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Proton sharing and transfer in some zwitterionic compounds based on 4-oxo-4-((1-phenethylpiperidin-4-yl)(phenyl)amino)alcanoic acids[†]

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Abstract

Three compounds, each derived from Fentanyl and differing essentially only in the length of a carboxylic acid chain, were synthesized and yielded four crystal structures three of which share several structural similarities, including the length of the chain, while the fourth, with a shorter chain, is quite different. The chain length has a significant influence on the crystal structures formed. The ‘three atom’ chain compounds are all solvated zwitterions which feature a hydrogen-bonded ‘dimer’ between adjacent zwitterions. The formation of this large dimer leaves available a second carboxylate O atom to take part in hydrogen bonding interactions with solvent molecules. The shorter ‘two atom’ chain compound was difficult to crystallize and required the use of synchrotron radiation to measure X-ray diffraction data. It does not form the same dimer motif observed in the ‘three atom’ chain compounds and has not formally formed a zwitterion; although there is evidence of proton sharing or disorder X-ray data are insufficient to create a disordered model, and the compound was modeled as formally neutral based on O–H and N–H distances. Room temperature analyses showed the proton transfer behavior to be independent of crystal temperature, and nuclear magnetic resonance studies show proton transfer behavior in solution. The formation of a zwitterionic hydrogen-bonded dimer is implicated in providing some stability during crystal growth of the easily crystallized ‘three atom’ chain compounds.

Introduction

We have a long standing research interest in the synthesis and bioactivity of novel opioid compounds for the treatment of neuropathic pain. Although existing opioid analgesics are very potent and commonly used, μ opioids have serious side effects and dependence caused by long term usage.^{1–5} Our research, therefore, aims to synthesize a range of new opioids derived from Fentanyl, with the aim of developing compounds with reduced side effects but which remain potent analgesics.^{6–9} We investigated the three new compounds presented in this manuscript which were found to possess weak analgesic activity. Upon determining the crystal structure, initially of **3**, we observed that the compound had crystallized as a zwitterion, with proton transfer between the carboxylic acid and piperidine groups of adjacent molecules. To examine this further we determined the structures of **1**, **2** and **4**

[†] Electronic supplementary information (ESI) available: Tables of bond lengths and angles for each compound. CCDC reference numbers 753887–753890. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b923698h

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which differ only in the length of the carboxylic acid chain (in **2** a C atom has been replaced by O to form an ether link). In the case of **1** the proton appears to be shared between N and O but formally resides on the O atom based on X–H distances. Nuclear magnetic resonance (NMR) studies indicate that the compounds also exist as zwitterions in solution.

Results and discussion

The molecular structures of **1**, **2** and **3** are shown in Fig. 1 and the two independent molecules of **4** are shown in Fig. 2. Other than the N–H...O proton behavior, covalent bond distances are unexceptional. The molecular conformation of **1** is quite different from **2**, **3** and **4** and is also the only example in the series which has not crystallized as a formal zwitterion (Scheme 1). Experimental crystallographic parameters are given in Table 1 and hydrogen bonding geometry is given in Table 2.

Compound 1: 4-oxo-4-((1-phenethylpiperidin-4-yl)(phenyl)amino)-butanoic acid

In this particular structure the location of the acidic H atom is difficult to determine since the electron density associated with H(2O) (Fig. S1[†]) shows it to be disordered across two sites. However, with X-ray data it is not possible to refine an H atom as disordered[‡] and so an ordered model is used and since the N–H distance, 1.34(2) Å, is longer than the O–H distance, 1.22(2) Å (Table 2), then formally the H atom resides on the O atom, and was refined freely.

The molecular conformation of this structure is quite different from all others in the series. In this structure the butanoic acid group is in an essentially *anti* arrangement with respect to the aminophenyl ring; in **2–4** these groups are in an essentially *syn* arrangement. Furthermore the angle between mean planes fitted through the piperazine ring (rms deviation = 0.241 Å) and the benzyl group (rms deviation = 0.013 Å) is 80.28(4)°, whereas in other structures this angle is much smaller (discussed later). In the crystal packing this is the only example where molecules/ions do not pack such that they form a hydrogen-bonded ‘dimer’ consisting of N–H...O interactions. Instead one O–H...N and one C–H...O interaction link adjacent interactions, by way of an $R^2_3(13)$ graph-set motif¹⁰ to form a chain which propagates along the *a* axis (Fig. 3, top). Further C–H...O interactions (Fig. 3, bottom) are present in the structure. These are weaker as they involve less acidic H atoms and bifurcated O acceptor sites. O(2) acts as a bifurcated acceptor with H(13A) and H(17B) in forming an $R^1_2(7)$ motif while O3 acts as a bifurcated acceptor with H(14B) and H(16A) in forming an $R^1_2(6)$ motif. The combination of these interactions forms a two-dimensional sheet in the *ab* plane.

Compound 2: 2-(2-oxo-2-((1-phenethylpiperidin-4-yl)(phenyl)-amino)ethoxy)acetic acid

The conformation of **2** is mostly extended and with the acetate group essentially *syn* with respect to the aminophenyl ring. The compound crystallizes with one molecule of solvent

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[‡] In this instance restraints are required to control a disordered H atom (since the disorder model is then based on a fraction of one electron). Free refinement, in conjunction with an electron density plot, is perhaps a better evaluation of the data than a disorder model laden with restraints which are not necessarily consistent with maxima in a difference map.

water in the asymmetric unit, along with one molecule of solvent methanol which has been refined as disordered across a crystallographic inversion center with occupancy fixed at 1/2. The compound has crystallized as a zwitterion as evidenced by the carboxylate C–O distances ($O(3)–C(4) = 1.255(2) \text{ \AA}$ and $O(4)–C(4) = 1.251(2) \text{ \AA}$) and the identification of H(2N) from a difference map. The coordinates and isotropic displacement parameter of H(2N) were freely refined to give an $N(2)–H(2N)$ bond distance of $0.98(3) \text{ \AA}$. The presence of water and methanol was confirmed by analysis of difference Fourier maps which show the location of electron density associated with O-bound and methyl H atoms. The angle between mean planes fitted through the piperazine ring (rms deviation = $0.237 \text{ \AA}$) and the benzyl group (rms deviation = $0.013 \text{ \AA}$) is $44.56(7)^\circ$, almost half that observed in **1**.

The crystal packing makes extensive use of hydrogen bonding in the formation of thick two-dimensional sheets (Fig. 4). Overall the structure is composed of four different graph-set motifs. Two are quite obvious: the $R^2_4(8)$ motif formed by water H and carboxylate O atoms and the $R^2_2(12)$ motif formed by symmetry-equivalent C–H...O interactions. A third, large $R^2_2(24)$ motif corresponds to the formation of a hydrogen-bonded ‘dimer’ between adjacent zwitterions while the fourth is a long chain $C^4_4(14)$ motif which passes through methanol, water, carboxylate and amine groups. In the figure the symmetry-equivalent H atoms, which define the extent of the chain, are indicated with arrows.

Compounds **3** and **4**: 5-oxo-5-((1-phenethylpiperidin-4-yl)(phenyl)-amino)pentanoic acid

The final compound in the series yields two separate species: structure **3**, which was the first to be obtained, and structure **4**, obtained in order to remove the problem of disordered solvent in **3**. The zwitterionic identity of **3** was established by analysis of carboxylate C–O bond distances and a difference Fourier map shows the location of H(2N). The freely refined N–H distance is $1.13(2) \text{ \AA}$ and forms an N–H...O hydrogen bond linking adjacent molecule into hydrogen-bonded dimers, as was observed in **2**. The use of SQUEEZE¹¹ (discussed later) on this structure prevents further analysis of the crystal packing. Molecules **2** and **3** have similar conformations (Fig. S3[†]), as might be anticipated from the similarity of the unit cell parameters. However, the two are not isomorphous since the coordinates of one structure cannot be refined against the data of another; this prevents the coordinates of the solvent in **2** being used to locate solvent in **3**.

Compound **4** contains two crystallographically unique molecules of 5-oxo-5-((1-phenethylpiperidin-4-yl)(phenyl)amino)-pentanoic acid along with two molecules of water and one molecule of methanol. The identity of water was established by means of difference Fourier maps and possibly comes from contaminated methanol used in recrystallization of the compound. The two unique molecules are identified as molecule **A** (atoms O(1) to C(24)) and molecule **B** (atoms O(51) to C(71), values presented in square brackets). An overlay of the two molecules is shown in Fig. 5 and from this it can be seen that while the propanoate groups of both unique molecules have similar conformations the phenyl rings do not.

Molecules **A** and **B** are present as zwitterions. This is clearly shown in both the C–O distances of the propanoate group ($O(2)–C(5)$ is $1.250(3) [1.240(3)] \text{ \AA}$ and $O(3)–C(5)$ is

1.267(3) [1.287(3)] Å) and by difference Fourier map analysis of the N(2)–H(2N)···O(3) [N(52)–H(52N)···O(53)] interaction. In both cases the N–H H atom was allowed to refine freely without restraints on the N–H distance and it is clear that in the case of N(2)–H(2N)···O(3) the N–H distance of 0.93(3) Å full proton transfer has taken place while in N(52)–H(52N)···O(53) the N(52)–H(52N) distance of 1.12(3) Å moves the H atom a little closer to O(53) but the electron density associated with this H atom is still suggestive of formal proton transfer.

The classical hydrogen bonding patterns found in **4** are shown in Fig. 6. One of the propanoate O atoms is involved in an N–H···O hydrogen bond resulting in hydrogen-bonded zwitterionic “pairs” while the second O atom is involved in an O–H···O interaction with an adjacent water molecule. The solvent molecules form a large $R^6_6(12)$ motif and propagation of this hydrogen bonding forms a two-dimensional sheet (Fig. 7). By plotting this in space fill representation it can be seen that small voids are present although in the crystal packing this does not result in channel-like voids.

NMR spectroscopy

Direct observation of protonation by NMR spectroscopy for any of these compounds is not possible as MeOD was the most suitable solvent in terms of solubility, and the resonances from the solvent occupy the same chemical shift region as the N–H proton. However, evidence of protonation can be inferred by examining the behavior of methylene protons at the 2 and 6 positions on the piperidine ring, and by comparison with NMR spectra of Fentanyl and Fentanyl·HCl (Fig. S5 and S6[†]). In all cases there is a significant downfield shift of the resonances when compared with the spectrum of Fentanyl, and this pattern is consistent with a downfield shift observed in Fentanyl·HCl. The shift is most pronounced for **2**, around 0.5 ppm downfield, and weakest for **1**. The carboxylic acid region is entirely blank in all three spectra.

Experimental

General method for the synthesis of the 4-oxo-4-((1-phenethylpiperidin-4-yl)(phenyl)amino)alcanoic acids

A mixture of 0.01 mol of [1-(2-phenyl)-ethyl-piperidin-4-yl]-phenyl-amine, 0.011 mol of appropriate acid anhydride (succinic, glutaric or diglycolic) and 2–3 drops of acetic acid in 30 ml of dichloromethane was heated in a closed pressure proof flask on boiling water bath for 5 hours and left for the night at room temperature. The solvent was evaporated; ether was added and on cooling (ice) 0.022 mol of NaHCO₃ as a 5% solution was added. The ether layer was separated, to water solution was added 50 ml of chloroform and it was neutralized on cooling and stirring by 0.022 mol of acetic acid. Chloroform solution was dried on MgSO₄ and after evaporation of solvent the product was dissolved in the minimum quantity of boiling methanol or ethyl acetate from which on cooling crystals of appropriate acid were separated with 75–90% yield.

4-Oxo-4-((1-phenethylpiperidin-4-yl)(phenyl)amino)butanoic acid (1)

Crystalline solid (89.7%), obtained by slow cooling of an ethyl acetate solution, mp 119–120 °C. ¹H NMR (600 MHz, MeOD) δ 7.50 (2H, t, J = 7.3 Hz), 7.48–7.43 (1H, m), 7.32–7.25 (4H, m), 7.25–7.18 (3H, m), 4.70 (1H, tt, J = 12.0, 3.5 Hz), 3.42 (2H, d, J = 12.2 Hz), 2.99 (2H, dd, J = 10.6, 6.1 Hz), 2.89 (2H, dd, J = 10.5, 6.1 Hz), 2.80 (2H, t, J = 12.0 Hz), 2.42 (2H, t, J = 6.8 Hz), 2.18 (2H, t, J = 6.8 Hz), 2.00 (2H, d, J = 12.2 Hz), 1.62 (2H, dq, J = 3.3, 13.1 Hz). ¹³C NMR (150 MHz, MeOD) δ 172.77, 138.08, 137.48, 130.16, 129.40, 128.65, 128.31, 126.44, 58.09, 51.92, 50.76, 30.85, 30.47, 30.25, 28.14. EI-MS: m/z 381; HRMS calcd for C₂₃H₂₉N₂O₃: 381.2178; found (ESI, [M + H]⁺): 381.2183.

2-(2-Oxo-2-((1-phenethylpiperidin-4-yl)(phenyl)amino)ethoxy)-acetic acid (2)

Crystalline solid (75.7%), obtained by slow cooling of a methanol solution, mp 143–144 °C. ¹H NMR (600 MHz, MeOD) δ 7.55–7.45 (3H, m), 7.35–7.26 (4H, m), 7.25–7.22 (3H, m), 4.73 (1H, tt, J = 12.1, 3.6 Hz), 3.86 (4H, d, J = 6.0 Hz), 3.56 (2H, d, J = 12.3 Hz), 3.15 (2H, dd, J = 10.3, 6.6 Hz), 3.01 (2H, t, J = 12.2 Hz), 2.95 (2H, dd, J = 10.3, 6.6 Hz), 2.09 (2H, d, J = 12.7 Hz), 1.72 (2H, dd, J = 12.8, 2.8 Hz). ¹³C NMR (150 MHz, MeOD) δ 174.52, 170.05, 136.78, 136.17, 129.90, 129.70, 129.28, 128.46, 128.33, 126.67, 69.40, 68.52, 57.60, 51.69, 50.81, 30.36, 27.41, 19.81. EI-MS: m/z 397; HRMS calcd for C₂₃H₂₉N₂O₄: 397.2127; found (ESI, [M + H]⁺): 397.2123.

5-Oxo-5-((1-phenethylpiperidin-4-yl)(phenyl)amino)pentanoic acid (3 and 4)

Crystalline solid (3) (84.9%), obtained by slow cooling of a ethyl acetate solution, mp 104–105 °C. Subsequent recrystallization from methanol gave (4) as a crystalline solid. ¹H NMR (600 MHz, MeOD) δ 7.51 (2H, t, J = 7.3 Hz), 7.47 (1H, d, J = 7.2 Hz), 7.31 (2H, t, J = 7.2 Hz), 7.26–7.21 (5H, m), 4.74 (1H, tt, J = 12.0, 3.6 Hz), 3.44 (2H, d, J = 12.3 Hz), 3.01 (2H, dd, J = 11.4, 5.4 Hz), 2.91 (2H, dd, J = 10.6, 5.9 Hz), 2.81 (2H, t, J = 11.9 Hz), 2.12 (2H, t, J = 7.3 Hz), 2.07–1.97 (4H, m), 1.81 (2H, dd, J = 14.7, 7.3 Hz), 1.63 (2H, dd, J = 12.8, 3.2 Hz). ¹³C NMR (150 MHz, MeOD) δ 173.27, 138.07, 137.56, 130.05, 129.44, 128.66, 128.32, 126.43, 58.11, 51.87, 50.78, 34.52, 33.99, 30.89, 28.19, 21.05. EI-MS: m/z 395; HRMS calcd for C₂₄H₃₁N₂O₃: 395.2325; found (ESI, [M + H]⁺): 395.2323.

X-Ray crystallography

For **1** data were measured using synchrotron radiation (λ = 0.7794 Å) at beam line 11.3.1 of the Advanced Light Source (ALS) on a Bruker SMART APEXII goniometer with a crystal temperature of 100 K. For **2**, **3**, and **4** data were measured on a Bruker Kappa APEXII DUO CCD diffractometer with silicon-monochromated CuK α radiation (λ = 1.54178 Å) and a crystal temperature of 100 K. Standard software was used: APEX2 was used for diffractometer control and unit cell indexing (CELL_NOW for **1**); SAINT was used for integration.¹² A semi-empirical absorption correction based on symmetry-equivalent and repeated reflections was applied with TWINABS¹³ (**1**) and numerical absorption corrections were applied with SADABS¹⁴ (**2**, **3**, and **4**). All structures were solved by direct methods and refined by full-matrix least-squares on F^2 with SHELXTL.¹⁵ Molecular graphics were produced with ORTEP-3 for Windows¹⁶ and Mercury 2.2.¹⁷ Experimental crystallographic parameters are summarized in Table 1.

For all structures H atoms were located in a difference Fourier map. N-bound H atoms were freely refined. In **4** methanol and water H atoms were identified from difference Fourier maps and their positions were restrained to target locations based on optimal hydrogen bonding. C-Bound H atoms were refined with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ for all H atoms except methyl H atoms which were refined with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$. C–H distances were constrained to 1.0 Å (methine), 0.99 Å (methylene), 0.98 Å (methyl) and 0.95 Å (aromatic).

The crystal used for **1** was twinned. The two components of the diffraction pattern were easily deconvoluted (twin law: $-1\ 0\ 0/0\ 1\ 0/0\ 0\ -1$) and the refined twin scale fraction is 0.4938(8). For the structure of **3** one molecule of solvent ethyl acetate is present per asymmetric unit. This cannot be modeled using discrete atoms due to a combination of whole-molecule disorder and disorder across an inversion center, and so the residual electron density associated with this molecule was removed using the SQUEEZE routine of PLATON.¹¹

Conclusions

Three compounds, each derived from Fentanyl and differing essentially only in the length of a carboxylic acid chain, have yielded four crystal structures three of which share several structural similarities, including the length of the chain, while the fourth, with a shorter chain, is quite different. Compounds **2–4** all have a ‘three atom’ chain between the carbonyl and carboxylate C atoms.[§] This chain is of sufficient length to allow the carboxylic acid group to interact with the N atom of the piperidine ring without steric strain caused by the aminophenyl rings. A space fill view of the large $R^2_2(24)$ hydrogen-bonded ‘dimer’ motif between adjacent zwitterions dimer, shown in Fig. S2[†], shows how two adjacent zwitterions interlock quite well in the crystal packing. Such a motif is not possible with the ‘two atom’ chain of compound **1** since this is not long enough to defeat the steric problems posed by bulkier groups. Compounds **2–4** were also all solvate structures whereas **1** is solvent-free. The formation of this large dimer leaves available a second carboxylate O atom to take part in hydrogen bonding interactions with solvent molecules. In **1** this is not possible as the packing of hydrogen-bonded chains orients the second carboxylate O atom towards C–H groups and so there is little scope for participation in hydrogen bonding with solvent molecules. Crystals of **2–4** were also easily grown. With **1** repeated recrystallization was needed and even then the best crop of crystals required the use of synchrotron radiation. Based on this it may be reasonable to assume that the three-chain acid group allows for the formation of the zwitterionic ‘dimer’ which provides for some stability in crystal growth not present with a two atom chain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

[§]Although in **2** a methylene group has been replaced by an ether link, the preference of O for *pseudo*-tetrahedral geometry, and the unhindered rotation of C–O bonds, makes this link structurally similar to CH₂. Since we are only concerned here with chain length then we can consider the three atom chain in **2** to be no different from **3** and **4**.

Acknowledgments

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Fig. 1.
The molecular structures of **1–3** (top, center, and bottom, respectively) with displacement ellipsoids at the 50% probability level. Solvent molecules and C-bound H atoms have been omitted.

Fig. 2.
The two unique molecules (top and bottom) in **4**. Displacement ellipsoids are at the 50% probability level; solvent molecules and C-bound H atoms have been omitted.

Fig. 3. Top: propagation of a hydrogen-bonded chain along the *a* axis in **1**. Bottom: bifurcated C–H...O interactions in the crystal packing of **1**. In both diagrams blue dashed lines indicate hydrogen bonding and red dashed lines indicate hydrogen bond continuation.

Fig. 4. Hydrogen bonding interactions in **2** form a thick two-dimensional sheet. The color scheme used is the same as in Fig. 3.

Fig. 5.
An overlay of molecule A (orange) and molecule B (black) in **4** formed by a least-squares fit of all six non-hydrogen atoms of the two piperidine rings, with an rms deviation of 0.0159 Å.

Fig. 6. Hydrogen bonding patterns formed between symmetry-equivalent zwitterions (colored according to the scheme in Fig. 5) and solvent methanol and water in **4**.

Fig. 7.

The hydrogen-bonded sheet structure of **4**, shown in space fill representation with the same view direction as Fig. 6.

Scheme 1.

Table 1Experimental crystallographic parameters for **1–4**

Compound reference	1	2	3	4
Chemical formula	C ₂₃ H ₂₈ N ₂ O ₃	C ₂₃ H ₂₈ N ₂ O ₄ ·H ₂ O·0.5CH ₄ O	C ₂₄ H ₃₀ N ₂ O ₃ ·C ₄ H ₈ O ₂	2C ₂₄ H ₃₀ N ₂ O ₃ ·2H ₂ O·CH ₄ O
Formula mass	380.47	430.51	482.60	857.07
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
<i>a</i> /Å	19.1839(8)	9.2383(5)	9.3005(4)	9.3807(4)
<i>b</i> /Å	9.7221(4)	9.3034(5)	9.7222(5)	14.8290(7)
<i>c</i> /Å	22.3927(10)	14.4329(8)	14.4230(7)	17.4244(9)
<i>α</i> /°	90	75.858(3)	78.622(4)	85.655(4)
<i>β</i> /°	99.843(10)	80.777(3)	75.813(3)	78.993(4)
<i>γ</i> /°	90	74.672(3)	74.623(3)	76.609(3)
Unit cell volume/Å ³	4114.9(3)	1154.00(11)	1206.84(10)	2313.31(19)
Temperature/K	100(2)	100(2)	100(2)	100(2)
Space group	<i>I</i> 2/ <i>a</i>	<i>P</i> 1 [−]	<i>P</i> 1 [−]	<i>P</i> 1 [−]
No. of formula units per unit cell, <i>Z</i>	8	2	2	2
Radiation type	Synchrotron	CuKα	CuKα	CuKα
No. of reflections measured	77 585	7213	12 803	19 578
No. of independent reflections	5087	4051	4181	8140
<i>R</i> _{int}	0.043	0.016	0.040	0.046
Final <i>R</i> ₁ values (<i>I</i> > 2σ(<i>I</i>))	0.041	0.044	0.050	0.052
Final w <i>R</i> (<i>F</i> ²) values (<i>I</i> > 2σ(<i>I</i>))	0.106	0.126	0.129	0.138
Final <i>R</i> ₁ values (all data)	0.047	0.053	0.064	0.070
Final w <i>R</i> (<i>F</i> ²) values (all data)	0.110	0.134	0.137	0.148

Table 2Hydrogen bonds for **1–4** (Å and °)^a

D–H...A	<i>d</i> (D...H)	<i>d</i> (H...A)	<i>d</i> (D...A)	∠(DHA)
Compound 1				
O(2)–H(2O)···N(2 ⁱ)	1.22(2)	1.34(2)	2.5505(12)	170(2)
C(23)–H(23)···O(1 ⁱⁱ)	0.95	2.42	3.3311(14)	160
C(13)–H(13A)···O(2 ⁱⁱⁱ)	0.99	2.40	3.2783(13)	147
C(14)–H(14B)···O(3 ^{iv})	0.99	2.39	3.2398(13)	144
C(16)–H(16A)···O(3 ^{iv})	0.99	2.45	3.3148(13)	146
Compound 2				
N(2)–H(2N)···O(3 ^v)	0.98(3)	1.66(3)	2.640(2)	171(2)
O(5)–H(5A)···O(4)	0.95(4)	1.88(4)	2.826(2)	175(4)
O(5)–H(5B)···O(4 ^{vi})	0.91(5)	2.01(5)	2.861(3)	155(4)
O(6)–H(6A)···O(5)	0.84	1.84	2.654(6)	162
C(10)–H(10)···O(1 ^{vii})	0.95	2.50	3.395(2)	157
C(23)–H(23)···O(6 ^{viii})	0.95	2.58	3.384(5)	142
Compound 3				
N(2)–H(2N)···O(3 ^{viii})	1.13(2)	1.47(2)	2.5800(18)	168(2)
Compound 4				
N(2)–H(2N)···O(3 ^{ix})	0.93(3)	1.72(3)	2.648(2)	176(3)
N(2)–H(2N)···O(2 ^{ix})	0.93(3)	2.61(3)	3.230(2)	125(2)
N(52)–H(52N)···O(53 ^x)	1.13(3)	1.44(3)	2.563(2)	176(3)
N(52)–H(52N)···O(52 ^x)	1.13(3)	2.60(3)	3.336(3)	122(2)
O(4)–H(4O)···O(6)	0.84	1.95	2.783(3)	171
O(5)–H(51O)···O(2)	0.863(10)	1.909(12)	2.764(3)	171(3)
O(5)–H(52O)···O(4)	0.866(10)	1.942(11)	2.798(3)	169(3)
O(6)–H(61O)···O(5 ^{xi})	0.855(10)	1.966(17)	2.788(4)	161(4)
O(6)–H(62O)···(52 ^{xii})	0.838(10)	2.104(14)	2.925(3)	167(4)

^aSymmetry operations for equivalent atoms: (i) $x - 1/2, -y + 2, z$; (ii) $x + 1/2, -y + 2, z$; (iii) $-x + 1/2, -y + 3/2, -z + 1/2$; (iv) $-x + 1/2, -y + 5/2, -z + 1/2$; (v) $-x + 1, -y + 1, -z + 1$; (vi) $-x + 1, -y + 2, -z$; (vii) $x + 1, -y + 2, -z + 1$; (viii) $-x, -y + 1, -z + 1$; (ix) $-x, -y + 1, -z + 1$; (x) $-x, -y + 1, -z$; (xi) $-x + 1, -y + 2, -z + 1$; (xii) $x + 1, y, z$.