

Synthesis, crystal structure and antibacterial properties of 6-methyl-2-oxo-4-(quinolin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate

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Abstract

The synthesis and investigation of a new biologically active derivative of dihydropyrimidine are reported. The structure of the synthesized compound was investigated by X-ray single crystal diffraction method. In order to understand the molecular interactions, the Hirshfeld surface and contacts enrichment analyses were performed. The crystal packing is mainly stabilized by strong N-H...O hydrogen bonds and aromatic cycle stacking. Among the different types of oxygen atoms, the most electronegative had the highest propensity to form H-bonds. Biological activity of the synthesized compound was studied against *E.coli*, *P. aeruginosa* and *S. aureus* bacteria.

Key words: dihydropyrimidine, Biginelli reaction, Hirshfeld surface analysis, crystal structure, bifurcated hydrogen bond, antibacterial activity.

1. Introduction

One-pot multicomponent reactions are a highly powerful synthetic strategy and versatile tool for the construction of various classes of compounds with a wide spectrum of application area. Interest in multicomponent reactions is increasing due to the fact that they provide a synthetic chemist with intrinsic significant advantages over conventional linear-type synthesis mostly including simple operation, simple starting materials, high product complexity and large product diversity [1-3]. Among such type of reactions that found application in the synthesis of heterocycles is a three-component one-pot Biginelli reaction. A combination of aldehyde, urea derivative and methylene active compound leads to the obtaining of dihydropyrimidine - a class of organic compounds which are widely used in medicine due to their broad spectrum of biological activities [4]. The reason of their popularity in medicine is caused by the multicomponent nature

of this reaction allowing introducing various pharmacophoric groups in the structure of dihydropyrimidines [5-8]. Various investigations using molecular manipulations allow determining that this class of compounds demonstrate such activities as antiviral, antifungal [6, 7], anti-leishmanial, antiproliferative [9], antitumor [10-15], antibacterial [16-19], anti-inflammatory [20-22], anti-hypertensive [23-27], anti-HIV [28], antiepileptic [29], antidiabetic, anti-malarial [30], mPGES-1 inhibitors [31], antitubercular [32], miscellaneous [33-35], potassium [36-38] and calcium channels [39] and α_1 adrenergic antagonists [40]. On this basis, different drugs were synthesized and found their application in medicine, such as batzelladine A and B [28], (S)-monastrol [10-15], (S)-enastron [10-15], mon-97 [10-15], (R)-fluorastrol [11], terazosin [34]. But the superiority of dihydropyrimidines goes beyond this. They are used as a favorable core for developing heterocyclic compounds with novel optical properties [34]. It is also found that dihydropyrimidines have also been exploited as a design element in the development of functional materials such as dyes [40], polymers [41], adhesive [42] etc. Such broad application of dihydropyrimidines has prompted scientists to develop their chemistry by expanding the list of building blocks in the Biginelli reaction. Analysis of modified compounds as well as structure-activity correlations allow deeper understanding of the stereochemical-conformational requirements for activity, which significantly depend on the presence of various interactions, i.e. hydrogen bonds in the structure [43, 44].

On the other hand, quinoline is mainly used in the production of various speciality chemicals, which provide a wide variety of effects, on which many other industry sectors rely. In addition to this, quinoline has several anti-malarial derivatives, including quinine, chloroquine, amodiaquine and primaquine [45].

Concerning biological activity of quinoline and dihydropyrimidine core, a new dihydropyrimidine was synthesized by Biginelli reaction in microwave condition in the presence of cerium chloride on the basis of quinoline-2-carbaldehyde. As crystals of this compound were obtained, its structure was investigated by X-ray single crystal diffraction. In addition, the Hirshfeld surface and contacts enrichments analysis was done to quantify the molecular interactions and understand their importance in the crystal packing. Due to the fact that dihydropyrimidines demonstrate a wide spectrum of biological activities, their antibacterial activity was analyzed against *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus* (*S. aureus*) and promising results were obtained.

2. Materials and methods

2.1 General Information

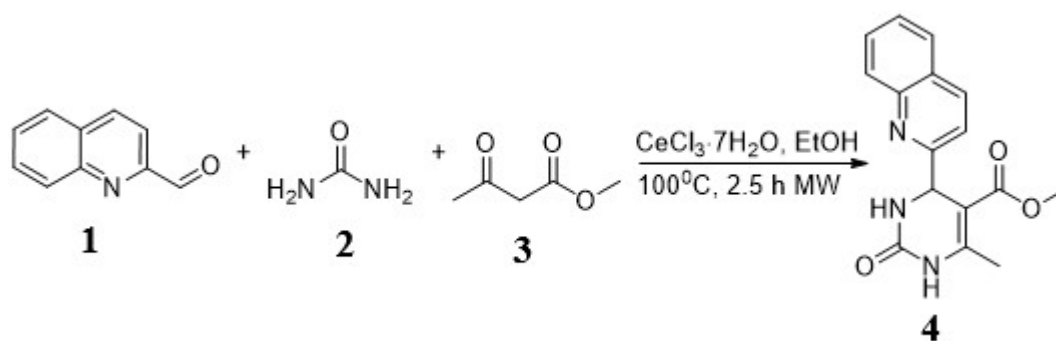
All the solvents and reagents were purchased from commercial suppliers and were of analytical grade and used without further purification. The control of the reactions progress and the determination of the synthesized compounds purity were done by thin layer chromatography (TLC) on Merck silica gel plates (60 F254 aluminium sheets) which were visualized under UV

light. Melting points were recorded in open capillary tubes on a Buchi B-540 apparatus and were uncorrected. Elemental analysis was performed on the Carlo Erba 1108 analyzer.

2.2 Experimental synthesis procedure

Synthesis of 6-methyl-2-oxo-4-(quinolin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate by Biginelli reaction (Scheme 1). 0.5 mmol of quinoline-2-carbaldehyde (**1**), 0.75 mmol (45 mg) of urea and 0.03 mmol (0.0118 mg) of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ were added to a microwave vial with a magnetic stirrer and dissolved in 1 ml of ethanol. Subsequently, 0.46 mmol (50 μl) of methyl acetoacetate were added to a vial, which was sealed and irradiated at 100°C in a microwave reactor for 2.5 h at a maximum power of 200W (CEM Discover System).

Purification of compound (**4**) was performed by the Biotage Isolera One Flash Chromatography System (cyclohexane-ethylacetate-methanol). After purification and removing of the solvent, a yellow precipitate was formed. Single crystals of compound (**4**) were obtained by crystallization in methanol. Yield 61.1 %. M.p. $271\text{--}272^\circ\text{C}$. ^1H NMR spectrum: (DMSO- d_6 , δ , ppm), 2.47 s (3H, CH_3), 3.39 s (3H, OCH_3), 6.1 s (1H, CH), 7.62–7.68 t (2H, 2C_{ArH} , $J=9$ Hz), 7.71–7.75 m (2H, 2C_{ArH}), 7.83 s (1H, NH), 7.96–7.98 d (1H, C_{ArH} , $J=6$ Hz), 8.38–8.41 t (1H, C_{ArH} , $J=6$ Hz), 9.34 s (1H, NH). ^{13}C NMR spectrum: (DMSO- d_6 , δ , ppm), 17.97 (CH_3), 50.09 (CH), 50.77 (OCH_3), 98.08 (C), 122.7 (C_{ArH}), 123.45 (C_{ArH}), 124.35 (C_{ArH}), 126.62 (C_{ArH}), 126.92 (C_{ArH}), 129.25 (C), 129.63 (C_{Ar}), 130.49 (C_{Ar}), 130.95 (C_{Ar}), 149.8 (C_{Ar}), 151.85 (COO), 165.8 (CO). HRMS (ESI-MS): 298.11 [$\text{M}^+ + \text{H}^+$], 320.11 [$\text{M}^+ + \text{Na}^+$]. Elemental analysis calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$, %: C, 64.64; H, 5.09; N, 14.13. Found, %: C, 64.75; H, 5.02; N, 14.09.



Scheme 1. Synthesis of targeted dihydropyrimidine.

2.3 NMR experiments

The NMR experiments were performed on a BRUKER FT NMR spectrometer AVANCE 300 (Bruker, Karlsruhe, Germany) (300 MHz for ^1H and 75 MHz for ^{13}C) with a BVT 3200 variable temperature unit in 5 mm sample tubes using Bruker Standard software (TopSpin 3.1). Chemical shifts were given in ppm (δ) and were referenced to internal tetramethylsilane (TMS). Multiplicities are declared as follow: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Coupling constants J are given in Hz. The experimental parameters for ^1H are as follows: digital resolution=0.23 Hz, SWH=7530 Hz, TD=32 K, SI=16 K, 90° pulse-length=10 ms, $PL1=3$ dB, $ns=1$, $ds=0$, $d1=1$ s and for ^{13}C as follows: digital resolution=0.27 Hz, SWH=17985 Hz,

$TD=64$ K, $SI=32$ K, 90° pulse-length=9 ms, $PL1=1.5$ dB, $ns=300$, $ds=2$, $dl=3$ s. The NMR-grade DMSO- d_6 (99.7%, containing 0.3% H_2O) was used for the solutions of synthesized compound.

2.4 Mass experiments

High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) in positive-ion or negative-ion detection mode.

2.5 X-Ray analysis

X-Ray analyses were performed on Bruker SMART APEX II Single Crystal X-ray Diffractometer equipped with graphite-monochromated Mo- $K\alpha$ radiation ($\lambda = 0.71073$ Å) at 298(2) K, respectively. The crystal structure was solved by direct methods and refined on F^2 by full matrix least-squares using Bruker's SHELXTL-97 [46]. The details of the crystallographic data for synthesized compound are summarized in Table 1. Crystallographic data for the structural analysis have been deposited to the Cambridge Crystallographic Data Center under number CCDC 1988673. H atoms treatment was $U_{iso}(H) = 1.2 U_{eq}$ of the bound atom except for the methyl group for which or $U_{iso}(H) = 1.5 U_{eq}$. H atoms bound to carbon were constrained at their standard geometry. H atoms bound to nitrogen were refined freely. Mercury 3.9 was used to obtain the crystalline structure images.

2.6 Biological assay

The antibacterial activity of synthesized dihydropyrimidine against *E.coli*, *P.aeruginosa*, *S.aureus* was assessed by determining minimal inhibitory concentrations (MIC). The MIC, which is the lowest concentration of compound that prevents the growth of bacterial cells after incubation, was determined by the twofold micro-dilution method as described in [48]. The compounds were prepared according to CLSI guidelines and diluted in U-bottom 96 well microtiter plates which contained Muller Hinton Broth (MHB). The freshly prepared bacterial strains at about 10^5 CFU (colony forming unit) in MHB medium were added to each well of the microplate and incubated at $37^\circ C$ for 24 hours. At the end of the experiment, the concentration of the tested compounds ranged from 256 to 2 $\mu g/mL$. The growth of the bacterial cells was determined by resazurin method. The solution of resazurin sodium salt (0.01%) was freshly prepared in sterile distilled water. After incubation, 30 μL of this solution was added in each microplate well and incubated again at the same condition for about 4 h. MIC was represented as the lowest concentration of the compounds which inhibited the color change from blue to pink since pink color indicated the growth of bacteria [48]. MIC of the studied compound was compared with MICs of pristine antibiotics (cefotaxime and ceftriaxone).

In addition to this, the efficiency of the synthesized dihydropyrimidine against the above-mentioned bacteria was also tested by disc-diffusion method as described by Mayrhofer [49]. In details, the surface of the nutrient medium (meat-peptone agar, Potato Dextrose Agar) was stratified with 1 mL of the diurnal suspension of the test culture (10^5 CFU/mL), which was used during 15 min after preparation. Previously prepared discs with certain concentrations were

stratified on the surface of the nutrient medium by the sterile tweezers. Dishes were incubated at 37°C during 24 h. DMSO (40%V/V) was used as a solvent. Record of the results was carried out, compared with control dishes without compound and with the known drugs cefotaxime and ceftriaxone. The biological assays were carried out in triplicate. Standard deviations data were also calculated.

3. Results and discussion

3.1 Chemical synthesis.

It is known that a lot of protocols were developed for performing Biginelli reaction, leading to the synthesis of dihydropyrimidines with high yields and simple work-up procedure. Using catalyst types such as Cu(OTf)₂, InCl₃, InBr₃, CF₃COOH, Yb(OTf)₃, YbCl₃, HCl, acetic acid, CeCl₃ and others [1-6, 44], it was not possible to perform a Biginelli reaction on the basis of quinoline-2-carbaldehyde (**1**), urea (**2**) and methylacetoacetate (**3**). Only improving the procedure [47] by performing the reaction in microwave conditions allowed us to obtain a targeted dihydropyrimidine (Scheme 1). The structure of synthesized novel dihydropyrimidine was determined by ¹H, ¹³C NMR, mass spectroscopy and elemental analysis. As it can be seen from ¹H NMR spectrum, the signals from methyl and methoxy groups are observed at 2.47 and 3.39 ppm correspondingly, whereas CH group position is at 6.1 ppm. Their positions on ¹³C NMR spectra are at 17.97, 50.09 and 50.77 ppm. The signals from amine groups of dihydropyrimidine core are observed at 7.83 and 9.34 ppm respectively (Supplementary material).

3.2 Structure description.

It was also possible to obtain single crystals of the title compound (Fig. 1). Crystallographic data and details of refinement for the synthesized compound are given in Table 1. The synthesized dihydropyrimidine crystallizes in the monoclinic space group P2₁/c with Z=4 molecules in the unit cell (Table 1). The molecular structure of the 6-methyl-2-oxo-4-(quinolin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (DHPM) from single crystal X-ray data is shown in Fig. 1. The asymmetric unit of the title compound contains two C₁₆H₁₅N₃O₃ moieties (**Fig. 1**). The two molecules have a very different conformation as the dihedral angles on the bond linking the two rings are N3-C5-C4-N1=71.1° and N6-C21-C20-N4 = 114.4°. The tetrahydropyrimidine ring in both molecules is significantly twisted with twist angles C1-N1-C4-C3 equal to 36.5° and C17-N5-C18-C19 equal to -7.4° with the presence of the C2=C3 and C18=C19 double bonds [50, 51]. The tetrahydropyrimidine ring is in twist-boat conformation; the C4 and N2 atoms form the flagpole atoms in the first molecule and the C20 and N5 atoms in the second molecule (**Fig. 1**) [50, 51]. The main bond lengths and bond angles are depicted in Table 2 (Supplementary material). The intermolecular hydrogen bonds observed in the crystal structure are listed in Table 3. The dihedral angles between the planes of the quinoline rings and the six membered rings in both molecules of the title compound are 80.84 and 87.35° respectively, underlining non-orthogonal arrangement of these rings (**Fig. 2 a & b**).

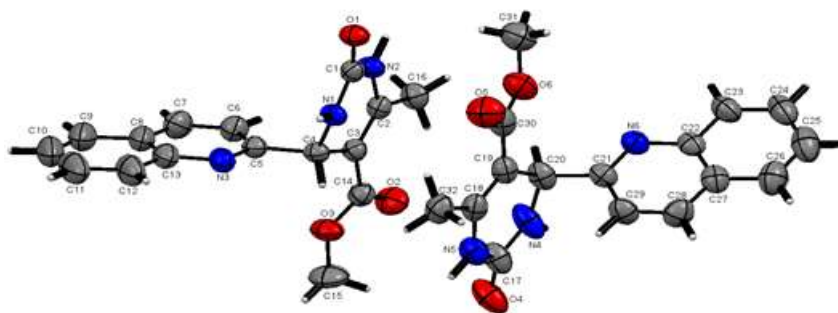


Figure 1. View of the two independent molecules of the asymmetric unit in the crystal structure. Thermal ellipsoids are shown 40% probability.

Molecules of the DHPM are interconnected via N-H...O=C and C-H...O=C hydrogen bonds giving rise to a sheet-like structure, forming polar sheets involving polar functional groups while the quinoline moieties takes the role of hydrophobic spacer [48, 49]. These polar sheets are extended parallel to the *c*-axis (**Fig. 3, Table 3**) [51].

Furthermore, there are two characteristic distances d_1 and d_2 , which are defined between the polar sheets in the like-sheet structure. The d_1 distance represents the special separation between the successive polar sheets including the quinoline moieties (hydrophobic moieties) and d_2 represents the spatial separation between two consecutive polar sheets. The corresponding distances d_1 and d_2 are 10.261 Å and 4.622 Å, respectively (**Fig. 3**) [50].

The crystal packing of the title compound, C₁₆H₁₅N₃O₃ is consolidated by several intermolecular N-H...O strong hydrogen bond, involving namely the donors H1N, H2N, H4N and H5N and the four potential acceptors O1, O1, O2, O4 and O5 (**Fig. 4a, Table 3**). The crystal packing is also stabilized by an intermolecular C-H...O=C hydrogen bond connecting the quinoline moieties to the carbonyl oxygen O5 (C9-H9...O5^v ($v=x+1, y, z$)) and by intramolecular interaction (C16-H16A...O2) involving the methyl hydrogen of C16 with the carbonyl oxygen O2 to form a S(6) motif (**Fig. 4a**) [52, 53]. Some of hydrogen bonds are bifurcated on the acceptors (O2, O1, **Fig. 4a**). A R₂²(8) graph-set motif connecting two adjacent molecules is observed within the sheets (**Fig. 4a**). Previous studies have been performed on the packing motifs of the tetrahydropyrimidine (DHPM) [54, 55]. No aromatic stacking interactions are observed between neighbouring six membered rings and quinoline moieties.

The molecular packing is stabilized by weak C-H... π intermolecular interactions between the quinoline moieties (**Fig. 4b**). The distances between the hydrogen atoms and the different centroids of the quinoline rings vary between 3.262 Å and 3.788 Å.

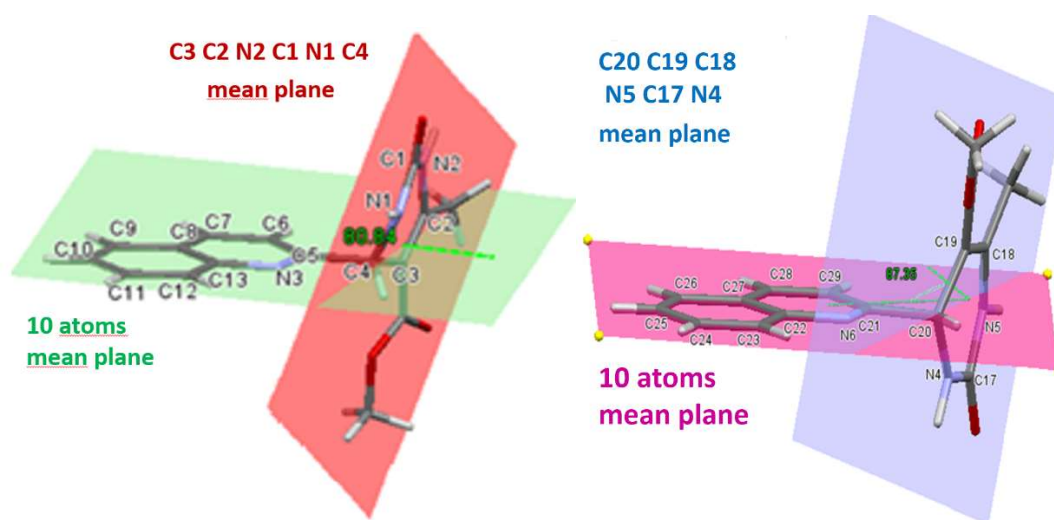
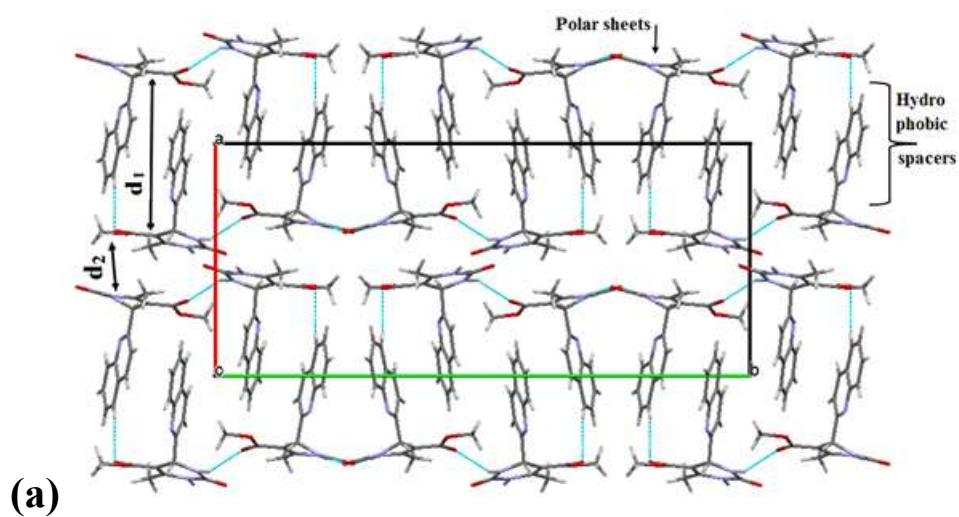


Figure 2. Dihedral angle between the planes of quinoline rings and tetrahydropyrimidine moieties **(a)** in the first molecule **(b)** in the second molecule of the asymmetric unit.



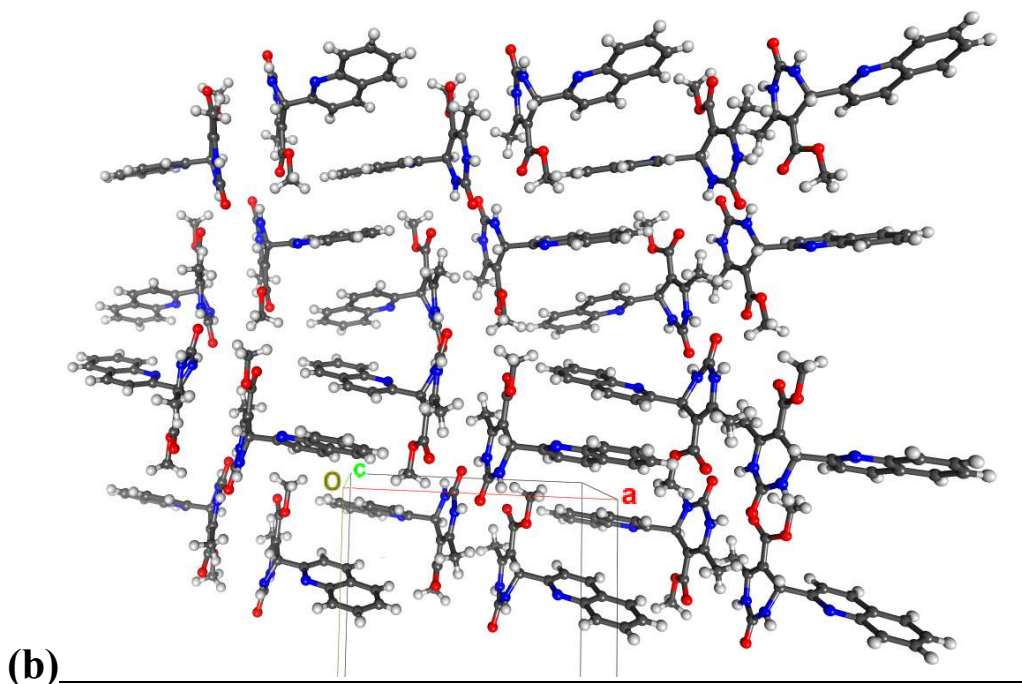
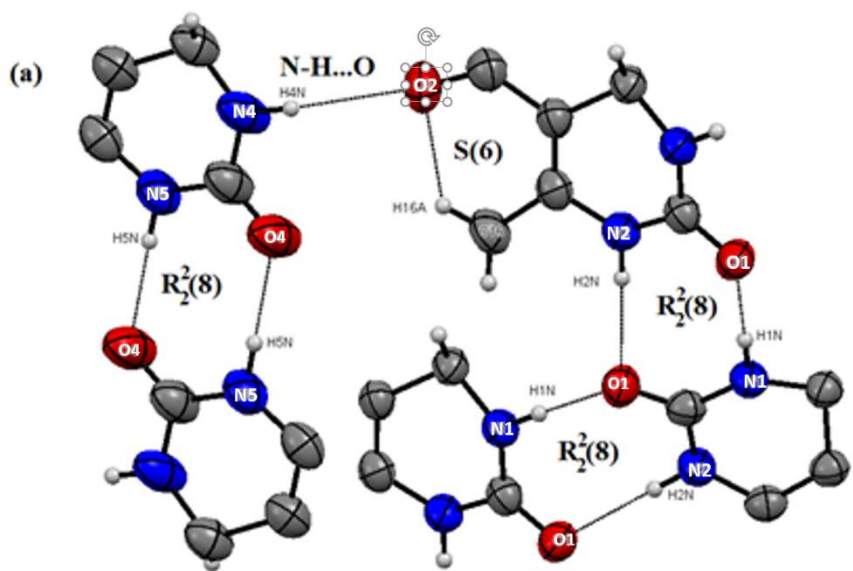


Figure 3. (a) Crystallographic autostereogram view of a sheet-like structure along the **c** axis in $(C_{16}H_{15}N_3O_3)_2$. Dotted lines indicate N-H...O and C-H...O hydrogen bonds. d_1 represents the spatial separation between the polar sheets intercalating the hydrophobic quinoline moieties while d_2 represents the spatial separation between two consecutive polar sheets. (b) crystallographic autostereogram of the crystal packing along the c axis.



No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	20297, 5063 2938
R_{int}	0.053

Structure Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.058, 0.155, 1.02
No. of reflections	5063
No. of parameters	413
No. of restraints	4
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ ($\text{e } \text{\AA}^{-3}$)	0.19, -0.17

Table 3. Geometric details (distances in Å, angles in °) of hydrogen bonds (D-donor; A-acceptor; H-hydrogen) of the synthesized DHPM.

Interactions	$d(\text{D}—\text{H})$	$d(\text{H}\cdots\text{A})$	$d(\text{D}\cdots\text{A})$	$\angle\text{D}—\text{H}\cdots\text{A}$	Symmetry code
N1—H1N \cdots O1 ⁱ	0.89 (2)	2.05 (2)	2.9333	173 (2)	$x, -y+1/2, z-1/2$
N2—H2N \cdots O1 ⁱⁱ	0.90 (2)	2.10 (2)	3.0011	179 (2)	$x, -y+1/2, z+1/2$
N4—H4N \cdots O2 ⁱⁱⁱ	0.90 (2)	2.38 (2)	3.1778	148 (2)	$-x+1, -y, -z+2$
N5—H5N \cdots O4 ^{iv}	0.90 (2)	1.96 (2)	2.8624	178 (2)	$-x+1, -y, -z+1$
C9—H9 \cdots O5 ^v	0.93	2.56	3.410 (5)	152	$x+1, y, z$
C16—H16A \cdots O2	0.96	2.20	2.914 (4)	130	x, y, z

3.3 Hirshfeld surface analysis.

Analysis of intermolecular interactions using the Hirshfeld surface represents a major tool to gain insights into understanding the crystal packing. Crystal Explorer software [56] enables to compute distances of atoms external, d_e , and internal, d_i , to the surface. The intermolecular distance information on the surface can be condensed into a two-dimensional histogram of d_e and d_i , which is a unique fingerprint for molecules in a crystal structure (Fig. 5). The spikes in the fingerprint plot at the shortest distance can be attributed to the $\text{O}\cdots\text{H}$ hydrogen bonds. The N5-H5N \cdots O4=C17 contact is the shortest hydrogen bond with $d(\text{O}\cdots\text{H})=1.96$ Å. The N \cdots H contacts appear at much longer distances in the fingerprint plot, as there is only one N \cdots H hydrogen bond (N4-H4N \cdots N4) at $d_{\text{HN}}=2.680$ Å. The H \cdots H contacts appear in the middle of the scattered points in the two-dimensional fingerprint map (Fig. 5b) with shortest distance in the packing at ca 2.2 Å. C \cdots C contact arise at a minimal distance of ca. 3.4 Å and involve both the aromatic double ring and the non-flat 6-membered ring.

The different chemical contact types and their enrichment in the crystal packing were also analyzed with MoProViewer software [57]. The enrichment ratio E_{XY} for a pair of elements (X,Y) is defined as the ratio between the proportion of actual contacts C_{XY} in the crystal and the theoretical proportion R_{XY} of equi-distributed random contacts [58]. An enrichment ratio larger

than unity reveals that a contact type is over-represented in the crystal, while pairs which tend to avoid contacts with each other should yield an E value lower than unity.

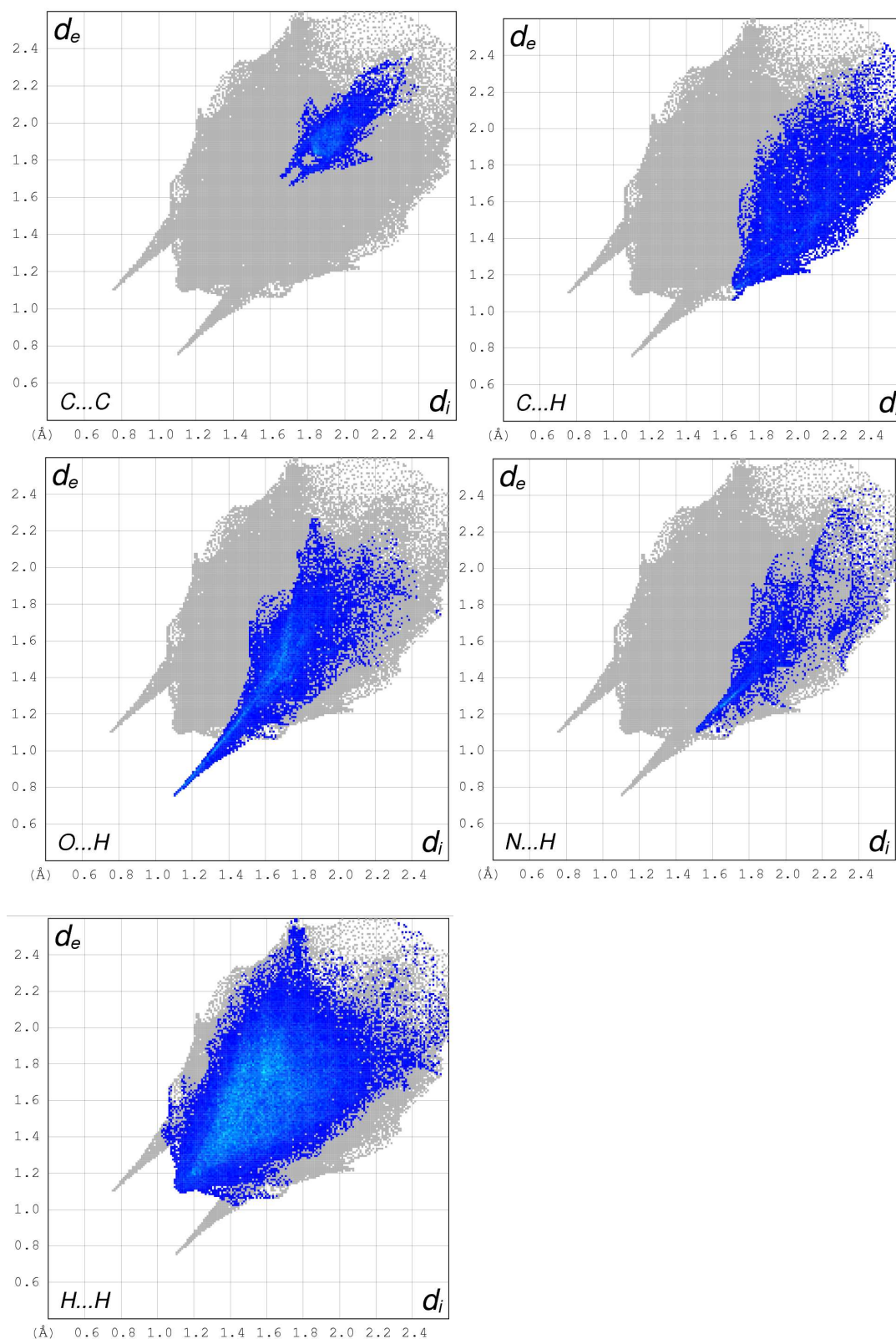


Figure 5. 2D fingerprint (d_i, d_e) plots of the Hirshfeld surface around the two independent molecules. The areas of main intermolecular contact types are shown and the reciprocal contacts can be deduced from the plots as they are symmetrical.

The nature of the intermolecular contacts and their enrichments in the crystal structure is shown in Table 4 and proportions C_{xy} of the actual contacts around the two independent molecules are given in Table 5 (Supplementary material). The Hirshfeld surfaces, which highlight the regions of the surface with the strongest electron density, are shown in Fig. 6. The proportion of contact types are 95% correlated on the two independent molecules of the asymmetric unit. Therefore, the contacts statistical analysis was performed on the ensemble of two molecules. Two molecules, not in contact with each other in the crystal were selected in order to obtain integral Hirshfeld surfaces.

More than three quarters of the Hirshfeld surface is associated to hydrophobic atoms Hc and C (Table 4). The contacts involving Hc and C represent 65% of the contacts, of which only C...C is significantly enriched at $E_{cc}=1.41$ due to several cycle stacking occurring.

Table 4. Analysis of contacts on the Hirshfeld surface. Reciprocal contacts X...Y and Y...X are merged. The second line shows the chemical content on the surface. The % of contact types between chemical species is given followed by their enrichment ratio. The major contacts as well as the major enriched ones are highlighted in bold characters. The hydrophobic hydrogen atoms bound to carbon (Hc) were distinguished from the more polar one bound to nitrogen (Hn). Three chemically different oxygen types were distinguished: O=c (carbonyl), Occ (ether oxygen within ester group) and O=coc (carbonyl oxygen within ester group). $e/\text{\AA}^3$

atom	C	Hc	N	Hn	Occ	O=coc	O=c
%	31.0	46.6	4.8	6.3	1.7	4.0	5.6
C	12.8						
Hc	29.2	23.1					
N	1.6	6.3	0.0				
Hn	0.9	2.6	0.4	0.8			
Occ=o	0.3	2.4	0.1	0.1	0.0		
O=coc	2.2	4.2	0.2	1.8	0.0	0.0	
O=c	0.6	4.3	0.5	5.7	0.0	0.0	0.0
C	1.41						
Hc	1.02	1.02					
N	0.6	1.46	0				
Hn	0.23	0.41	0.67	1.9			
Occ=o	0.29	1.76	0.41	0.66	0		
O=coc	0.86	1.06	0.46	3.3	0	0	
O=c	0.17	0.81	0.98	7.8	0.23	0	0

The three kinds of oxygen atoms have differentiated behaviors. The Hn...O=c hydrogen bond with the most electronegative O atom represents the most enriched contact at $E=7$. This is due to a bifurcated hydrogen bond between C1=O1 acceptor and the N2-H2N + N1-H1N donors of molecule #1. A similar double hydrogen bond (O4...H5N, H5N...O4) occurs within a dimer of molecule #2 around an inversion centre.

The Hn...O strong hydrogen bond involving the other carbonyl O=coc atom type is the next most enriched contact ($E=3.27$), as there is one such interaction: O2...H4N-N4.

The ether Occ oxygen atom which is less electronegative prefers to interact with Hc less polar hydrogen atoms ($E=1.76$). The nitrogen N3 and N6 atoms which are potential strong acceptors interact also more with the Hc atoms. This is related to the fact that the molecule has only two strong H-bond donors (Hn) compared to four strong acceptors but there is an abundance of Hc weak donors.

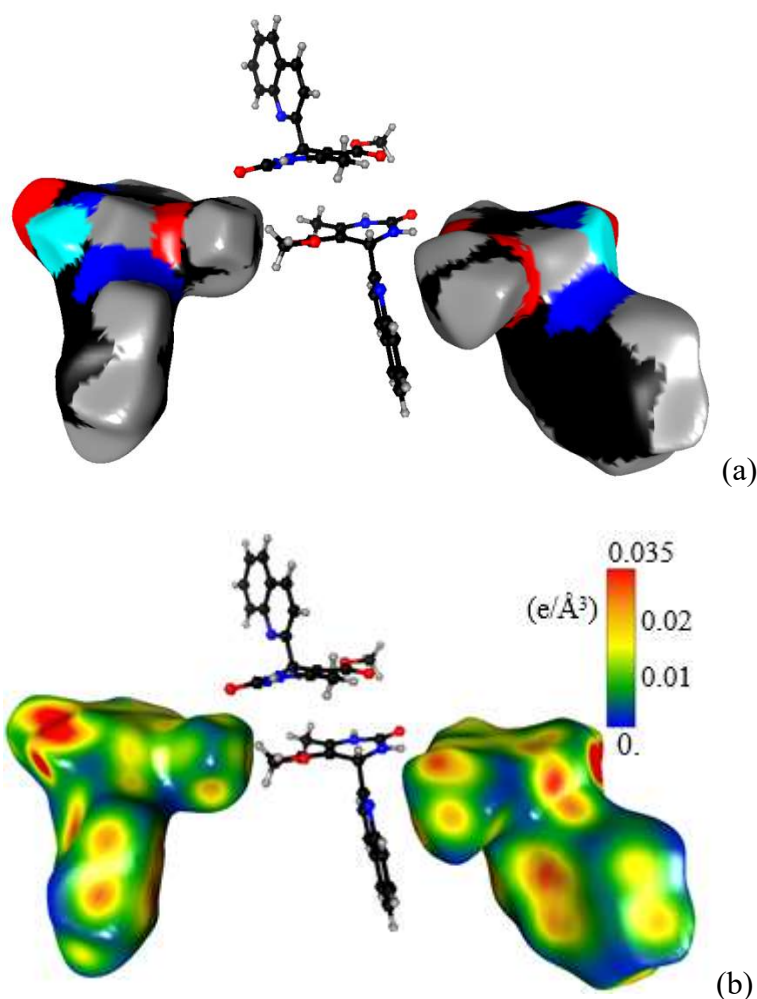


Figure 6. View of the Hirshfeld surface around the two independent molecules. (a) The surface is colored according to the inner atom type; blue: nitrogen, red: oxygen, black: carbon, light blue: Hn, grey: Hc. (b) according to the inner electron density value ($e/\text{\AA}^3$).

3.4 Biological assays

The antibacterial activity of the synthesized dihydropyrimidine was investigated against *E. coli*, *P. aeruginosa* and *S. aureus* bacteria. At first, minimum inhibitory concentration (MIC) for

the investigated compound and pristine antibiotics (cefotaxime and ceftriaxone) was studied by twofold micro-dilution method. As shown in Table 6, the synthesized dihydropyrimidine demonstrated a similar MIC to that of Cefotaxime for all three bacteria. Compound (4) displayed a high activity at the concentration of 2 $\mu\text{g}/\mu\text{l}$ against *E. coli* and this result was better than that of ceftriaxone (3 $\mu\text{g}/\mu\text{L}$). MIC in case of *P. aeruginosa* and *S. aureus* was a bit weaker (3 $\mu\text{g}/\mu\text{L}$), but it was better than the effect of ceftriaxone in case of *P. aeruginosa* (5 $\mu\text{g}/\mu\text{L}$).

Table 6. Minimum inhibitory concentration (MIC, $\mu\text{g}/\mu\text{L}$) of the studied compounds.

Bacteria	Compound (4)	Cefotaxime	Ceftriaxone
<i>E.coli</i>	2	2	3
<i>P.aeruginosa</i>	3	3	5
<i>S.aureus</i>	3	3	3

Taking into account the MIC of the compounds, antibacterial activity was also investigated by disc-diffusion method. Results were compared with the antibacterial activity of pristine antibiotics. As it can be seen from Table 7, antibacterial activity of the studied compound against *E. coli* was higher than that of pristine antibiotics, equal to 28, 20 and 19 mm inhibition disk radius correspondingly.

Table 7. Antibacterial activity of studied compound.

<i>Escherichia coli</i>	compound (4)					cefotaxime	ceftriaxone
Concentration ($\mu\text{g}/\mu\text{l}$)	2	4	8	16	32	32	32
Inhibition zone (mm)	3 \pm 0.5	5 \pm 0.44	9 \pm 0.47	15 \pm 0.5	28 \pm 0.38	20 \pm 0.32	19 \pm 0.48

<i>Pseudomonas aeruginosa</i>	compound (4)					cefotaxime	ceftriaxone
Concentration ($\mu\text{g}/\mu\text{l}$)	3	6	12	24	48	48	48
Inhibition zone (mm)	2 \pm 0.46	5 \pm 0.4	9 \pm 0.4	19 \pm 0.5	39 \pm 0.5	39 \pm 0.45	36 \pm 0.48

<i>Staphylococcus aureus</i>	compound (4)					cefotaxime	ceftriaxone
Concentration ($\mu\text{g}/\mu\text{l}$)	3	6	12	24	48	48	48
Inhibition zone (mm)	2 \pm 0.4	4 \pm 0.38	7 \pm 0.43	16 \pm 0.5	35 \pm 0.52	35 \pm 0.5	35 \pm 0.46

The same tendency was not observed in the case of *P. aeruginosa* (Table 7), where the inhibition zone of dihydropyrimidine was equal to that of cefotaxime and a bit higher than the ceftriaxone one. In case of *gram*-positive bacteria *S. aureus*, dihydropyrimidine and both antibiotics demonstrated the same results equal to 35 mm (Table 7). As DMSO was used as a solvent, the record of the results was also carried out with control dishes, without investigated compound. It was determined that DMSO does not influence on the above mentioned *gram*-positive and *gram*-negative bacteria.

3. Conclusion.

The new derivative **4** of dihydropyrimidine and quinolone was synthesized by Biginelli reaction in microwave conditions in presence of cerium chloride. The structure of it was investigated by X-ray single crystal diffraction. Along with it, Hirshfeld surface analysis was carried out to gain insight into crystal packing and molecular interactions. The crystal structure is made of an alternation of hydrophobic and hydrophilic layers parallel to the (**b,c**) plane. The shortest hydrogen bond N5-H5N...O4=C17 with $d(O...H)=1.96\text{\AA}$ involves an electronegative carbonyl group. Considering that the proposed substance **4** can have an ability to act as an antibacterial drug, it was tested for the biological activity against *E. coli*, *P. aeruginosa* and *S. aureus* bacteria. In addition, its activity was also compared with that of pristine antibiotics. The results obtained are promising and suggest that the synthesized compound indeed represents interest as it is potential biologically active with antibacterial activity.

Conflict of Interest

The authors declare no conflict of interest.

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_diffrn_standards_decay_% 0
_diffrn_reflns_number 20297
_diffrn_reflns_av_unetl/netl 0.0491
_diffrn_reflns_av_R_equivalents 0.0528
_diffrn_reflns_limit_h_min -15
_diffrn_reflns_limit_h_max 15
_diffrn_reflns_limit_k_min -34
_diffrn_reflns_limit_k_max 35
_diffrn_reflns_limit_l_min -8
_diffrn_reflns_limit_l_max 8
_diffrn_reflns_theta_min 1.574
_diffrn_reflns_theta_max 25.016
_diffrn_reflns_theta_full 25.016
_diffrn_measured_fraction_theta_max 0.995
_diffrn_measured_fraction_theta_full 0.995
_diffrn_reflns_Laue_measured_fraction_max 0.995
_diffrn_reflns_Laue_measured_fraction_full 0.995
_diffrn_reflns_point_group_measured_fraction_max 0.995
_diffrn_reflns_point_group_measured_fraction_full 0.995
_reflns_number_total 5063
_reflns_number_gt 2938
_reflns_threshold_expression 'I > 2\sigma(I)'
_reflns_Friedel_coverage 0.000
_reflns_Friedel_fraction_max .
_reflns_Friedel_fraction_full .

_reflns_special_details
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Reflections were merged by SHELXL according to the crystal class for the calculation of statistics and refinement.

_reflns_Friedel_fraction is defined as the number of unique Friedel pairs measured divided by the number that would be possible theoretically, ignoring centric projections and systematic absences.

;

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_computing_data_collection    'SMART (Bruker-Axs Inc)'  
_computing_cell_refinement    'SAINT (Bruker-Axs Inc)'  
_computing_data_reduction     'SAINT (Bruker-Axs Inc)'  
_computing_structure_solution  'SIR-97 (Altomare et al., 1999)'  
_computing_structure_refinement 'SHELXL-2018/1 (Sheldrick, 2018)'  
_computing_molecular_graphics  'Mercury (Macrae et al., 2008)'  
_computing_publication_material 'WinGX publication routines (Farrugia, 1999)'
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_refine_special_details      ?  
_refine_ls_structure_factor_coef Fsqd  
_refine_ls_matrix_type       full  
_refine_ls_weighting_scheme   calc  
_refine_ls_weighting_details  
'w=1/[\s^2^(Fo^2^)+(0.0649P)^2^+0.3048P] where P=(Fo^2^+2Fc^2^)/3'  
_atom_sites_solution_primary  DIRECT  
_atom_sites_solution_secondary DIFMAP  
_atom_sites_solution_hydrogens mixed  
_refine_ls_hydrogen_treatment mixed  
_refine_ls_extinction_method  none  
_refine_ls_extinction_coef    .  
_refine_ls_number_reflns      5063  
_refine_ls_number_parameters   413  
_refine_ls_number_restraints   4  
_refine_ls_R_factor_all        0.1095  
_refine_ls_R_factor_gt         0.0580  
_refine_ls_wR_factor_ref       0.1553  
_refine_ls_wR_factor_gt        0.1289  
_refine_ls_goodness_of_fit_ref 1.017  
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_refine_ls_shift/su_mean        0.000
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_atom_site_site_symmetry_order  
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_atom_site_refinement_flags_occupancy  
_atom_site_disorder_assembly  
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C1 C 0.6423(2) 0.21865(9) 0.7971(3) 0.0484(7) Uani 1 1 d . . . . .  
C2 C 0.6646(2) 0.14834(9) 0.9595(3) 0.0489(7) Uani 1 1 d . . . . .
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C3 C 0.6885(2) 0.12691(9) 0.8108(3) 0.0482(7) Uani 1 1 d
C4 C 0.7109(2) 0.15361(9) 0.6472(3) 0.0485(7) Uani 1 1 d
H4 H 0.683006 0.136920 0.540160 0.058 Uiso 1 1 calc R U . . .
C5 C 0.8245(2) 0.16239(9) 0.6282(4) 0.0506(7) Uani 1 1 d
C6 C 0.9019(3) 0.15703(10) 0.7710(4) 0.0649(8) Uani 1 1 d
H6 H 0.885404 0.147288 0.883530 0.078 Uiso 1 1 calc R U . . .
C7 C 1.0012(3) 0.16626(12) 0.7424(5) 0.0794(10) Uani 1 1 d
H7 H 1.053423 0.162859 0.835578 0.095 Uiso 1 1 calc R U . . .
C8 C 1.0250(3) 0.18088(11) 0.5730(6) 0.0772(10) Uani 1 1 d
C9 C 1.1273(3) 0.19027(14) 0.5304(7) 0.1064(15) Uani 1 1 d
H9 H 1.182492 0.187187 0.618423 0.128 Uiso 1 1 calc R U . . .
C10 C 1.1442(5) 0.20364(17) 0.3626(10) 0.128(2) Uani 1 1 d
H10 H 1.211421 0.209133 0.334976 0.154 Uiso 1 1 calc R U . . .
C11 C 1.0627(5) 0.20927(15) 0.2311(8) 0.1226(19) Uani 1 1 d
H11 H 1.076197 0.218923 0.116816 0.147 Uiso 1 1 calc R U . . .
C12 C 0.9630(3) 0.20102(12) 0.2650(5) 0.0957(13) Uani 1 1 d
H12 H 0.909139 0.205166 0.175272 0.115 Uiso 1 1 calc R U . . .
C13 C 0.9430(3) 0.18612(10) 0.4382(5) 0.0691(9) Uani 1 1 d
C14 C 0.6982(2) 0.07843(10) 0.8015(4) 0.0572(8) Uani 1 1 d
C15 C 0.7491(3) 0.01921(10) 0.6162(5) 0.0955(13) Uani 1 1 d
H15A H 0.801367 0.007898 0.704270 0.143 Uiso 1 1 calc R U . . .
H15B H 0.770204 0.014520 0.497303 0.143 Uiso 1 1 calc R U . . .
H15C H 0.685226 0.003828 0.627543 0.143 Uiso 1 1 calc R U . . .
C16 C 0.6468(2) 0.12888(10) 1.1378(4) 0.0636(8) Uani 1 1 d
H16A H 0.636311 0.097245 1.125410 0.095 Uiso 1 1 calc R U . . .
H16B H 0.586767 0.142347 1.181115 0.095 Uiso 1 1 calc R U . . .
H16C H 0.705936 0.134490 1.222099 0.095 Uiso 1 1 calc R U . . .
C17 C 0.4450(3) 0.01905(13) 0.7398(4) 0.0725(10) Uani 1 1 d
C18 C 0.4251(2) 0.09564(11) 0.6326(4) 0.0613(8) Uani 1 1 d
C19 C 0.3962(2) 0.10937(11) 0.7914(4) 0.0608(8) Uani 1 1 d
C20 C 0.3745(2) 0.07672(11) 0.9378(4) 0.0648(9) Uani 1 1 d
H20 H 0.410811 0.086934 1.051762 0.078 Uiso 1 1 calc R U . . .
C21 C 0.2609(2) 0.07324(9) 0.9624(4) 0.0547(8) Uani 1 1 d
C22 C 0.1283(3) 0.07629(9) 1.1458(4) 0.0574(8) Uani 1 1 d
C23 C 0.0959(3) 0.08455(11) 1.3171(5) 0.0761(10) Uani 1 1 d
H23 H 0.143542 0.093597 1.411123 0.091 Uiso 1 1 calc R U . . .
C24 C -0.0059(3) 0.07929(12) 1.3461(6) 0.0874(12) Uani 1 1 d
H24 H -0.027062 0.084865 1.460003 0.105 Uiso 1 1 calc R U . . .
C25 C -0.0778(3) 0.06576(14) 1.2074(7) 0.0956(13) Uani 1 1 d
H25 H -0.146797 0.062417 1.229055 0.115 Uiso 1 1 calc R U . . .
C26 C -0.0486(3) 0.05745(13) 1.0422(6) 0.0887(11) Uani 1 1 d
H26 H -0.097605 0.048353 0.950382 0.106 Uiso 1 1 calc R U . . .
C27 C 0.0556(3) 0.06235(10) 1.0062(5) 0.0663(9) Uani 1 1 d
C28 C 0.0918(3) 0.05419(12) 0.8375(5) 0.0755(10) Uani 1 1 d
H28 H 0.046140 0.044866 0.741110 0.091 Uiso 1 1 calc R U . . .
C29 C 0.1922(3) 0.05982(11) 0.8150(4) 0.0683(9) Uani 1 1 d
H29 H 0.216273 0.054882 0.702754 0.082 Uiso 1 1 calc R U . . .
C30 C 0.3854(3) 0.15710(14) 0.8299(5) 0.0727(9) Uani 1 1 d
C31 C 0.3797(3) 0.21141(13) 1.0612(5) 0.1011(13) Uani 1 1 d
H31A H 0.428653 0.229075 1.003090 0.152 Uiso 1 1 calc R U . . .
H31B H 0.394295 0.213616 1.189841 0.152 Uiso 1 1 calc R U . . .
H31C H 0.311088 0.222168 1.027061 0.152 Uiso 1 1 calc R U . . .
C32 C 0.4416(3) 0.12310(11) 0.4708(4) 0.0742(9) Uani 1 1 d
H32A H 0.379681 0.123098 0.389576 0.111 Uiso 1 1 calc R U . . .
H32B H 0.497435 0.110722 0.410880 0.111 Uiso 1 1 calc R U . . .
H32C H 0.458307 0.153184 0.507491 0.111 Uiso 1 1 calc R U . . .
N1 N 0.65558(18) 0.19595(7) 0.6479(3) 0.0503(6) Uani 1 1 d D
H1N H 0.650(2) 0.2104(8) 0.543(2) 0.060 Uiso 1 1 d D U . . .
N2 N 0.65591(19) 0.19441(8) 0.9549(3) 0.0531(6) Uani 1 1 d D

H2N H 0.644(2) 0.2089(8) 1.057(2) 0.064 Uiso 1 1 d D U . . .
 N3 N 0.8433(2) 0.17653(8) 0.4672(3) 0.0611(7) Uani 1 1 d
 N4 N 0.4141(2) 0.03260(11) 0.8961(3) 0.0836(9) Uani 1 1 d D
 H4N H 0.413(3) 0.0104(8) 0.977(4) 0.100 Uiso 1 1 d D U . . .
 N5 N 0.4433(2) 0.05092(10) 0.6069(3) 0.0680(7) Uani 1 1 d D
 H5N H 0.468(2) 0.0411(10) 0.505(3) 0.082 Uiso 1 1 d D U . . .
 N6 N 0.2316(2) 0.08139(8) 1.1226(3) 0.0598(7) Uani 1 1 d
 O1 O 0.61772(15) 0.25855(6) 0.7988(2) 0.0578(5) Uani 1 1 d
 O2 O 0.67849(19) 0.05134(7) 0.9126(3) 0.0832(7) Uani 1 1 d
 O3 O 0.73508(18) 0.06638(6) 0.6456(3) 0.0740(7) Uani 1 1 d
 O4 O 0.4736(2) -0.01931(9) 0.7129(3) 0.0943(9) Uani 1 1 d
 O5 O 0.3761(2) 0.18711(9) 0.7216(3) 0.0995(8) Uani 1 1 d
 O6 O 0.38749(19) 0.16527(9) 1.0066(3) 0.0865(7) Uani 1 1 d

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 C3 0.0521(18) 0.0481(16) 0.0446(15) 0.0041(13) 0.0053(13) -0.0027(13)
 C4 0.0593(19) 0.0446(15) 0.0416(15) 0.0007(12) 0.0055(13) -0.0015(13)
 C5 0.057(2) 0.0471(16) 0.0483(16) 0.0000(13) 0.0089(15) -0.0014(14)
 C6 0.064(2) 0.071(2) 0.0590(19) 0.0032(16) 0.0032(17) -0.0040(17)
 C7 0.060(2) 0.091(3) 0.086(3) -0.009(2) -0.003(2) -0.0036(19)
 C8 0.065(2) 0.069(2) 0.101(3) -0.015(2) 0.027(2) -0.0127(18)
 C9 0.071(3) 0.097(3) 0.155(4) -0.035(3) 0.036(3) -0.017(2)
 C10 0.103(4) 0.109(4) 0.185(6) -0.040(4) 0.082(4) -0.035(3)
 C11 0.149(5) 0.088(3) 0.145(5) -0.004(3) 0.094(4) -0.027(3)
 C12 0.113(3) 0.085(3) 0.097(3) 0.011(2) 0.055(3) -0.012(2)
 C13 0.073(3) 0.058(2) 0.080(2) -0.0022(17) 0.026(2) -0.0063(17)
 C14 0.059(2) 0.0568(19) 0.0558(18) 0.0020(15) 0.0053(15) -0.0057(15)
 C15 0.132(4) 0.047(2) 0.108(3) -0.0131(19) 0.011(3) 0.001(2)
 C16 0.077(2) 0.070(2) 0.0456(17) 0.0106(15) 0.0111(15) -0.0031(17)
 C17 0.071(2) 0.095(3) 0.053(2) 0.0185(19) 0.0142(17) 0.019(2)
 C18 0.054(2) 0.082(2) 0.0468(17) 0.0088(16) 0.0002(15) -0.0089(16)
 C19 0.0509(19) 0.081(2) 0.0499(18) 0.0060(16) 0.0015(15) 0.0018(16)
 C20 0.061(2) 0.089(2) 0.0441(17) 0.0083(16) 0.0038(15) 0.0100(18)
 C21 0.061(2) 0.0587(18) 0.0441(17) 0.0050(14) 0.0043(15) 0.0086(15)
 C22 0.064(2) 0.0499(17) 0.0595(19) 0.0061(14) 0.0116(17) 0.0085(15)
 C23 0.086(3) 0.078(2) 0.068(2) -0.0036(18) 0.027(2) 0.0081(19)
 C24 0.094(3) 0.077(3) 0.098(3) 0.012(2) 0.045(3) 0.016(2)
 C25 0.078(3) 0.090(3) 0.123(4) 0.029(3) 0.034(3) 0.018(2)
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 C27 0.063(2) 0.065(2) 0.072(2) 0.0144(17) 0.0088(19) 0.0078(16)
 C28 0.069(3) 0.089(3) 0.065(2) 0.0021(18) -0.0082(19) -0.0084(19)
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 C30 0.059(2) 0.101(3) 0.058(2) 0.007(2) 0.0039(17) -0.0024(19)
 C31 0.110(3) 0.098(3) 0.096(3) -0.016(2) 0.018(2) 0.006(2)
 C32 0.078(2) 0.087(2) 0.0586(19) 0.0108(17) 0.0093(17) -0.0152(19)
 N1 0.0633(16) 0.0493(14) 0.0387(13) 0.0030(11) 0.0079(12) 0.0018(11)
 N2 0.0703(17) 0.0507(15) 0.0392(13) -0.0005(11) 0.0091(12) 0.0001(12)
 N3 0.0669(18) 0.0603(15) 0.0584(16) 0.0032(12) 0.0182(13) -0.0020(13)
 N4 0.088(2) 0.111(2) 0.0552(17) 0.0321(16) 0.0255(15) 0.0446(19)
 N5 0.081(2) 0.080(2) 0.0447(15) 0.0114(14) 0.0114(14) 0.0041(15)

N6 0.0659(19) 0.0647(16) 0.0493(15) 0.0000(12) 0.0075(13) 0.0035(13)
 O1 0.0756(15) 0.0459(12) 0.0520(11) -0.0003(9) 0.0071(10) 0.0028(10)
 O2 0.115(2) 0.0566(13) 0.0816(16) 0.0149(12) 0.0258(14) -0.0079(13)
 O3 0.1085(19) 0.0471(12) 0.0691(14) -0.0065(10) 0.0221(13) -0.0006(11)
 O4 0.116(2) 0.103(2) 0.0688(15) 0.0280(14) 0.0356(14) 0.0485(16)
 O5 0.128(2) 0.0909(19) 0.0784(17) 0.0106(15) 0.0063(16) 0.0023(16)
 O6 0.098(2) 0.0952(19) 0.0672(15) -0.0072(13) 0.0120(13) 0.0096(14)

_geom_special_details

;

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.

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loop_

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 C1 N1 1.326(3) . ?
 C1 N2 1.377(3) . ?
 C2 C3 1.340(4) . ?
 C2 N2 1.384(3) . ?
 C2 C16 1.486(4) . ?
 C3 C14 1.459(4) . ?
 C3 C4 1.507(3) . ?
 C4 N1 1.457(3) . ?
 C4 C5 1.519(4) . ?
 C4 H4 0.9800 . ?
 C5 N3 1.314(3) . ?
 C5 C6 1.403(4) . ?
 C6 C7 1.354(4) . ?
 C6 H6 0.9300 . ?
 C7 C8 1.395(5) . ?
 C7 H7 0.9300 . ?
 C8 C13 1.402(5) . ?
 C8 C9 1.422(5) . ?
 C9 C10 1.348(7) . ?
 C9 H9 0.9300 . ?
 C10 C11 1.384(7) . ?
 C10 H10 0.9300 . ?
 C11 C12 1.364(6) . ?
 C11 H11 0.9300 . ?
 C12 C13 1.410(5) . ?
 C12 H12 0.9300 . ?
 C13 N3 1.364(4) . ?
 C14 O2 1.202(3) . ?
 C14 O3 1.345(3) . ?
 C15 O3 1.443(3) . ?
 C15 H15A 0.9600 . ?
 C15 H15B 0.9600 . ?
 C15 H15C 0.9600 . ?
 C16 H16A 0.9600 . ?

C16 H16B 0.9600 . ?
C16 H16C 0.9600 . ?
C17 O4 1.229(4) . ?
C17 N4 1.328(4) . ?
C17 N5 1.372(4) . ?
C18 C19 1.337(4) . ?
C18 N5 1.375(4) . ?
C18 C32 1.489(4) . ?
C19 C30 1.466(5) . ?
C19 C20 1.509(4) . ?
C20 N4 1.461(4) . ?
C20 C21 1.508(4) . ?
C20 H20 0.9800 . ?
C21 N6 1.307(3) . ?
C21 C29 1.406(4) . ?
C22 N6 1.376(4) . ?
C22 C23 1.401(4) . ?
C22 C27 1.401(4) . ?
C23 C24 1.369(5) . ?
C23 H23 0.9300 . ?
C24 C25 1.386(5) . ?
C24 H24 0.9300 . ?
C25 C26 1.343(5) . ?
C25 H25 0.9300 . ?
C26 C27 1.412(4) . ?
C26 H26 0.9300 . ?
C27 C28 1.402(4) . ?
C28 C29 1.341(4) . ?
C28 H28 0.9300 . ?
C29 H29 0.9300 . ?
C30 O5 1.205(4) . ?
C30 O6 1.335(4) . ?
C31 O6 1.446(4) . ?
C31 H31A 0.9600 . ?
C31 H31B 0.9600 . ?
C31 H31C 0.9600 . ?
C32 H32A 0.9600 . ?
C32 H32B 0.9600 . ?
C32 H32C 0.9600 . ?
N1 H1N 0.891(10) . ?
N2 H2N 0.898(10) . ?
N4 H4N 0.898(10) . ?
N5 H5N 0.900(10) . ?

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O1 C1 N1 123.9(2) . . ?
O1 C1 N2 120.9(2) . . ?
N1 C1 N2 115.2(2) . . ?
C3 C2 N2 118.8(2) . . ?
C3 C2 C16 128.1(3) . . ?
N2 C2 C16 113.2(2) . . ?
C2 C3 C14 122.9(2) . . ?

C2 C3 C4 119.3(2) . . ?
C14 C3 C4 117.7(2) . . ?
N1 C4 C3 109.0(2) . . ?
N1 C4 C5 109.5(2) . . ?
C3 C4 C5 115.4(2) . . ?
N1 C4 H4 107.6 . . ?
C3 C4 H4 107.6 . . ?
C5 C4 H4 107.6 . . ?
N3 C5 C6 123.2(3) . . ?
N3 C5 C4 113.8(3) . . ?
C6 C5 C4 123.0(3) . . ?
C7 C6 C5 118.9(3) . . ?
C7 C6 H6 120.5 . . ?
C5 C6 H6 120.5 . . ?
C6 C7 C8 120.0(3) . . ?
C6 C7 H7 120.0 . . ?
C8 C7 H7 120.0 . . ?
C7 C8 C13 117.6(3) . . ?
C7 C8 C9 123.6(4) . . ?
C13 C8 C9 118.8(4) . . ?
C10 C9 C8 120.1(5) . . ?
C10 C9 H9 120.0 . . ?
C8 C9 H9 120.0 . . ?
C9 C10 C11 120.7(5) . . ?
C9 C10 H10 119.6 . . ?
C11 C10 H10 119.6 . . ?
C12 C11 C10 121.6(5) . . ?
C12 C11 H11 119.2 . . ?
C10 C11 H11 119.2 . . ?
C11 C12 C13 119.0(5) . . ?
C11 C12 H12 120.5 . . ?
C13 C12 H12 120.5 . . ?
N3 C13 C8 122.2(3) . . ?
N3 C13 C12 118.0(4) . . ?
C8 C13 C12 119.8(3) . . ?
O2 C14 O3 121.8(3) . . ?
O2 C14 C3 127.8(3) . . ?
O3 C14 C3 110.3(2) . . ?
O3 C15 H15A 109.5 . . ?
O3 C15 H15B 109.5 . . ?
H15A C15 H15B 109.5 . . ?
O3 C15 H15C 109.5 . . ?
H15A C15 H15C 109.5 . . ?
H15B C15 H15C 109.5 . . ?
C2 C16 H16A 109.5 . . ?
C2 C16 H16B 109.5 . . ?
H16A C16 H16B 109.5 . . ?
C2 C16 H16C 109.5 . . ?
H16A C16 H16C 109.5 . . ?
H16B C16 H16C 109.5 . . ?
O4 C17 N4 123.2(3) . . ?
O4 C17 N5 121.1(3) . . ?
N4 C17 N5 115.6(3) . . ?
C19 C18 N5 119.2(3) . . ?
C19 C18 C32 128.1(3) . . ?
N5 C18 C32 112.7(3) . . ?
C18 C19 C30 120.8(3) . . ?
C18 C19 C20 121.7(3) . . ?
C30 C19 C20 117.6(3) . . ?

N4 C20 C19 109.8(2) . . ?
N4 C20 C21 109.3(3) . . ?
C19 C20 C21 112.5(2) . . ?
N4 C20 H20 108.4 . . ?
C19 C20 H20 108.4 . . ?
C21 C20 H20 108.4 . . ?
N6 C21 C29 123.2(3) . . ?
N6 C21 C20 118.0(3) . . ?
C29 C21 C20 118.8(3) . . ?
N6 C22 C23 118.2(3) . . ?
N6 C22 C27 122.6(3) . . ?
C23 C22 C27 119.2(3) . . ?
C24 C23 C22 119.9(4) . . ?
C24 C23 H23 120.0 . . ?
C22 C23 H23 120.0 . . ?
C23 C24 C25 120.8(4) . . ?
C23 C24 H24 119.6 . . ?
C25 C24 H24 119.6 . . ?
C26 C25 C24 120.4(4) . . ?
C26 C25 H25 119.8 . . ?
C24 C25 H25 119.8 . . ?
C25 C26 C27 120.8(4) . . ?
C25 C26 H26 119.6 . . ?
C27 C26 H26 119.6 . . ?
C28 C27 C22 117.2(3) . . ?
C28 C27 C26 123.9(4) . . ?
C22 C27 C26 118.9(3) . . ?
C29 C28 C27 120.0(3) . . ?
C29 C28 H28 120.0 . . ?
C27 C28 H28 120.0 . . ?
C28 C29 C21 119.5(3) . . ?
C28 C29 H29 120.2 . . ?
C21 C29 H29 120.2 . . ?
O5 C30 O6 120.9(4) . . ?
O5 C30 C19 127.0(3) . . ?
O6 C30 C19 112.1(3) . . ?
O6 C31 H31A 109.5 . . ?
O6 C31 H31B 109.5 . . ?
H31A C31 H31B 109.5 . . ?
O6 C31 H31C 109.5 . . ?
H31A C31 H31C 109.5 . . ?
H31B C31 H31C 109.5 . . ?
C18 C32 H32A 109.5 . . ?
C18 C32 H32B 109.5 . . ?
H32A C32 H32B 109.5 . . ?
C18 C32 H32C 109.5 . . ?
H32A C32 H32C 109.5 . . ?
H32B C32 H32C 109.5 . . ?
C1 N1 C4 123.5(2) . . ?
C1 N1 H1N 118.6(18) . . ?
C4 N1 H1N 114.9(18) . . ?
C1 N2 C2 123.4(2) . . ?
C1 N2 H2N 116.6(18) . . ?
C2 N2 H2N 118.6(18) . . ?
C5 N3 C13 118.1(3) . . ?
C17 N4 C20 127.0(3) . . ?
C17 N4 H4N 113(2) . . ?
C20 N4 H4N 120(2) . . ?
C17 N5 C18 124.6(3) . . ?

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C17 N5 H5N 113(2) . . ?
C18 N5 H5N 121(2) . . ?
C21 N6 C22 117.6(3) . . ?
C14 O3 C15 117.0(3) . . ?
C30 O6 C31 117.1(3) . . ?

_refine_diff_density_max 0.188
_refine_diff_density_min -0.171
_refine_diff_density_rms 0.034

_shelx_res_file
;
TITL DOR24_CCD run in space group P 1 21/c 1
shelx.res
created by SHELXL-2018/1 at 09:40:58 on 05-Mar-2018
CELL 0.7107 12.9912 29.9305 7.4380 90.000 95.312 90.000
ZERR 4.00 0.0031 0.0071 0.0018 0.000 0.005 0.000
LATT 1
SYMM -X, 1/2 + Y, 1/2 - Z
SFAC C H N O
UNIT 128 120 24 24
MERG 2
FMAP 2
PLAN 25
ACTA
BOND $H
DFIX 0.9 0.01 N1 H1N
DFIX 0.9 0.01 N2 H2N
DFIX 0.9 0.01 N4 H4N
DFIX 0.9 0.01 N5 H5N
OMIT O 2 O
L.S. 10
TEMP 25.00
SIZE 0.43 0.11 0.03
WGHT 0.064900 0.304800
FVAR 0.10851
C1 1 0.642275 0.218654 0.797081 11.00000 0.05105 0.05136 =
0.04286 0.00154 0.00515 -0.00540
C2 1 0.664616 0.148337 0.959529 11.00000 0.04813 0.05355 =
0.04431 0.00597 0.00077 -0.00354
C3 1 0.688539 0.126913 0.810821 11.00000 0.05206 0.04814 =
0.04461 0.00410 0.00528 -0.00267
C4 1 0.710857 0.153609 0.647151 11.00000 0.05935 0.04462 =
0.04155 0.00072 0.00548 -0.00149
AFIX 13
H4 2 0.683006 0.136920 0.540160 11.00000 -1.20000
AFIX 0
C5 1 0.824537 0.162392 0.628154 11.00000 0.05728 0.04709 =
0.04833 -0.00004 0.00895 -0.00139
C6 1 0.901949 0.157026 0.771011 11.00000 0.06407 0.07103 =
0.05905 0.00323 0.00319 -0.00400
AFIX 43
H6 2 0.885404 0.147288 0.883530 11.00000 -1.20000
AFIX 0
C7 1 1.001166 0.166261 0.742354 11.00000 0.05958 0.09056 =
0.08626 -0.00930 -0.00254 -0.00363
AFIX 43
H7 2 1.053423 0.162859 0.835578 11.00000 -1.20000
AFIX 0

```

C8 1 1.024976 0.180877 0.573012 11.00000 0.06545 0.06850 =
 0.10112 -0.01531 0.02678 -0.01273
 C9 1 1.127257 0.190271 0.530420 11.00000 0.07104 0.09742 =
 0.15540 -0.03515 0.03567 -0.01654
 AFIX 43
 H9 2 1.182492 0.187187 0.618423 11.00000 -1.20000
 AFIX 0
 C10 1 1.144218 0.203638 0.362648 11.00000 0.10327 0.10915 =
 0.18539 -0.04034 0.08234 -0.03493
 AFIX 43
 H10 2 1.211421 0.209133 0.334976 11.00000 -1.20000
 AFIX 0
 C11 1 1.062706 0.209272 0.231146 11.00000 0.14911 0.08839 =
 0.14535 -0.00408 0.09366 -0.02738
 AFIX 43
 H11 2 1.076197 0.218923 0.116816 11.00000 -1.20000
 AFIX 0
 C12 1 0.963044 0.201023 0.265026 11.00000 0.11329 0.08479 =
 0.09748 0.01128 0.05451 -0.01152
 AFIX 43
 H12 2 0.909139 0.205166 0.175272 11.00000 -1.20000
 AFIX 0
 C13 1 0.943024 0.186117 0.438234 11.00000 0.07260 0.05803 =
 0.08015 -0.00223 0.02630 -0.00634
 C14 1 0.698197 0.078433 0.801482 11.00000 0.05896 0.05676 =
 0.05580 0.00201 0.00527 -0.00570
 C15 1 0.749146 0.019211 0.616213 11.00000 0.13158 0.04678 =
 0.10820 -0.01306 0.01111 0.00121
 AFIX 137
 H15A 2 0.801367 0.007898 0.704270 11.00000 -1.50000
 H15B 2 0.770204 0.014520 0.497303 11.00000 -1.50000
 H15C 2 0.685226 0.003828 0.627543 11.00000 -1.50000
 AFIX 0
 C16 1 0.646834 0.128884 1.137810 11.00000 0.07675 0.06952 =
 0.04560 0.01056 0.01108 -0.00310
 AFIX 137
 H16A 2 0.636311 0.097245 1.125410 11.00000 -1.50000
 H16B 2 0.586767 0.142347 1.181115 11.00000 -1.50000
 H16C 2 0.705936 0.134490 1.222099 11.00000 -1.50000
 AFIX 0
 C17 1 0.444961 0.019050 0.739765 11.00000 0.07133 0.09536 =
 0.05250 0.01847 0.01420 0.01874
 C18 1 0.425098 0.095637 0.632559 11.00000 0.05431 0.08178 =
 0.04684 0.00881 0.00022 -0.00888
 C19 1 0.396194 0.109367 0.791442 11.00000 0.05087 0.08097 =
 0.04989 0.00596 0.00149 0.00178
 C20 1 0.374499 0.076718 0.937809 11.00000 0.06072 0.08933 =
 0.04412 0.00834 0.00378 0.01000
 AFIX 13
 H20 2 0.410811 0.086934 1.051762 11.00000 -1.20000
 AFIX 0
 C21 1 0.260865 0.073242 0.962413 11.00000 0.06118 0.05865 =
 0.04408 0.00500 0.00425 0.00856
 C22 1 0.128342 0.076286 1.145793 11.00000 0.06388 0.04986 =
 0.05953 0.00611 0.01159 0.00848
 C23 1 0.095925 0.084548 1.317109 11.00000 0.08605 0.07770 =
 0.06817 -0.00363 0.02681 0.00808
 AFIX 43
 H23 2 0.143542 0.093597 1.411123 11.00000 -1.20000

AFIX 0
 C24 1 -0.005899 0.079293 1.346054 11.00000 0.09384 0.07716 =
 0.09793 0.01234 0.04535 0.01598
 AFIX 43
 H24 2 -0.027062 0.084865 1.460003 11.00000 -1.20000
 AFIX 0
 C25 1 -0.077845 0.065760 1.207444 11.00000 0.07807 0.09035 =
 0.12296 0.02889 0.03380 0.01781
 AFIX 43
 H25 2 -0.146797 0.062417 1.229055 11.00000 -1.20000
 AFIX 0
 C26 1 -0.048625 0.057447 1.042199 11.00000 0.06592 0.09294 =
 0.10695 0.02066 0.00655 0.00184
 AFIX 43
 H26 2 -0.097605 0.048353 0.950382 11.00000 -1.20000
 AFIX 0
 C27 1 0.055638 0.062354 1.006213 11.00000 0.06272 0.06508 =
 0.07165 0.01437 0.00878 0.00779
 C28 1 0.091796 0.054190 0.837495 11.00000 0.06903 0.08937 =
 0.06526 0.00213 -0.00820 -0.00844
 AFIX 43
 H28 2 0.046140 0.044866 0.741110 11.00000 -1.20000
 AFIX 0
 C29 1 0.192213 0.059818 0.815001 11.00000 0.07035 0.08595 =
 0.04832 -0.00161 0.00419 0.00432
 AFIX 43
 H29 2 0.216273 0.054882 0.702754 11.00000 -1.20000
 AFIX 0
 C30 1 0.385383 0.157100 0.829857 11.00000 0.05878 0.10131 =
 0.05764 0.00683 0.00391 -0.00240
 C31 1 0.379730 0.211406 1.061242 11.00000 0.11026 0.09843 =
 0.09605 -0.01613 0.01800 0.00647
 AFIX 137
 H31A 2 0.428653 0.229075 1.003090 11.00000 -1.50000
 H31B 2 0.394295 0.213616 1.189841 11.00000 -1.50000
 H31C 2 0.311088 0.222168 1.027061 11.00000 -1.50000
 AFIX 0
 C32 1 0.441596 0.123100 0.470750 11.00000 0.07796 0.08666 =
 0.05859 0.01084 0.00927 -0.01521
 AFIX 137
 H32A 2 0.379681 0.123098 0.389576 11.00000 -1.50000
 H32B 2 0.497435 0.110722 0.410880 11.00000 -1.50000
 H32C 2 0.458307 0.153184 0.507491 11.00000 -1.50000
 AFIX 0
 N1 3 0.655583 0.195949 0.647950 11.00000 0.06334 0.04934 =
 0.03869 0.00299 0.00793 0.00184
 H1N 2 0.649837 0.210423 0.542772 11.00000 -1.20000
 N2 3 0.655911 0.194409 0.954900 11.00000 0.07034 0.05066 =
 0.03920 -0.00045 0.00911 0.00014
 H2N 2 0.644323 0.208865 1.056928 11.00000 -1.20000
 N3 3 0.843266 0.176532 0.467194 11.00000 0.06692 0.06029 =
 0.05845 0.00322 0.01821 -0.00200
 N4 3 0.414073 0.032595 0.896149 11.00000 0.08777 0.11118 =
 0.05522 0.03214 0.02546 0.04464
 H4N 2 0.412762 0.010430 0.977347 11.00000 -1.20000
 N5 3 0.443317 0.050920 0.606934 11.00000 0.08068 0.07974 =
 0.04466 0.01138 0.01145 0.00415
 H5N 2 0.467559 0.041068 0.504617 11.00000 -1.20000
 N6 3 0.231575 0.081387 1.122610 11.00000 0.06590 0.06471 =

0.04927 0.00003 0.00753 0.00354
 O1 4 0.617720 0.258549 0.798811 11.00000 0.07558 0.04595 =
 0.05204 -0.00026 0.00706 0.00275
 O2 4 0.678493 0.051336 0.912614 11.00000 0.11456 0.05664 =
 0.08161 0.01490 0.02580 -0.00793
 O3 4 0.735083 0.066381 0.645551 11.00000 0.10854 0.04706 =
 0.06908 -0.00650 0.02212 -0.00060
 O4 4 0.473592 -0.019314 0.712851 11.00000 0.11627 0.10303 =
 0.06879 0.02799 0.03558 0.04849
 O5 4 0.376087 0.187114 0.721629 11.00000 0.12847 0.09094 =
 0.07836 0.01064 0.00633 0.00230
 O6 4 0.387489 0.165270 1.006634 11.00000 0.09790 0.09515 =
 0.06720 -0.00716 0.01197 0.00957
 HKLF 4

REM DOR24_CCD run in space group P 1 21/c 1
 REM R1 = 0.0580 for 2938 Fo > 4sig(Fo) and 0.1095 for all 5063 data
 REM 413 parameters refined using 4 restraints

END

WGHT 0.0595 0.3676