Seven 3-methylidene-1,3-dihydro-2H-indol-2-ones related to the multiple receptor tyrosine kinase inhibitor sunitinib.

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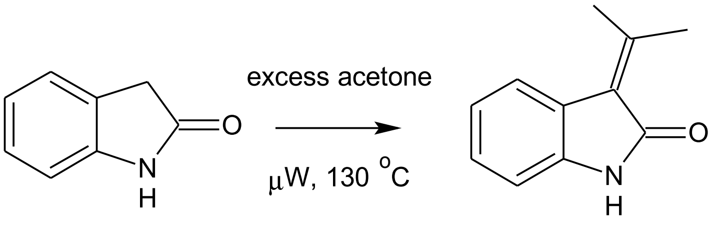
Details of Synthetic Optimisation Studies

Brief optimisation studies were conducted in the microwave mediated synthesis of **4a** and are presented in Table S1. An initial conversion of 60% to **4a** (Entry 1) was observed. Entries 3 and 4 show that increasing the initial power (from 150 W to 300 W) or the reaction time (from 10 to 20 min) does not lead to improved conversions. An absence of piperidine leads to low or zero conversion to **4a** (Entries 2 and 6). The highest conversions were observed when the reaction was carried out in the presence of piperidine, in EtOH, using a large excess of acetone, for 30 min at either 130 or 150 ºC (90%, Entry 5) although isolated yields were lower (*vide infra*, Entry 5, Table S2) due to losses during extraction/purification.



oxindole **4a**

Table S1. Optimised microwave mediated route to **4a**.

Entry	Initial Power (W)[a]	Time (min)	Added reagents	% Conversion to **4a**[b]
1	150	10	EtOH, piperidine.	60
2	150	10	EtOH	20
3	300	10	EtOH, piperidine.	60
4	150	20	EtOH, piperidine.	60
5	150	30	EtOH, piperidine.	90, 90[c]
6	150	20	-	0

[a] with Pmax (constant cooling). [b] by ^{1}H-NMR. [c] at 150 ºC, 0.5 h.

A series of condensation products, **2**-**4**, were synthesised using either the literature (thermal) route, or employing the microwave mediated method optimised for **4a** (Entry 5, Table S1). The thermal method gave higher yields of isolated product and the regiochemical outcome of both routes was identical, by ^{1}H-NMR spectroscopic comparison; for example, **3b** was found to exist as a *ca.* 5:1 ratio of regioisomers, with the major product assigned as the (*E*)-isomer (Boiadjiev & Lightner, 2003). The attempted microwave mediated syntheses of the thiophene and the cyclohexyl analogues **2b** and **4c**, respectively, were far inferior to the thermal mediated routes.

Table S2. Microwave mediated Knoevenagel condensations of oxindole.

Entry	Compound Number	Thermal method % isolated yield[a]	Microwave method % isolated yield[b]
1	**2a**	84	60
2	**2b**	79	-
3	**3a**	79	72
4	**3b**[c]	90	71
5	**4a**	92	70
6	**4c**	88	36

[a]3h, reflux in EtOH. [b]0.5h, 150 ºC, Pmax (constant cooling). [c] mixture of regiosiomer.

Figures S1 – S4: Views of the hydrogen-bonded dimers formed in structures 2a, 2b, 4c and 5

Figure S1. View of the hydrogen-bonded dimer found in structure **2a** showing the N-H…O intramolecular interaction. Carbon atoms are shown in black, nitrogen in blue, oxygen in red and hydrogen in gold. The symmetry operation used to generate the equivalent position of the lower molecule is: 1-x, -y, 1-z.

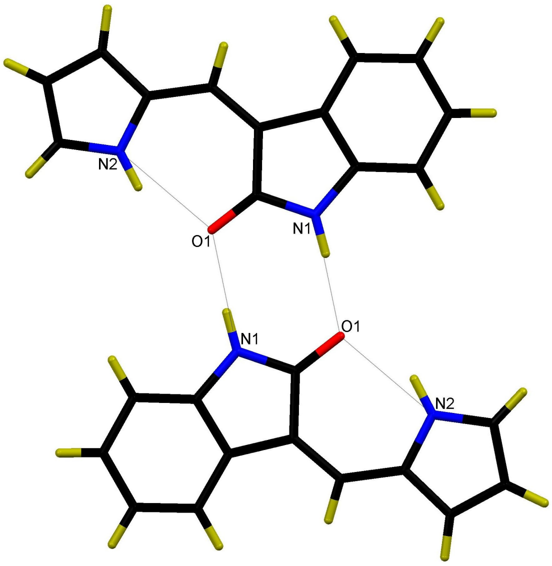


Figure S2. View of the hydrogen-bonded dimer found in structure **2b** showing the S…O intramolecular interaction. Carbon atoms are shown in black, nitrogen in blue, oxygen in red, sulphur in yellow and hydrogen in gold. The symmetry operation used to generate the equivalent position of the lower molecule is: 1-x, 1-y, 1-z.

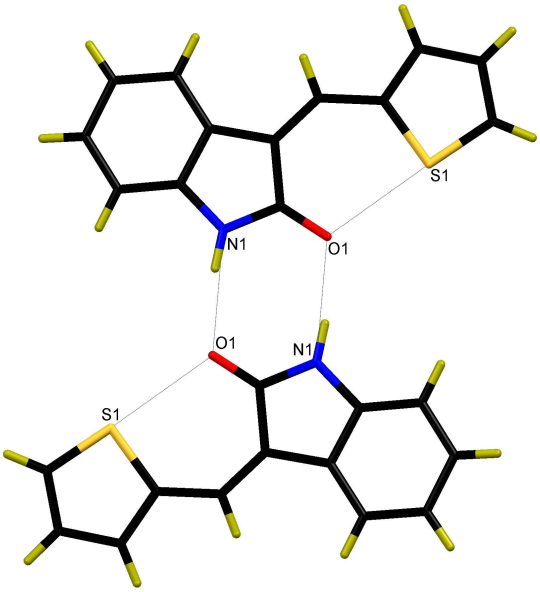


Figure S3. View of the hydrogen-bonded dimer found in structure **4c**. Carbon atoms are shown in black, nitrogen in blue, oxygen in red and hydrogen in gold. The symmetry operation used to generate the equivalent position of the right hand molecule containing O1 is: 3-x, 1-y, -z while that used to generate the equivalent position of the left hand molecule containing O101 is: 2-x, -y, 1-z.

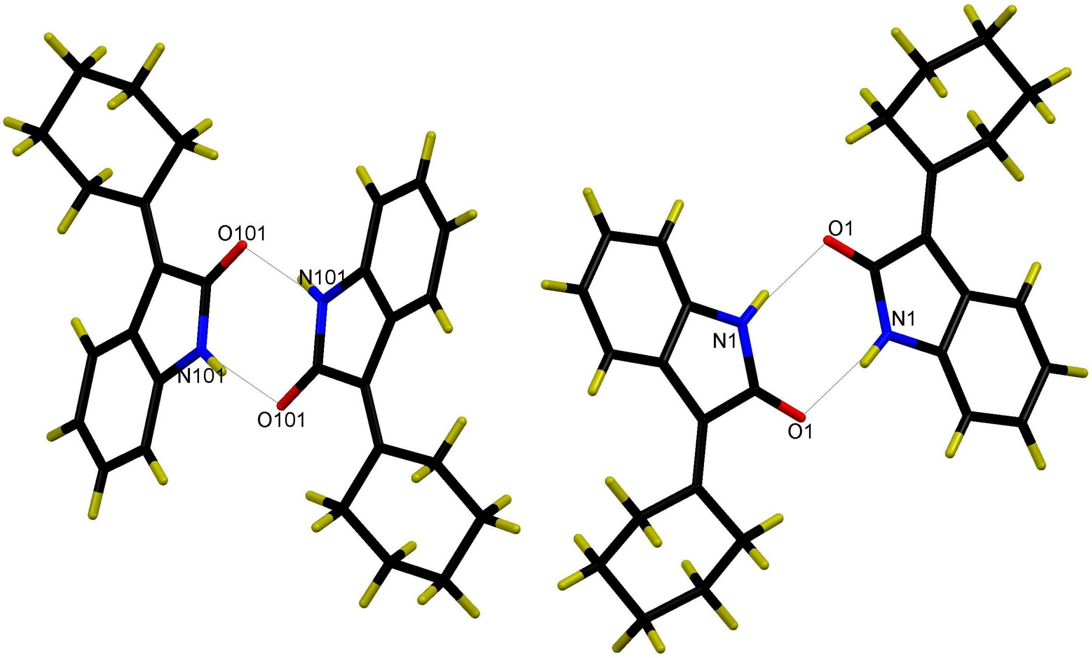
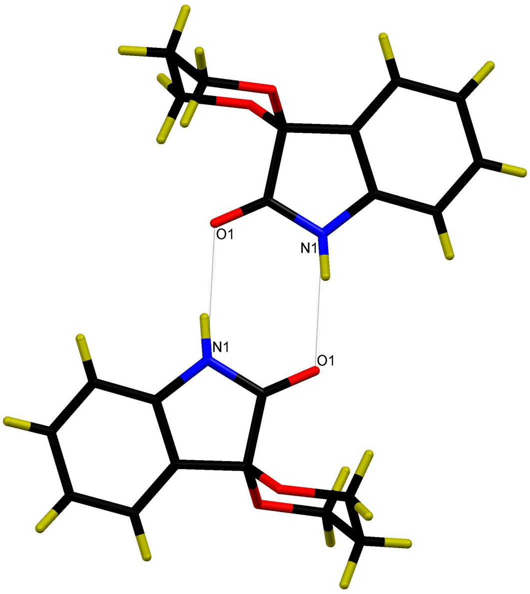


Figure S4. View of the hydrogen-bonded dimer found in structure **5**. Carbon atoms are shown in black, nitrogen in blue, oxygen in red and hydrogen in gold. The symmetry operation used to generate the equivalent position of the lower molecule is: 2-x, -y, 1-z.



Figures S5 – S10: Views of the structure packing in structures 2a, 2b, 4a, 4b, 4c and 5

Figure S5. Packing of the molecular hydrogen-bonded dimers in **2a** with hydrogen atoms omitted for clarity. Carbon atoms are shown in black, nitrogen in blue and oxygen in red. Molecules are connected via π -π stacking, (with an inter-planar separation of 3.3 Å), forming columns of dimers along the (0 1 0) direction. These columns are arranged side-by-side along the (1 0 0) (**A**) and (0 0 1) (**B**) directions in a herringbone arrangement.

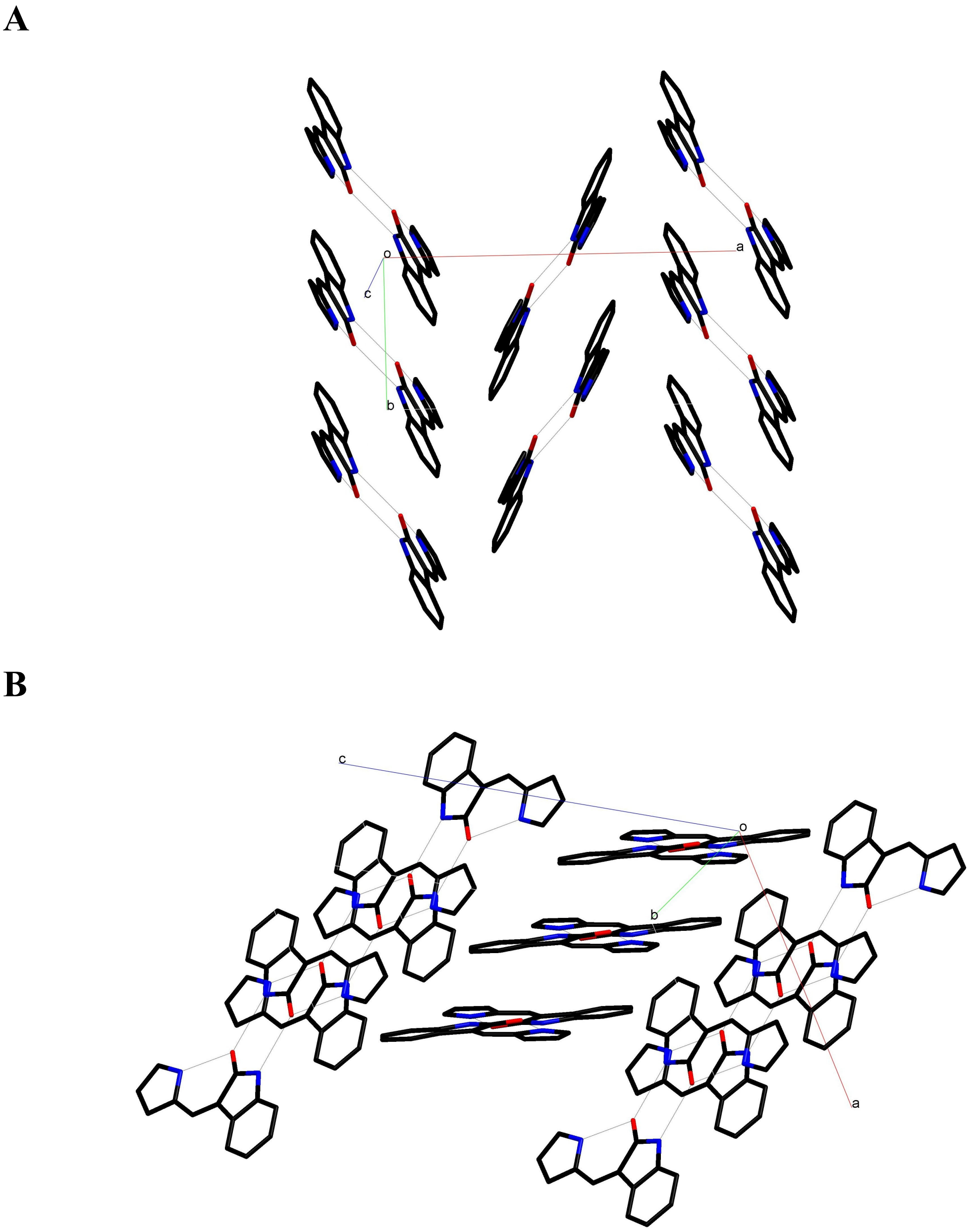
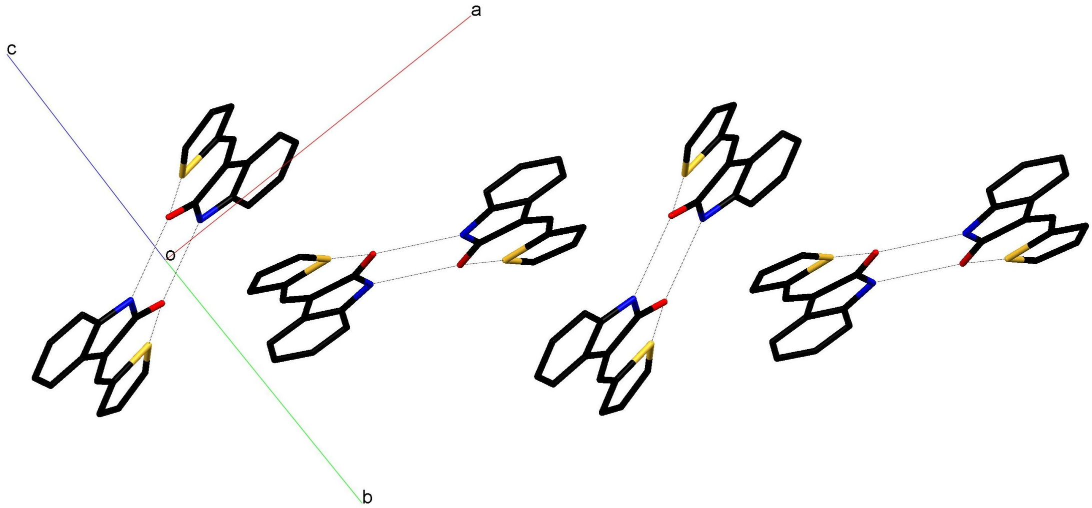


Figure S6. Packing of the molecular hydrogen-bonded dimers in **2b** with hydrogen atoms omitted for clarity. Carbon atoms are shown in black, nitrogen in blue, oxygen in red and sulphur in yellow. (**A**) The dimers form columns in the (1 1 0) direction with an inter-planar distance between molecules of approximately 3.6 Å. (**B**) The columns are arranged in the (0 0 1) direction in a herringbone arrangement.

A



B

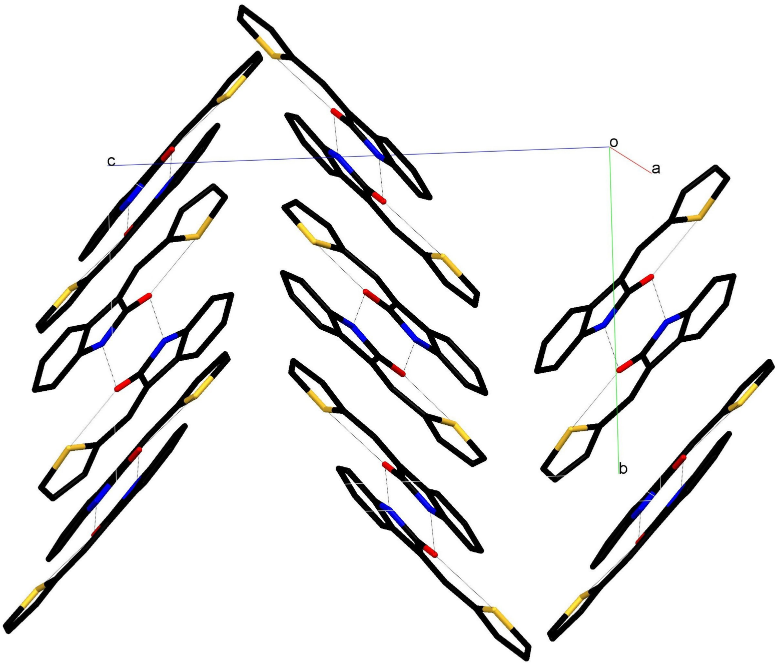


Figure S7. View of the packing of the molecular hydrogen-bonded dimers in **4a**. The three crystallographically unique molecules of the asymmetric unit are coloured green

(O1 etc), blue (O101 etc) and red (O201 etc). Layers of dimers are stacked along the (0 1 0) direction via π -π stacking interactions with inter-planar distances of approximately 3.4 Å

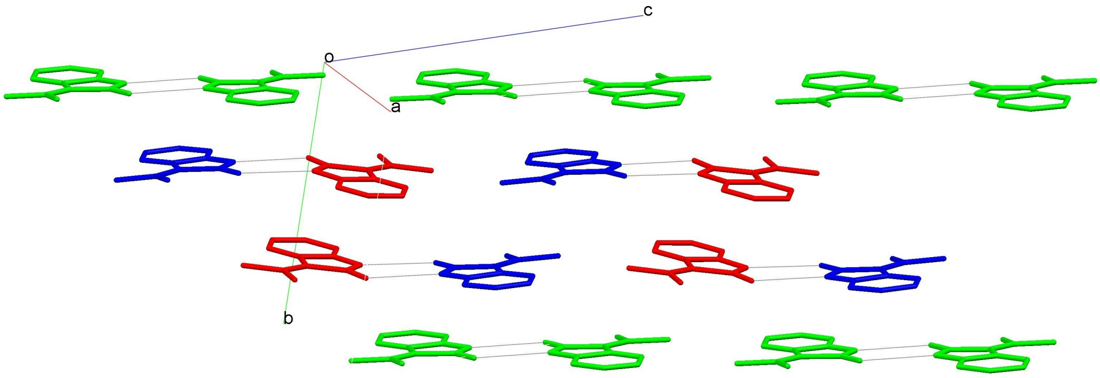


Figure S8. View of the packing of the molecular hydrogen-bonded dimers in **4b**. The two crystallographically unique molecules of the asymmetric unit are coloured red (O1 etc) and blue (O101 etc) and are arranged alternately in columns along the (1 0 1) direction forming π -π stacking interactions with inter-planar distances of approximately 3.4 Å and 3.5 Å.

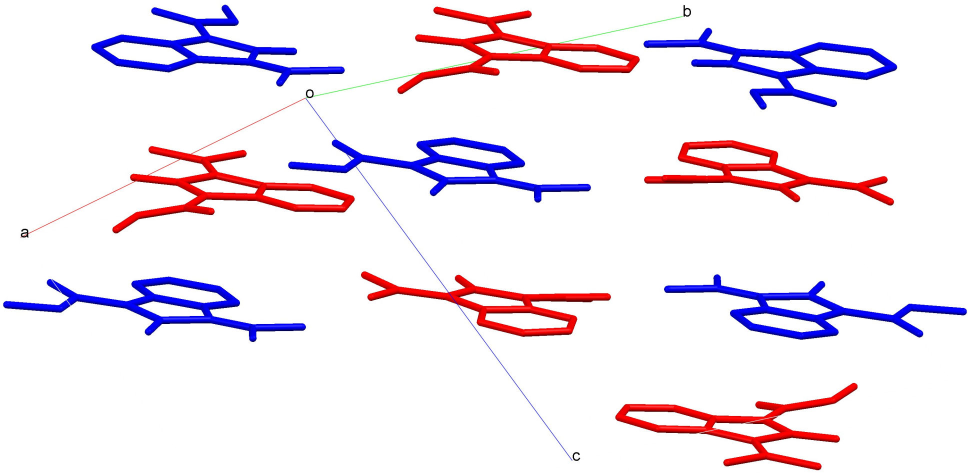


Figure S9. View of the packing of the molecular hydrogen-bonded dimers in **4c**. The two crystallographically unique molecules of the asymmetric unit are coloured red (O1 etc) and blue (O101 etc) and the two types of dimer they form are stacked in columns in the (1 0 0) direction via π -π interactions with close inter-planar separations of 3.1 Å in both cases. These columns are arranged side-by-side to form a herringbone pattern.

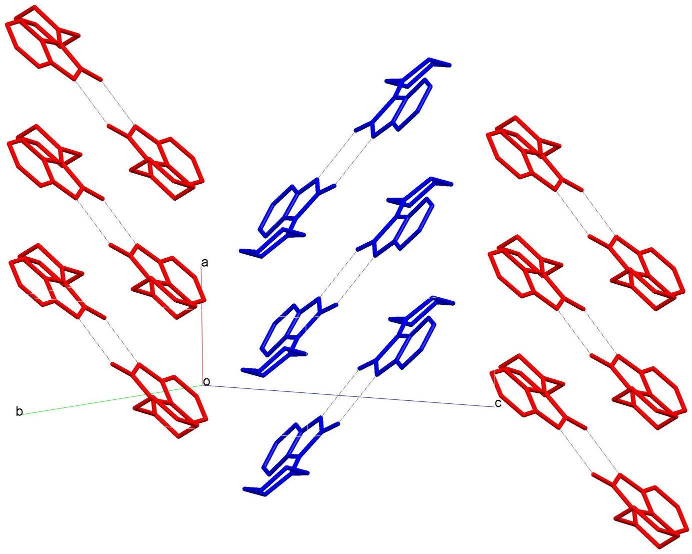
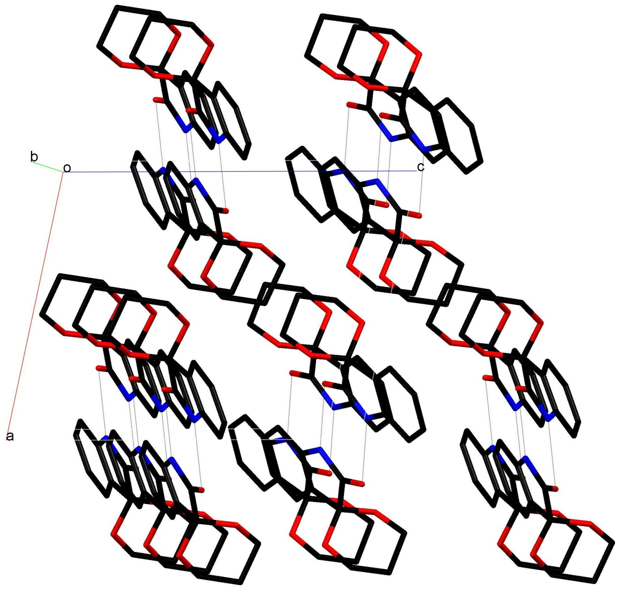


Figure S10. Packing of the molecular hydrogen-bonded dimers in **5** with hydrogen atoms omitted for clarity. Carbon atoms are shown in black, nitrogen in blue and oxygen in red. Molecules are connected via π -π stacking, (with an inter-planar separation of 3.4 Å), forming columns of dimers along the (0 1 0) direction. These columns are arranged side-by-side along the (1 0 0) and (0 0 1) directions.



Analysis of the least squares planes in the seven reported structures

Table S3. Analysis of the least squares planes in the seven reported structures.

	2a	2b	3a	4a	4b	4c	5
Largest Devation from Plane 1 / Å[i]	0.012 (1) for O1	0.032 (2) for N1	0.047 (1) for O1	0.028 (2) for C3 0.011 (2) for C103 0.024 (2) for O201	0.032 (1) for C2 0.073 (1) for O101	0.041 (2) for C2 0.081 (1) for O101	0.028 (1) for C2
Largest Deviation from Plane 2 / Å[i]	0.013 (1) for C9	0.014 (2) for C10	0.010 (1) for C9	N/A (3 atoms only)	0.002 (1) for C12 0.011(1) for C112	N/A (3 atoms only)	N/A (3 atoms only)
Angle Between Planes 1 and 2 / °[i]	5.0 (1)	6.8 (1)	4.3 (1)	3 (2)[ii]	10 (8)[ii]	11 (2)[ii]	88.8 (1)
Largest Deviation from Plane 3 / Å[i]	0.108 (2) for C13	0.155 (2) for C13	0.082 (2) for C13	0.086 (2) for C11 0.103 (2) for C110 0.029 (2) for O201	0.308 (1) for O2 0.166 (1) for O102	0.154 (2 for C10 0.859 (2) for C111	N/A

[i] Plane 1 is the least squares plane through atoms C1-C8, N1 and O1 (or C101 etc and C201 etc). For **2a**, **2b**, **3a** and **4a** Plane 2 is the least squares plane through the remaining non-hydrogen atoms, while for **4b** it is through atoms C12, C13, O2 and O3 (or C112 etc), for **4c** it is through atoms C9, C10 and C14 (or C109 etc) and for **5** it is through C2, O2 and O3. Plane 3 is the least squares plane through all non-hydrogen atoms in the molecule for **2a**, **2b**, **3a**, **4a** and **4b** and that through atoms C1-C10, C14, N1 and O1 (or C101 etc) for **4c**.

[ii] The reported values are averages of the parameters from the different crystallographically independent molecules in the asymmetric unit.

Boiadjiev, S. E. & Lightner, D. A. (2003). *Monatsh. Chem.* **134**, 489–499.