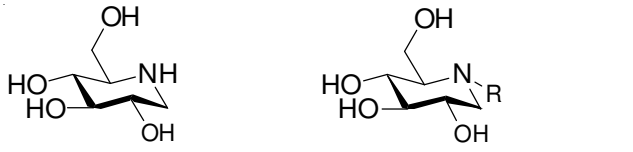
EXPERIMENTAL

All solvents were dried using standard procedures and distillated under N_2. Triol (**II**) was prepared according to our reported procedures[6]. Some other materials were available commercially. Melting points were determined on a SGW X-4 microscopic melting point apparatus and were uncorrected. IR spectra were recorded at room temperature on a Bruker Vector 22 infrared spectrophotometer. ^{1}H NMR was recorded on a Bruker AM-300 spectrometer. ^{19}F NMR was recorded on a Bruker AM-300 spectrometer ($FCCl_3$ as outside standard and low field is positive). ^{13}C NMR was recorded on a Bruker AM-400 spectrometer. Chemical shifts (δ) are reported in parts per million and coupling constants (*J*) are in hertz. Optical rotations were measured using a Perkin Elmer 241 polarimeter.



(**II**) (**I**)

Scheme-I: Synthesis of the title compound (**I**)



1-deoxynojirimycin (DNJ) Glyset (Miglitol) R = hydroxyethyl
Zavesca R = Bu

Fig. 1. Two approved iminosugar-based drugs

Synthetic procedure: Compound (**II**) (22 mg, 0.082 mmol)[6], DMAP (3 mg, 0.0246 mmol) was dissolved in dry pyridine (1 mL). The solution was cooled to 0 °C, then *p*-$NO_2C_6H_4COCl$ (200 mg, 1.08 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise. The mixture was warm to room temperature and stirred for 12 h, then at 50 °C for another 12 h. The mixture was cooled to room temperature, then CH_2Cl_2 (10 mL) was added in. The organic phase was washed with saturated sodium bicarbonate, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, v/v = 4:1) on silica gel to give compound (**I**) as a light yellow solid (37 mg, 80 % yield). m.p. 225-226 åC; $[\alpha]_D^{25}$ = 6.6° (c 2.3, CH_3OH); IR (KBr, ν_{max}, cm^{-1}): 3003, 1716, 1530, 1359, 1268, 1223, 1102, 721; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ/ppm: 8.32-8.02 (m, 12H), 7.26-7.20 (m, 5H), 5.75 (s, 1H), 5.40 (s, 1H), 4.96-4.86 (m, 2H), 4.70-4.64 (m, 1H), 3.64 (d, *J* = 13.5 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 2.96-2.56 (m, 5H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ/ppm: 161.5, 160.9, 148.3, 148.1, 134.7, 132.2, 132.0, 128.3, 128.2, 128.1, 126.1, 125.8, 124.8, 121.1, 120.1, 69.2, 59.5, 47.2, 36.4; ^{19}F NMR (282 MHz, $CDCl_3$)δ/ppm: -200.0 (m, 1F); MS (ESI) *m/z* 717 $(M + H)^+$; HRMS Calcd. for $C_{35}H_{30}N_4O_{12}F$: 717.1844; Found: 717.1839.

Crystal structure determination: Single crystal of the title compound (**I**) suitable for X-ray diffraction analysis was grown by slow evaporation of the CH_2Cl_2 solution at room temperature. The crystal of compound (**I**) with dimensions of 0.285 mm × 0.267 mm × 0.101 mm was mounted on a Rigaku RAXIS-RAPID diffractometer equipped with a graphite-monochromated MoKα radiation (λ = 0.71073 Å) by using an w scan mode at 293(2) K in the range of 1.79° ≤ θ ≤ 25.50°. The crystal belongs to monoclinic system with space group P21/n and crystal parameters of a = 7.2630 (14), b = 20.461 (4), c = 11.456 (2) Å, α = 90, β = 96.877 (4), γ = 90°, V = 1690.3 (6) $Å^3$, Dc = 1.408 g/cm^3. The absorption coefficient μ = 0.111 mm^{-1} and Z = 2. Absorption correction was performed by the CRYSTALCLEAR program[13]. The structure was solved by direct methods using the SHELXS-97 program[14] and refined by full-matrix least-squares techniques on F^2 data using SHELXL-97[15]. The empirical absorption corrections were applied to all intensity data. All the hydrogen atoms were located by using the geometric method, with d(C-H) = 0.95-0.98 Å and Uiso (H) = 1.2 Ueq (C) or 1.5 Ueq (Cmethyl). The final full-matrix least squares refinement gave R = 0.0824, wR = 0.2177 ($w = 1/[\sigma^2(F_o)^2 + (0.1523P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$), S = 0.988, $(\Delta/\sigma)_{max}$ = 0.027, $(\Delta\rho)_{max}$ = 0.739 and $(\Delta\rho)_{min}$ = -0.356 e/$Å^3$.

RESULTS AND DISCUSSION

The single crystal was obtained by slow evaporation of the dichloromethane solution of the title compound (**I**), which was recrystallized as air-stable light yellow crystals. The MS, IR and NMR spectra are in good agreement with the formula proposed by the X-ray crystallography.

Crystallographic and refinement parameters of the title compound (**I**) are listed in Table-1. The selected bond lengths and angles are given in Tables 2 and 3. The structure was solved by direct methods. Anisotropic displacement parameters were applied to all nonhydrogen atoms in full-matrix least-square refinements based on F^2. The hydrogen atoms were set in calculated positions with a common fixed isotropic thermal parameter.

The molecular structure of the title compound (**I**) is shown in Fig. 2. The crystal packing diagram of the title compound (**I**) is shown in Fig. 3.

From the capped sticks view of compound (**I**) (Fig. 4), it can be found that the piperidine ring takes the chair form conformation in which the C(1)-F(1), C(5)-C(6) and N(1)-C(15) have equatorial locations and C(2)-O(1) has axial orientation. Obviously, the preferred conformation of the piperidinyl ring is mainly determined by the group on C(5) because the large group tends to adopt equatorial orientation for avoiding steric strain. The distortions of several originally plane conjugated systems are also observed in this single crystal (Table-4). For example, the dihedral angles of O(2)-C(8)-C(9)-C(10), O(4)-N(2)-C(12)-C(13) and O(10)-C(29)-C(30)-C(31) are up to -169.4(10), 11.3(13) and -157.8(15) deg, respectively. In addition, it is interesting to find out that $O(6)^{sp2}$ and $O(9)^{sp3}$

TABLE-1
CRYSTAL DATA AND STRUCTURAL REFINEMENT FOR COMPOUND (**I**)

Items	Values
Empirical formula	$C_{35}H_{29}N_4O_{12}F$
Formula weight	716.62
Crystal system	Monoclinic
Unit cell dimensions	
a(Å)	7.2630(14)
b(Å)	20.461(4)
c(Å)	11.456(2)
Unit cell angles (°)	
α	90.00
β	96.877(4)
γ	90.00
Volume (Å^3)	1690.3(6)
Z	2
Temperature (K)	293(2)
Space group	P 21/n
Wavelength (Å)	0.71073
Calculated density (g cm^{-3})	1.408
Absorption coefficient ? (mm^{-1})	0.111
F(000)	744
Crystal size (mm^3)	0.285 × 0.267 × 0.101
θ range for data collection (°)	1.79 – 25.50
Limiting indices	-8<=h<=8, -24<=k<=24, -13<=l<=12
Reflection collected	8897
Independent reflection	3239 (R_{int} = 0.0562)
Completeness to θ_{max} (%)	99.8
Data/restraints/parameters	3239/3/454
Goodness-of-fit on F^2	0.960
Final R indices [I > 2σ (I)]	R_1 = 0.0824, wR_2 = 0.2177
R indices (all data)	R_1 = 0.1333, wR_2 = 0.2497
Largest diff. peak and hole (e A^{-3})	0.739 and -0.356

TABLE-2
SELECTED BOND LENGTHS (Å) FOR COMPOUND (**I**)

Bond	Bond length/Å
C(1)-F(1)	1.368(11)
C(1)-H(1)	0.9800
C(1)-C(2)	1.497(12)
C(2)-C(3)	1.510(14)
C(3)-N(1)	1.446(11)
N(1)-C(4)	1.446(10)
N(1)-C(15)	1.494(12)
C(4)-C(5)	1.562(13)
C(5)-C(1)	1.529(11)
N(2)-O(3)	1.165(10)
N(2)-O(4)	1.218(9)
N(3)-O(7)	1.191(11)
N(3)-O(8)	1.162(10)
N(4)-O(11)	1.06(2)
N(4)-O(12)	1.13(2)
O(2)-C(8)	1.193(10)
O(6)-C(22)	1.227(9)
O(10)-C(29)	1.218(14)
O(9)-C(7)	1.457(12)
O(9)-C(29)	1.214(13)
O(1)-C(8)	1.320(10)
O(5)-C(22)	1.334(9)

TABLE-3
SELECTED BOND ANGLES (°) FOR COMPOUND (**I**)

Bond	Bond angles/deg
F(1)-C(1)-H(1)	108.0
C(2)-C(1)-C(5)	112.4(7)
C(1)-C(2)-C(3)	111.4(7)
N(1)-C(3)-C(2)	111.5(8)
C(4)-N(1)-C(3)	110.4(7)
N(1)-C(4)-C(5)	110.6(6)
C(1)-C(5)-C(4)	106.9(7)
C(4)-N(1)-C(15)	111.0(6)
C(3)-N(1)-C(15)	109.3(7)
O(1)-C(2)-H(2)	110.5
C(6)-C(5)-H(5)	108.0
O(3)-N(2)-O(4)	124.3(9)
O(8)-N(3)-O(7)	121.4(10)
O(11)-N(4)-O(12)	133(2)

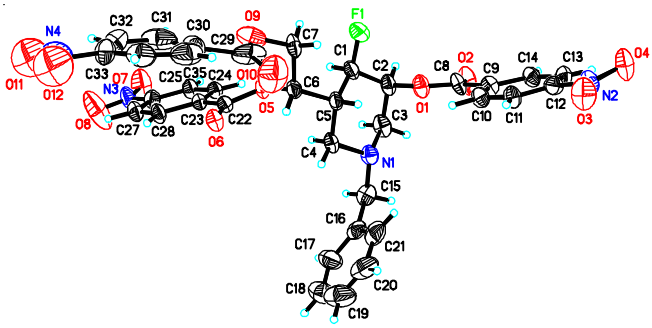


Fig. 2. Molecular structure of compound (**I**) with 30 % probability thermal ellipsoids

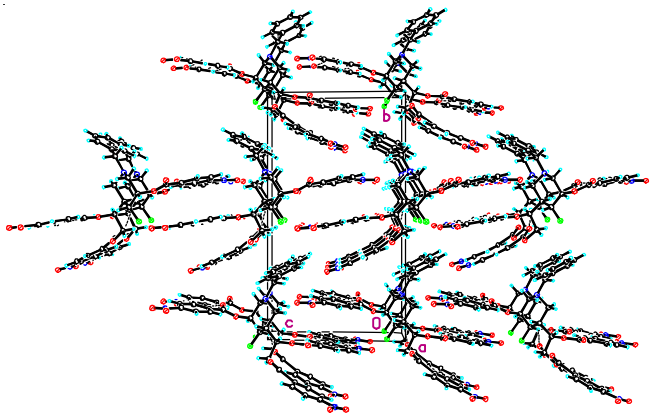


Fig. 3. Crystal packing diagram of compound (**I**)

contact in a distance of 3.022 Å which is with the sum of van der Walls radii of two oxygen atoms (3.040 Å) (Fig. 4, purple dash line).

With the preliminary view of molecular architecture established, we then turn our attention to analyze the intermolecular interactions in this piperidinyl crystal. It is noteworthy that orthogonal multipolar interactions as attractivew intermolecular forces play important roles in small-molecule crystal packing, protein-ligand assemblies or even enzymatic mechanisms[16]. In the crystal structure of compound (**I**), the orthogonal multipolar interaction C(1)$^{sp^3}$-F(1)···H(27)-C(27)$^{sp^2}$ contact in the length of 2.659 Å (Fig. 5). Given the fact that C-F bonds are poor hydrogen-bond acceptors[17], this orthogonal

TABLE-4
SELECTED DIHEDRAL ANGLES (°) OF DISTORTED CONJUGATIVE SYSTEMS IN COMPOUND (**I**)

Bond	Torsion angles/deg
O(2)-C(8)-C(9)-C(10)	-168.4(10)
O(2)-C(8)-C(9)-C(14)	10.7(14)
O(1)-C(8)-C(9)-C(10)	-168.4(10)
O(1)-C(8)-C(9)-C(14)	-170.0(8)
O(3)-N(2)-C(12)-C(11)	6.9(14)
O(3)-N(2)-C(12)-C(13)	-173.9(9)
O(4)-N(2)-C(12)-C(11)	-167.8(9)
O(4)-N(2)-C(12)-C(13)	11.3(13)
O(6)-C(22)-C(23)-C(24)	-169.5(8)
O(6)-C(22)-C(23)-C(28)	7.3(13)
O(5)-C(22)-C(23)-C(24)	9.3(11)
O(5)-C(22)-C(23)-C(28)	-173.9(8)
O(7)-N(3)-C(26)-C(25)	-7.4(16)
O(7)-N(3)-C(26)-C(27)	173.9(12)
O(8)-N(3)-C(26)-C(25)	173.5(14)
O(8)-N(3)-C(26)-C(27)	-5.2(17)
O(9)-C(29)-C(30)-C(31)	21.6(18)
O(9)-C(29)-C(30)-C(35)	-160.9(11)
O(10)-C(29)-C(30)-C(31)	-157.8(15)
O(10)-C(29)-C(30)-C(35)	19.7(19)
C(29)-C(30)-C(31)-C(32)	169.1(13)
C(29)-C(30)-C(35)-C(34)	-172.0(11)
C(31)-C(30)-C(35)-C(34)	5.7(18)
C(32)-C(33)-C(34)-C(35)	-7(2)
C(35)-C(30)-C(31)-C(32)	-8.4(19)
N(4)-C(33)-C(34)-C(35)	172.6(13)
O(11)-N(4)-C(33)-C(32)	3(3)
O(11)-N(4)-C(33)-C(34)	-177(2)
O(12)-N(4)-C(33)-C(32)	-177.2(19)
O(12)-N(4)-C(33)-C(34)	3(3)

multipolar interaction can be interpreted as electrostatic attraction between negative charge on F(1) and positive charge on acidic H(27) atom which was induced by the nearby electron-withdrawing $C(26)^{sp^2}$-NO_2 unit. The orthogonal multipolar interaction also exists in $C(1)^{sp^3}$-H(1)···O(10)=$C(29)^{sp^2}$ with the length of 2.484 Å in which the acidity of H(1) is greatly

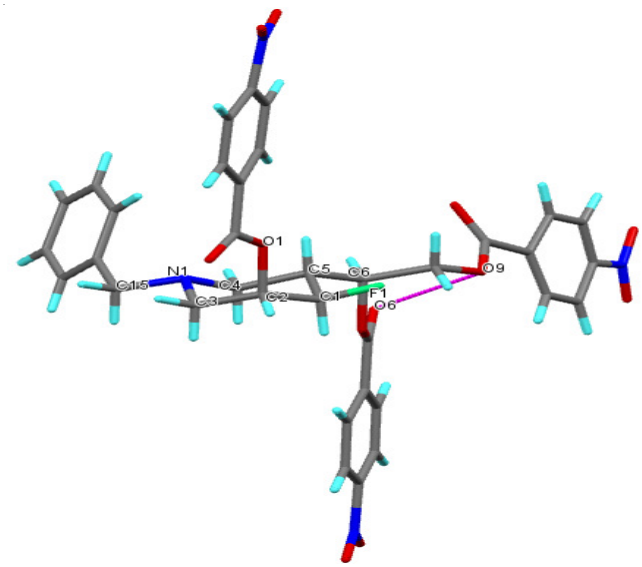


Fig. 4. Chair form conformation of compound (**I**) (capped sticks view)

enhanced by the neighbouring electronegative F(1) (Fig. 5). In addition, the similar orthogonal multipolar interactions $N(2)^{sp^2}$-O(3)···H(14)-$C(14)^{sp^2}$, $N(2)^{sp^2}$-O(4)···H(4A)-$C(4)^{sp^3}$, $N(3)^{sp^2}$-O(7)···H(28)-$C(28)^{sp^2}$, C(22)=O(6)···H(25)-$C(25)^{sp^2}$ and C(8)=O(2)···H(11)-$C(11)^{sp^2}$ are found to be contacted in the distances of 2.560 Å, 2.687 Å, 2.583 Å, 2.552 Å and 2.527 Å, respectively (Fig. 5, purple dash line). Moreover, the π binding forces are identified among the electron-deficient benzene rings which bear electron-withdrawing nitro and ester groups[18]. The π-π interaction $C(35)^{sp^2}$···$C(24)^{sp^2}$, $C(34)^{sp^2}$···$C(24)^{sp^2}$ and the polar-π interaction $N(2)^{sp^2}$-O(3)···$C(24)^{sp^2}$ contact in the lengths of 3.321 Å, 3.399 Å and 3.177 Å, respectively (Fig. 5, see yellow and orange dash line). Apparently, the above orthogonal multipolar interactions and π binding forces in their sum make great contribution to the crystal packing and topological structure.

Conclusion

In summary, we described herein the synthesis, characterization and X-ray crystal structure of monofluorinated

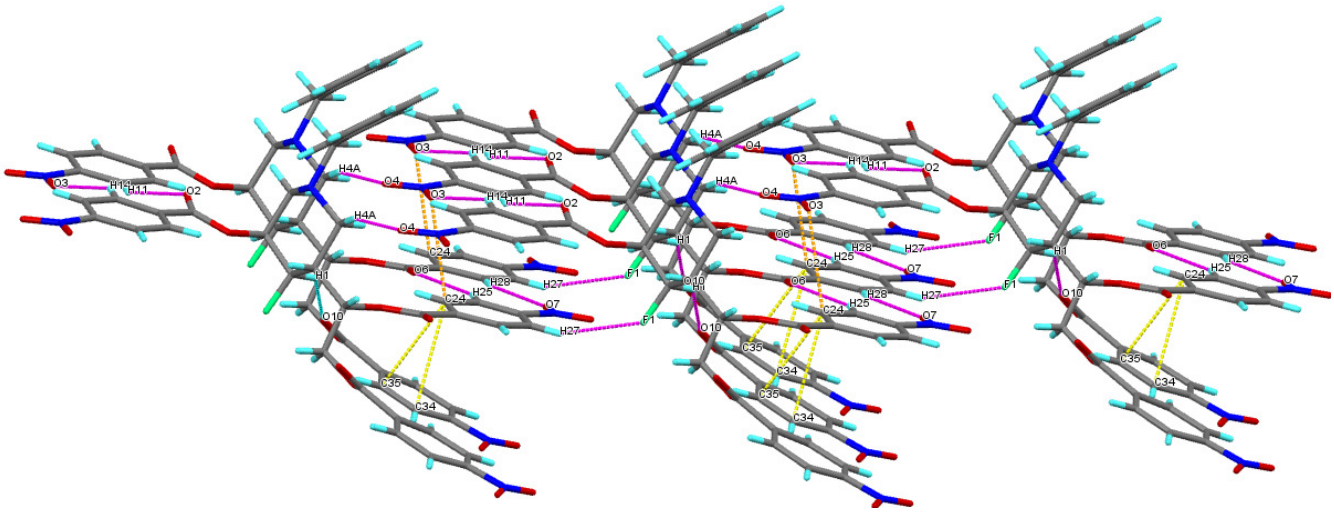


Fig. 5. Orthogonal multipolar interactions and π binding forces in crystal (**I**) (capped sticks view)

iminosugar derivative (*S*)-1-((3*R*,4*R*,5*S*)-1-benzyl-4-fluoro-5-((4-nitrobenzoyl)oxy)piperidin-3-yl)ethane-1,2-diyl *bis*(4-nitrobenzoate) (**I**). The X-ray crystal structure shows that the piperidinyl ring takes the chair form conformation with the large group equatorially oriented. The distortions of conjugated systems, orthogonal multipolar interactions and π binding forces in this single crystal are also manifested which are originated from electrostatic interactions. Further investigations about the application of orthogonal multipolar interactions and π binding forces on crystal engineering and target protein-ligand association are underway and the results will be reported in due course.

Supplementary data: CCDC-815092 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; or E-mail: deposit@ccdc.cam.ac.uk).

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