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Hantzsch 1,4-dihydropyridine esters and analogs: candidates for generating reproducible one-dimensional packing motifs

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Examination of the symmetric Hantzsch 1,4-dihydropyridine ester derivatives of the prototypical nifedipine molecule indicates the tendency of this class of molecule to form a common packing motif. Crystal structure analysis of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic diesters and analogs reveals that they form extended chains, characterized as the $C(6)$ packing motif, *via* intermolecular (amine) N—H···O═C (C3,C5 carbonyl) hydrogen bonds. In addition, all the prepared derivatives also satisfy the basic structural requirements for their high binding efficiency to the receptor. The reproducible $C(6)$ packing motif observed among these compounds has a use in the design of solid-state materials.

1. Introduction

Hantzsch 1,4-dihydropyridine (1,4-DHP) esters are the most studied class of organic calcium channel modulators (Bossert *et al.*, 1981; Triggle, 2003). Nifedipine, 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, a widely used popular drug for high blood pressure and angina pectoris (Wishart *et al.*, 2006; Drug Bank ID #DB01115), represents the prototypical molecule in this class, which specifically blocks the activity of L-type voltage-gated calcium channels. The structure–activity relationship studies on these compounds have revealed the basic structural requirements for their high-binding efficiency to the ion channel (Triggle, 2003). Following initial observations, we were motivated to pursue studies on such compounds primarily because of their efficacy in the design of solids. Identifying molecules or chemical groups that generate reproducible packing motifs is one of the challenging areas in engineering solid-state materials (Desiraju & Steiner, 1999; Desiraju, 2007). Anions with the combined strength of electrostatic and hydrogen-bonding interactions are one such system (Braga & Grepioni, 2007; Shylaja *et al.*, 2008). These motifs then could be employed as building modules for the design of novel solid materials with the desired structure and properties. Towards this purpose, we have prepared and examined some of the Hantzsch esters and analogs. The investigated compounds were: diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I), diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (II), 1,1′-[2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-diyl]diethanone (III) and diethyl 4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (IV).

2. Experimental

Melting points were determined in open capillary tubes with a Guna melting point apparatus (100 watts) and are uncor-

rected. Structures were confirmed by IR, ^{1}H NMR, mass spectrometry and elemental analysis. The IR spectra were obtained by using an AVATAR330 (Thermonicolet, USA) spectrometer (KBr disks). ^{1}H NMR spectra were obtained in chloroform-d_1 using a Bruker AMX-400 MHz spectrometer (Bruker Analytik, GmbH, Germany) with 5 mm PABBO BB-1H tubes. Chemical shifts are reported as p.p.m. relative to the tetramethylsilane (TMS). LC–MS (liquid chromatography–mass spectrometry) were obtained using an Agilent 1200 series LC and Micromass zQ 4000 spectrometer. The results of the elemental analyses, carried out using a Thermo Finnigan FLASH EA 1112 CHNS analyzer, are within ±0.4% of the calculated values with the exception of the *N* value in (IV). Compounds (I)–(IV) were synthesized in high yields using the classical Hantzsch condensation procedure (Fig. 1; Hantzsch, 1882; Li, 2006).

2.1. Diethyl-4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I)

4-Methoxybenzaldehyde (10 mmol), ethylacetoacetate (20 mmol) and ammonium acetate (10 mmol) were taken in the molar ratio 1:2:1 along with ethanol as a solvent in a conical flask and heated on a steam-bath for approximately 90 min until the color of the solution changed to reddish-orange; the flask was then kept under ice-cold conditions for solid formation. The solid was extracted using diethyl ether and acetone. The solid was collected separately and liquid kept for solidification. The purity of the crude product was checked through TLC (thin-layer chromatography). (I) was crystallized using chloroform and benzene mixture in a 1:1 ratio (yield, 81%); m.p. 428 K.

IR (KBr): ν (cm^{-1}), 3342.29 (NH), 3094 (Ar—H), 1689 (C═O); ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 6H, J = 8 Hz, C_3-$CO_2CH_2CH_3$, C_5-$CO_2CH_2CH_3$), 2.34 (s, 6H, C_2-CH_3, C_6-CH_3), 3.72 (s, 3H, —OCH_3), 4.09 (m, 4H, J = 4 Hz, C_3-CO_2CH_2, C_5-CO_2CH_2), 4.94 (s, 1H, C4-H), 5.58 (s, 1H, NH), 6.76 (d, 2H, J = 8 Hz, *ortho*), 7.21 (d, 2H, J = 8 Hz, *meta*); MS: *m*/*z* (%), 360 (M^+), base peak 323 (loss of —OCH_2CH_3); anal.: calc. for $C_{20}H_{25}NO_5$: C 66.82, H 7.02, N 3.90; found: C 66.44, H 6.90, N 4.11.

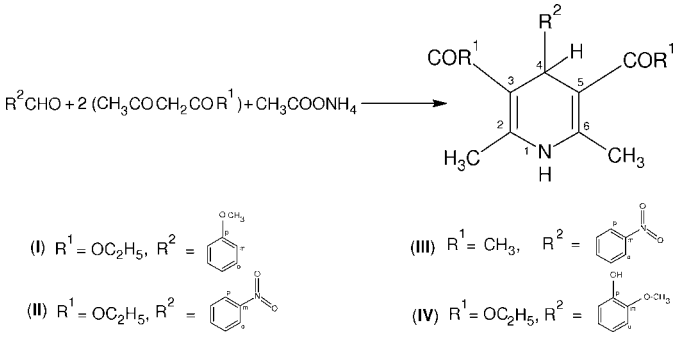

Figure 1
Synthetic scheme.

2.2. Diethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (II)

3-Nitrobenzaldehyde (10 mmol), ethylacetoacetate (20 mmol) and ammonium acetate (10 mmol) were taken in a 1:2:1 molar ratio along with ethanol as a solvent in a conical flask and heated on a steam bath until the color of the solution changed to reddish-orange. The flask was kept under ice-cold conditions to obtain the solid product, which was extracted using diethyl ether and then excess solvent was distilled off. The purity of the crude product was checked through TLC. (II) was recrystallized with a mixture of solvents using acetone and ether solution in a 1:1 ratio (yield, 88.2%); m.p. 438 K.

IR (KBr): ν (cm^{-1}), 3357 (NH), 3092.5 (Ar—H), 1692 (C═O); ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 6H, J = 8 Hz, C_3-$CO_2CH_2CH_3$, C_5-$CO_2CH_2CH_3$), 2.33 (s, 6H, C_2-CH_3, C_6-CH_3), 4.09 (m, 4H, J = 4 Hz, C_3-CO_2CH_2, C_5-CO_2CH_2), 5.90 (s, C_4-H), 5.73 (s, 1H, NH), 7.38 (d,1H, J = 8 Hz, *ortho*), 7.65 (t, 1H, J = 8 Hz, *meta*), 8.02 (d, 1H, J = 4 Hz, *para*), 8.14 (s, 1H, *ortho*); MS: *m*/*z* (%) 374 (M^+), base peak 329 (loss of —OCH_2CH_3); anal.: calc. for $C_{19}H_{22}N_2O_6$: C 60.94, H 5.93, N 7.49; found: C 60.87, H 5.92, N 7.31.

2.3. 1,1′-[2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-diyl]diethanone (III)

3-Nitrobenzaldehyde (10 mmol), acetylacetone (20 mmol) and ammonium acetate (10 mmol) were taken in a 1:2:1 molar ratio along with ethanol as a solvent in a conical flask and heated on a steam bath until the color of the solution changed to reddish-orange. This was kept under ice-cold conditions to obtain the solid product, which was extracted using diethyl ether and then excess solvent was distilled off. The purity of the crude product was checked through TLC. (III) was recrystallized from the mixture of solvents using acetone and ether solution in a 1:1 ratio (yield 86.6%); m.p. 453 K.

IR (KBr): υ (cm^{-1}), 3342.29 (NH), 3094 (Ar—H), 1689 (C═O), 1638.21 (C═C); ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 6H, C_2-CH_3, C_6-CH_3), 2.36 (s, 6H, C_3-$COCH_3$, C_5-$COCH_3$), 5.29 (s, C_4-H), 6.05 (s, 1H, NH), 7.40–8.04 (aromatic protons); anal.: calc. for $C_{17}H_{18}N_2O_4$: C 64.94, H 5.78, N 8.92; found: C 64.93, H 5.95, N 8.63.

2.4. Diethyl 4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (IV)

4-Hydroxy-3-methoxybenzaldehyde (10 mmol), ethylacetoacetate (20 mmol) and ammonium acetate (10 mmol) in the molar ratio 1:2:1 were placed along with ethanol as a solvent in a conical flask and heated on a steam-bath until the color of the solution changed to reddish-orange. This was kept under ice-cold conditions for solid formation, and extracted using diethyl ether and acetone. Purity was checked through TLC. The compound was crystallized using acetone and ether (1:1). Final yield, 89%, m.p 432 K.

IR (KBr): ν (cm^{-1}) 3443 (OH), 3332 (NH), 3094 (Ar—H), 1689 (C═O); anal.: calc. for $C_{20}H_{25}NO_6$: C 63.97, H 6.72, N 3.73; found: C 63.42, H 6.59, N 5.14.

Table 1
Experimental details.

	(I)	(II)	(III)	(IV)
Crystal data				
Chemical formula	$C_{20}H_{25}NO_5$	$C_{19}H_{22}N_2O_6$	$C_{17}H_{18}N_2O_4$	$C_{20}H_{25}NO_6$
M_r	359.41	374.39	314.33	375.41
Crystal system, space group	Monoclinic, $P2_1/n$	Orthorhombic, $Pna2_1$	Monoclinic, $P2_1/n$	Orthorhombic, $P2_12_12_1$
Temperature (K)	294	294	294	294
a, b, c (Å)	9.7834 (7), 7.4749 (5), 26.6788 (18)	14.3479 (10), 15.2867 (11), 8.6765 (6)	8.8420 (7), 16.0785 (14), 11.2188 (10)	7.5530 (9), 13.5745 (16), 19.154 (2)
β (°)	98.1710 (10)	90	104.606 (2)	90
V (Å^3)	1931.2 (2)	1903.0 (2)	1543.4 (2)	1963.9 (4)
Z	4	4	4	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.09	0.10	0.10	0.09
Crystal form, size	Block, 0.19 × 0.15 × 0.11	Plate, 0.24 × 0.21 × 0.13	Needle, 0.25 × 0.18 × 0.11	Plate, 0.26 × 0.20 × 0.14
Data collection				
Diffractometer	Bruker SMART CCD area-detector	Bruker SMART CCD area-detector	Bruker SMART CCD area-detector	Bruker SMART CCD area-detector
Data-collection method	φ and ω scans	φ and ω scans	φ and ω scans	φ and ω scans
Absorption correction	Multi-scan†	Multi-scan†	Multi-scan†	Multi-scan†
T_{min}, T_{max}	0.949, 0.994	0.890, 0.985	0.908, 0.986	0.938, 0.989
No. of measured, independent and observed reflections	14 550, 3778, 2680	14 270, 1999, 1592	11 818, 3025, 2030	7380, 3775, 2056
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.035	0.046	0.050	0.044
θ_{max} (°)	26.0	26.0	26.0	26.0
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.053, 0.149, 1.05	0.045, 0.107, 1.11	0.065, 0.126, 1.11	0.068, 0.222, 1.03
No. of reflections	3778	1999	3025	3775
No. of parameters	245	248	212	249
H-atom treatment	Constrained‡	Constrained‡	Constrained‡	Constrained‡
$(\Delta/\sigma)_{max}$	0.024	0.002	< 0.0001	< 0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.41, −0.29	0.15, −0.11	0.17, −0.17	0.48, −0.44

Computer programs used: *SMART* (Bruker, 2007*a*), *SAINT-Plus* (Bruker, 2007*b*), *SHELXTL* (Bruker, 2007*c*), *SADABS* (Bruker, 2007*d*), *SHELXL*97 (Sheldrick, 2008), *ORTEP*III (Farrugia, 1997), *PLATON* (Spek, 2003). † Based on symmetry-related measurements. ‡ Constrained to parent site.

Suitable single crystals of (I)–(IV) were mounted on a Bruker SMART CCD area-detector diffractometer. Intensities were measured with Mo $K\alpha$ radiation (λ = 0.71073 Å) at room temperature (294 K) and processed with *SAINT-Plus* (Bruker, 2007*b*). Crystals were stable during the data collection. Absorption corrections were applied using *SADABS* (Bruker, 2007*d*). Structures were solved by the application of direct phase-determination methods using *SHELXTL* (Bruker, 2007*c*) and refined by full-matrix least-squares carried out on F^2 using *SHELXL*97 (Sheldrick, 2008). H atoms were placed in the geometrically expected positions and refined with the riding options. The methyl H atoms were allowed to rotate such that the sums of their electron density were maximized. The distances with H atoms are: aromatic C—H = 0.93 Å, methyl C—H = 0.96 Å, methylene C—H = 0.97 Å, methine C—H = 0.98 Å, amine N—H = 0.86 Å, and hydroxyl O—H = 0.82 Å with U_{iso} = 1.2U_{eq} (parent), or 1.5U_{eq}(C,O) for methyl and hydroxyl groups. All structure calculations were performed with the *WinGX* suite of programs (Version, 1.70.01; Farrugia, 1999). Crystal data are summarized in Table 1. The terminal methyl C atom (C11) of the C3-ester in (I) is statistically disordered over two sites. The contributions of the major and minor components were 0.638 (5) and 0.362 (5), respectively. (I) was previously reported (refcode: JAVTIK; space group $P2_1/n$; R = 0.0973, wR = 0.0973; Srinivasan *et al.*, 2005). The present structure is a better refined version. The new refinement included a better treatment of the disorder of the C3-ester. In (I), (II) and (IV) a distance restraint was applied for the terminal ethyl group (C10—C11) of the C3-ester. Short contacts that were associated with the methyl groups were observed in the crystal structures, but as the C—H of the methyl group is of low acidity, these interactions are hardly of any significance.

Cambridge Structural Database (CSD; Allen, 2002) searches were carried out using *ConQuest* (Version 1.9). As the CSD search was quite time-consuming, it was carried out in stages. Firstly, a sub-database of 113 structures of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic diesters (henceforth

Table 2
Hydrogen-bonding geometry (Å, °).

Molecule	*D*	H	*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
(I)	N1	H1	O3^{i}	0.86	2.13	2.983 (2)	173
(II)	N1	H1	O3^{ii}	0.86	2.32	2.982 (4)	134
(III)	N1	H1	O1^{iii}	0.86	2.11	2.933 (3)	160
	C18	H18	O2^{iii}	0.93	2.56	3.305 (3)	137
(IV)	N1	H1	O3^{iv}	0.86	2.22	3.073 (5)	174

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

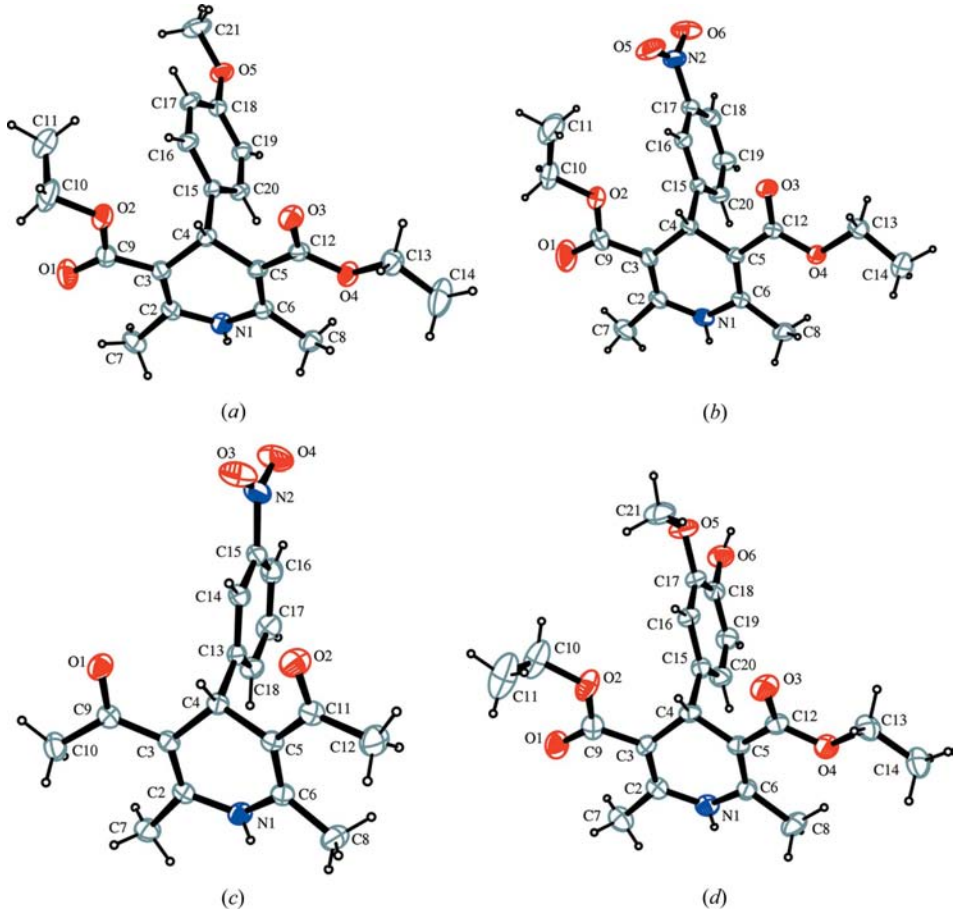

Figure 2
*ORTEP*3 plots (Farrugia, 1997) of (*a*) (I), (*b*) (II), (*c*) (III) and (*d*) (IV), in comparable orientations, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and the H atoms as small spheres of arbitrary radii. Only the major disordered component is shown in (I).

referred as *Hantzsch 4D esters*) was created. The remaining searches were performed on this sub-database, followed by manual inspections.

3. Results and discussion

3.1. Structural requirements of high binding efficiency

Compounds (I)–(V) satisfy the basic requirements for high biological activity. In view of the existing structural studies invariably reporting these aspects, initially it would be worthwhile to examine their structure–function correlations. Fig. 2 shows views of (I)–(IV). Selected torsion angles are reported in Table 3 which is in the supplementary material.[1] The stereochemistry of these compounds agrees with the basic structural requirements for their high activity, as indicated by structure–activity relationship studies (Goldmann & Stoltefuss, 1991; Metcalf & Holt, 2000; Triggle, 2003). The flattened boat conformation of the 1,4-DHP ring is one of the prerequisites. In (I)–(IV) the 1,4-DHP rings are characterized by a shallow or flattened-boat conformation. Atoms N1 and C4 are marginally displaced from the base of the boat plane, defined by (C2/C3/C5/C6) atoms. Their values of displacement (Å) are: N1 0.165 (2), C4 0.357 (2) (I); N1 0.111 (3), C4 0.217 (4) (II); N1 0.141 (2), C4 0.326 (2) (III); N1 0.139 (4), C4 0.325 (4) (IV). The deviation for the N1 atom from the base of the boat is generally smaller, occurring in the range 0.0–0.19 Å, while that of C4 is larger and spread around 0.30 Å (Linden *et al.*, 2004). The sum of the absolute values of the ring internal torsion angles as a quantitative measure of the flatness of the six-membered ring has been also suggested, which is 0° for an unpuckered ring and 240° for an ideal boat conformation (Fossheim *et al.*, 1988). These values in (I)–(IV) are 105.7, 65.8, 96.6 and 96.6°, respectively, indicating a significant amount of flattening from the ideal boat conformation. The sum of the angles is 72° for nifedipine (BICCIZ; Triggle *et al.*, 1980).

An orthogonal relationship between the pyridine ring and the aryl ring of the C4-substituent is yet another factor for high activity. The C4-nitrophenyl ring in (II) and (III), methoxyphenyl ring in (I) and methoxyphenol ring in (IV) are orthogonal to the 1,4-DHP ring, with the dihedral angle between the base of the pyridine ring (C2/C3/C5/C6) and the

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: EB5001). Services for accessing these data are described at the back of the journal.

benzene ring [C15–C20 in (I), (II) and (IV); C13–C18 in (III)] being 87.87 (7) (I), 88.8 (1) (II), 87.97 (8) (III) and 88.3 (2)° (IV), respectively. Another better quantitative description of the orthogonality relationship is an improper torsion angle between (N1, C4) and the two adjacent aromatic atoms lying over the pyridine ring. The angle N1···C4—C15—C20 in (I), (II) and (IV) is −23.1, −11.8 and −5.6°, respectively, while N1···C4—C13—C18 in (III) is 10.4°. This angle has been observed to vary in the 0 ± 30° range (Linden *et al.*, 2005). The *m*-nitro in the nitrophenyl, and *m*-methoxy group in the methoxyphenol ring are in prow positions, directing away from the 1,4-DHP ring and having a *syn periplanar* orientation with respect to the C4—H bond. There is no preferred orientation for *meta* or *para* sustituents in the C4-aryl ring for high affinity, except that the *ortho* substitution, such as the nitro group in nifedipine, should be in the prow position due to sterically unfavorable interactions.

The ester groups at the C3 and C5 positions are almost coplanar with the 1,4-DHP ring due to the electron delocalization of the conjugated system, C2═C3—C9═O1 and C6═C5—C12═O3 [C6═C5—C11═O2 in (III)]. The conformation of the carbonyl group with respect to the adjacent endocyclic double bond is *sp* (*syn periplanar*) and *ap* (*anti periplanar*) in (I), (II) and (IV), giving rise to the chiral character. (I) is a racemic mixture in the crystal. The corresponding conformation in (III) is (*ap*, *ap*) (see Table 3 in the

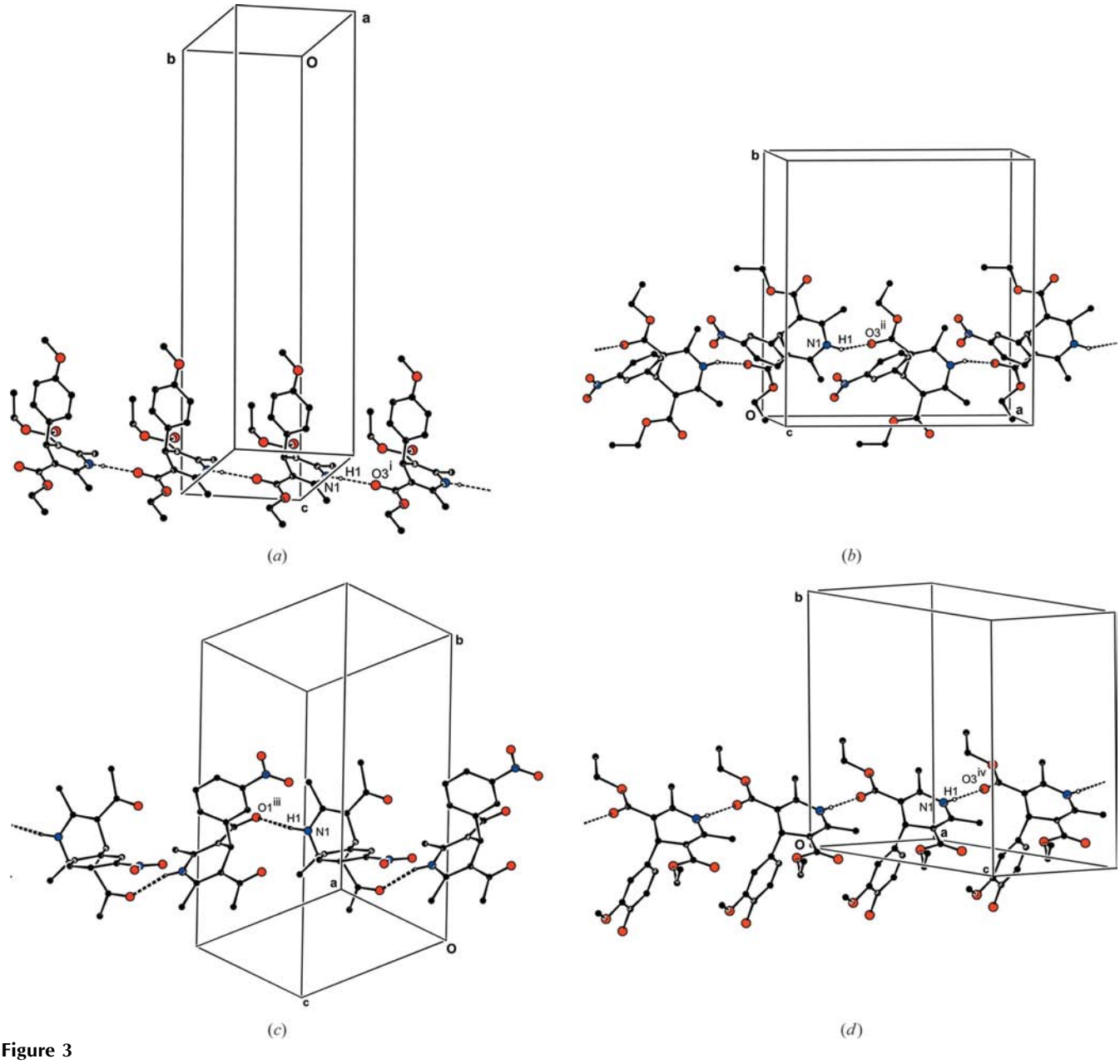

Figure 3
An extended chain forming an N—H···O hydrogen-bonded $C(6)$ packing motif in the crystals of (I)–(IV) along (*a*) the *b* axis (I), (*b*) the *a* axis (II), (*c*) the [101] direction (III) (accompanying C—H···O interaction is not shown) and (*d*) the *a* axis (IV). Only relevant H atoms are displayed. Symmetry codes are given in Table 2.

supplementary material). The switch from the ethyl ester in (I), (II) and (IV) to the corresponding methyl group in (III) has no major influence in the conformation of the molecule, except that both C=O groups are in the *ap* orientation and the molecule is achiral. It is pertinent to note that rotation of the C4-aryl substituent about the C4—C15 bond [C4—C13 in (III)] has no significant influence on the carbonyl orientation or the degree of orthogonality between aromatic and pyridine rings. The (*ap*, *ap*) conformation is rare, although there is no preferred conformation of the carbonyl groups in the C3/C5 substituent for high binding affinity. In a CSD search (Version 5.28; Allen, 2002), out of 113 *Hantzsch 4D esters* (in total 123 cases as a result of $Z' > 1$ for a few), 84 and 39 belong to the symmetric and asymmetric diesters, respectively. Among symmetric esters, the population of carbonyl groups in (*ap*, *ap*), (*ap*, *sp*) and (*sp*, *sp*) conformations was observed to be 6, 56 and 22, respectively, while among asymmetric esters, the corresponding populations were found to be 2, 22 and 14, respectively (Table 4 of the supplementary material).

3.2. Packing motif: extended *C*(6) chain

A noteworthy feature of the packing is molecular association into a one-dimensional chain of molecules. Intermolecular (1,4-DHP) NH···O=C (C3,C5 substituent) hydrogen bonds between the amine NH and the carbonyl O atom in the *ap* orientation interlink the molecules (Figs. 3*a–d*). The extended chain is described as a *C*(6) motif using graph-set notation (Bernstein *et al.*, 1995). The hydrogen-bonding details are: N1—H1···O3^{i} forms an extended chain along the *b* axis in (I), N1—H1···O3^{ii} and N1—H1···O3^{iv} along the *a* axis in (II) and (IV), respectively. The parameters and symmetry codes for intermolecular interactions are given in Table 2. The corresponding chain that runs parallel to the [101] direction in (III) is formed by N1—H1···O1^{iii} hydrogen bonds and is further reinforced by the C18—H18···O2^{iii} interaction. To examine the potency of *Hantzsch 4D esters* to generate the *C*(6) packing motif, the compounds archived in the Cambridge Structural Database were searched (Table 4 of the supplementary material). Among symmetric diesters, 37 and 9 form the intermolecularly (1,4-DHP) NH···O=C (C3,C5-substituent) linked extended *C*(6) motif, with the carbonyl group in *ap* and *sp* conformations, respectively. Likewise, 12 and 2 asymmetric compounds form this motif in *ap* and *sp* orientations, respectively. An overwhelming population of C=O bonds in the *ap* conformation are involved in hydrogen bonding (Metcalf & Holt, 2000). With the exception of BELHEF and ECEGEY, all of the esters form straight infinite chains. Although the steric bulk of the 1,4-DHP ring having substituents at the 2, 3, 4, 5 and 6 positions disfavors the formation of (1,4-DHP) NH···O=C (C3,C5-substituent) type hydrogen bonds with the carbonyl group in the *sp* orientation, it can still be formed with an adjacent symmetry-related molecule, generating a zigzag type of extended *C*(6) motif. The remaining *Hantzsch 4D esters* which fail to form a one-dimensional *C*(6) chain are those which possess either polar groups at the C4 substituent or include a polar solvent. A great majority of them form either a sheet structure with the solvent or (1,4-DHP) NH···(N,O) (C4-substituent) type of hydrogen bond, generating an extended chain of the *C*(*n*) type, where *n* is the number of intermediate atoms in between successive interactions.

4. Conclusions

The symmetrically substituted *Hantzsch 4D esters* demonstrate their potential to generate a common packing motif with a wide tolerance for multiple substitutions at the 3,4,5 positions. Additionally, the reported compounds satisfy all the structural requirements for high binding efficiency as potential β-blockers.

It is interesting to note that the tendency of molecules to maximize hydrogen-bonding interactions is consistently absent among this class of molecule. When there is an imbalance of hydrogen-bonding donors and acceptors in a molecule, such as among 1,4-DHP esters, it is fulfilled by factors like the utilization of the next weak interactions in the hierarchy, solvent inclusion or multi-centered hydrogen bonding. None of these factors seem to play any significant role in the packing, possibly due to the specific stereochemistry of the molecules. It turns out that apart from the pharmaceutical reasons, these compounds are also a good candidate in the repertoire of molecules to afford the desired supramolecular architecture.

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