Supplementary Material

Modulation of the acidity of the 8-carboxamide group in the temozolomide family of antitumor imidazo[5,1-*d*][1,2,3,5]tetrazines†

Helen S. Summers,[a] Magdalena B. Foreiter,[a] William Lewis,[a] Christopher J. Moody,[a]* Tracey D. Bradshaw,[b]* and Malcolm F. G. Stevens[b]*

[a]School of Chemistry, and [b]School of Pharmacy, University of Nottingham, NG7 2RD UK
Email: c.j.moody@nottingham.ac.uk; tracey.bradshaw@nottingham.ac.uk

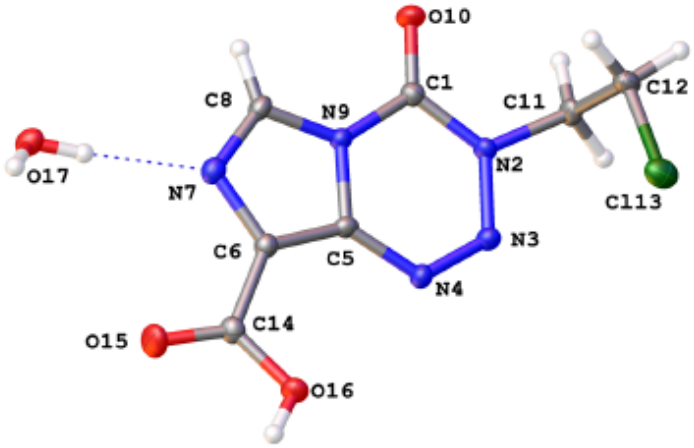
Table of Contents

Crystallography

Suitable crystals were selected and mounted in fomblin film on a Mitegen micromount on a SuperNova, Dual, Cu at zero, Atlas or SuperNova, Atlas S2 diffractometers. The crystals were kept at 120(2) K during data collection. Using Olex2,[ref 1] the structures were solved with the olex2 solve[ref 2] structure solution program using Charge Flipping and refined with the ShelXL[ref 3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. and Puschmann, H. *J. Appl. Cryst.* 2009, **42**, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. *Acta Cryst.* 2015, **A71**, 59-75.
3. Sheldrick, G.M. *Acta Cryst.* 2008, **A64**, 112-122.

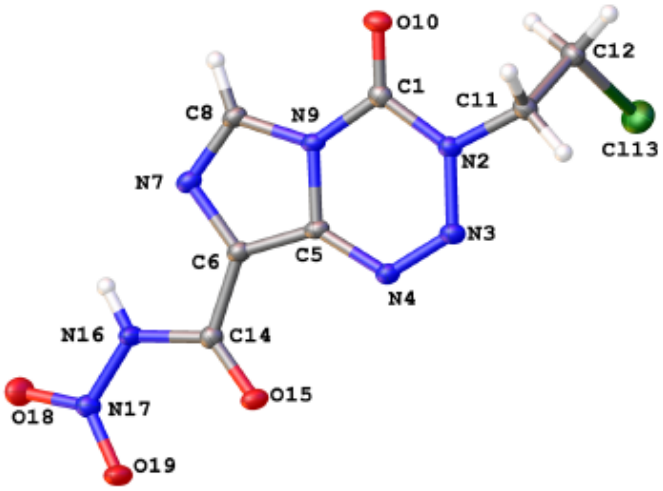
Figure S1. 3-(2-Chloroethyl)-4-oxoimidazo[5,1-*d*]-1,2,3,5-tetrazine-8-carboxylic acid (4) [CCDC 1896795].



Crystal data

Identification code	MBFCMI
Empirical formula	$C_7H_8ClN_5O_4$
Formula weight	261.63
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.0033(5)
b/Å	11.1738(4)
c/Å	7.5837(3)
α/°	90
β/°	97.003(4)
γ/°	90
Volume/Å³	1009.56(7)
Z	4
ϱ_{calc}g/cm³	1.721
μ/mm⁻¹	3.548
F(000)	536.0
Crystal size/mm³	0.2112 × 0.1306 × 0.1278
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.42 to 147.416
Index ranges	-14 ≤ h ≤ 10, -13 ≤ k ≤ 13, -9 ≤ l ≤ 9
Reflections collected	6041
Independent reflections	1982 [R_{int} = 0.0222, R_{sigma} = 0.0217]
Data/restraints/parameters	1982/0/164
Goodness-of-fit on F²	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0270, wR_2 = 0.0674
Final R indexes [all data]	R_1 = 0.0288, wR_2 = 0.0685
Largest diff. peak/hole / e Å⁻³	0.29/-0.23

Figure S2. 3-(2-Chloroethyl)-8-(*N*-nitrocarbamoyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (13) [CCDC 1894718].



Crystal data

Identification code	MBFCMD
Empirical formula	$C_7H_6ClN_7O_4$
Formula weight	287.64
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	5.2227(3)
b/Å	23.8305(14)
c/Å	8.9074(5)
α/°	90
β/°	96.809(6)
γ/°	90
Volume/Å^3	1100.79(11)
Z	4
ρ_{calc}g/cm^3	1.736
μ/mm^{-1}	3.379
F(000)	584.0
Crystal size/mm^3	0.5688 × 0.0612 × 0.0446
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.67 to 146.934
Index ranges	$-6 \le h \le 4$, $-29 \le k \le 20$, $-11 \le l \le 11$
Reflections collected	4075
Independent reflections	2151 [R_{int} = 0.0294, R_{sigma} = 0.0373]
Data/restraints/parameters	2151/0/172
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.1059
Final R indexes [all data]	R_1 = 0.0462, wR_2 = 0.1097
Largest diff. peak/hole / e Å^{-3}	0.41/-0.34

H-bonding interactions

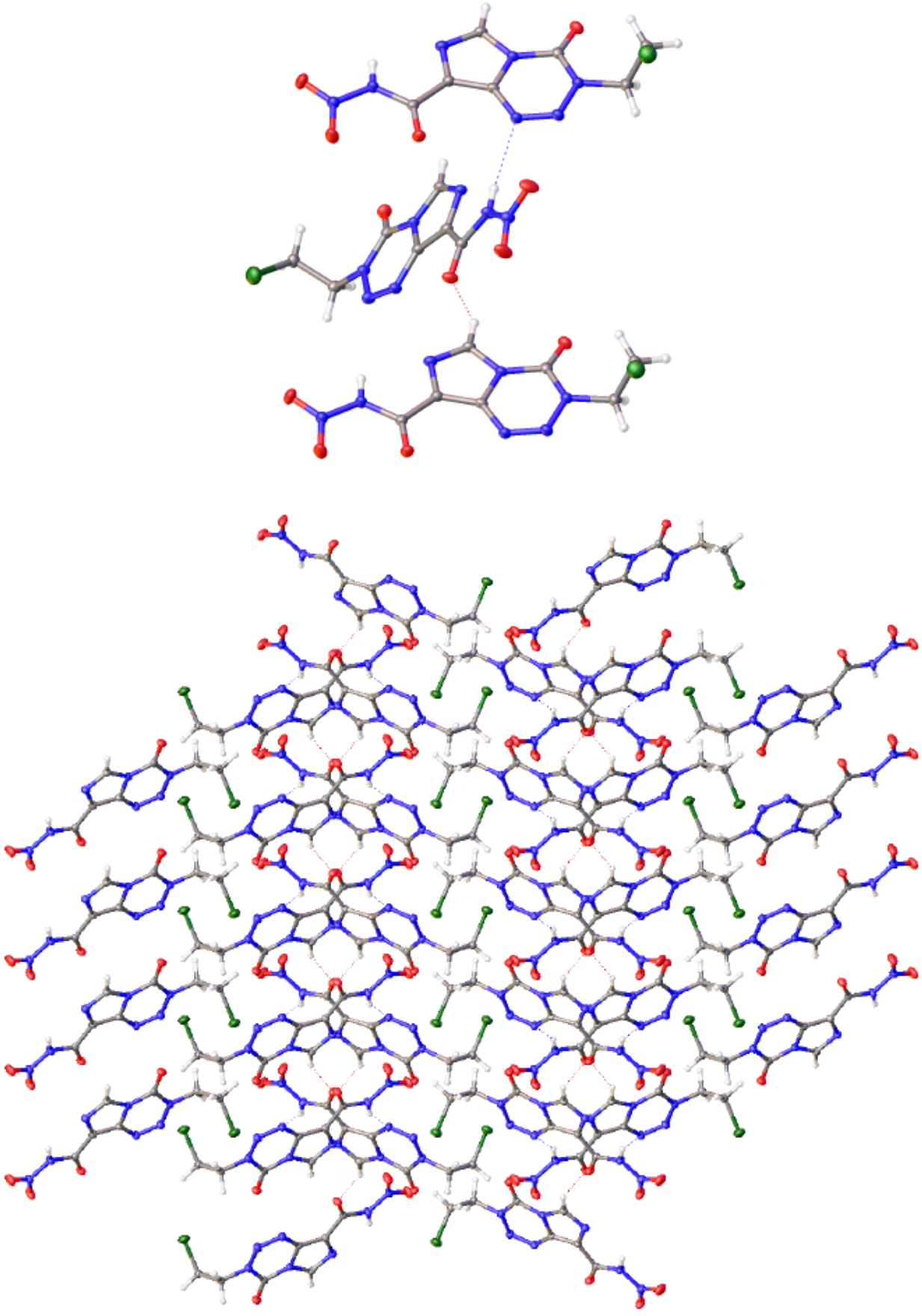
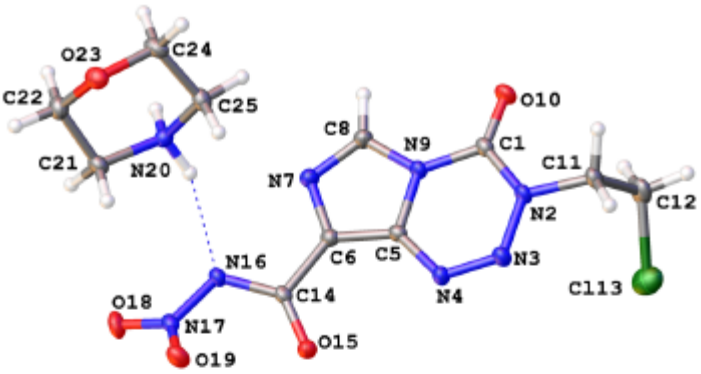


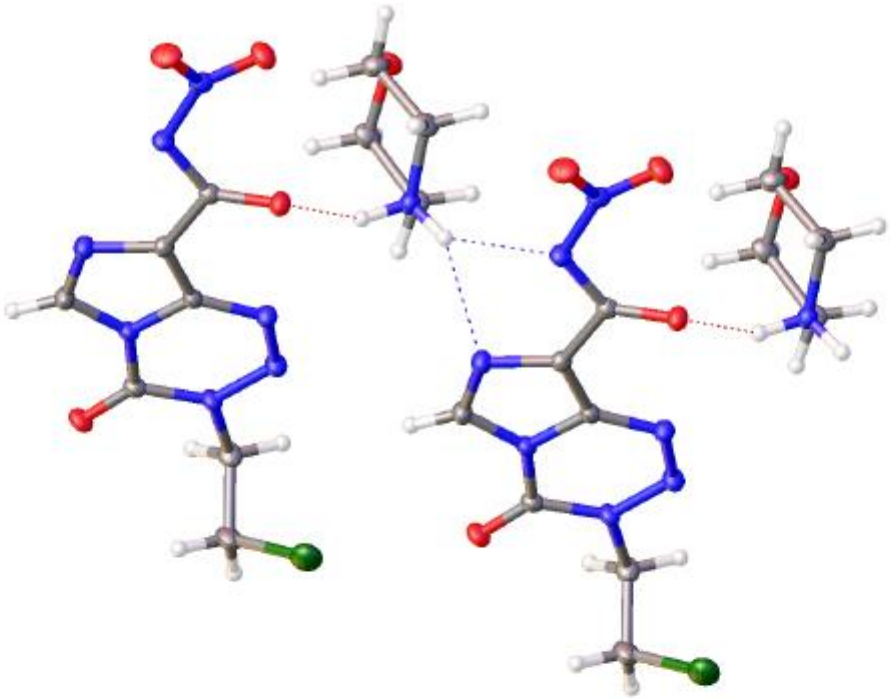
Figure S3. 3-(2-Chloroethyl)-8-(*N*-nitrocarbamoyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one morpholine salt [CCDC 1894720].

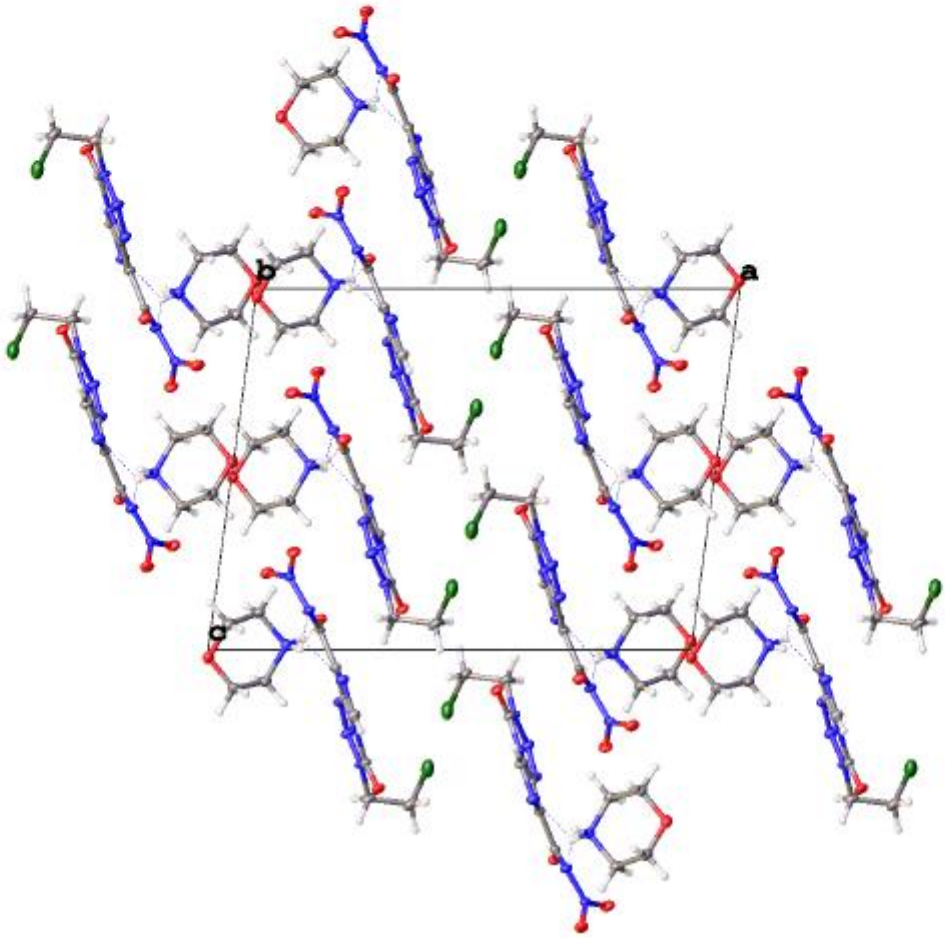


Crystal data

Identification code	MBFCMF
Empirical formula	$C_{11}H_{15}ClN_8O_5$
Formula weight	374.76
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	16.8896(15)
b/Å	7.2495(6)
c/Å	12.7286(11)
α/°	90
β/°	97.668(8)
γ/°	90
Volume/Å^3	1544.6(2)
Z	4
ρ_{calc}g/cm^3	1.612
μ/mm^{-1}	2.627
F(000)	776.0
Crystal size/mm^3	0.3783 × 0.2991 × 0.1806
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.57 to 147.44
Index ranges	$-18 \le h \le 20$, $-8 \le k \le 6$, $-15 \le l \le 15$
Reflections collected	6032
Independent reflections	3022 [R_{int} = 0.0302, R_{sigma} = 0.0296]
Data/restraints/parameters	3022/0/226
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0401, wR_2 = 0.1095
Final R indexes [all data]	R_1 = 0.0422, wR_2 = 0.1112
Largest diff. peak/hole / e Å^{-3}	0.35/-0.40

H-bonding interactions





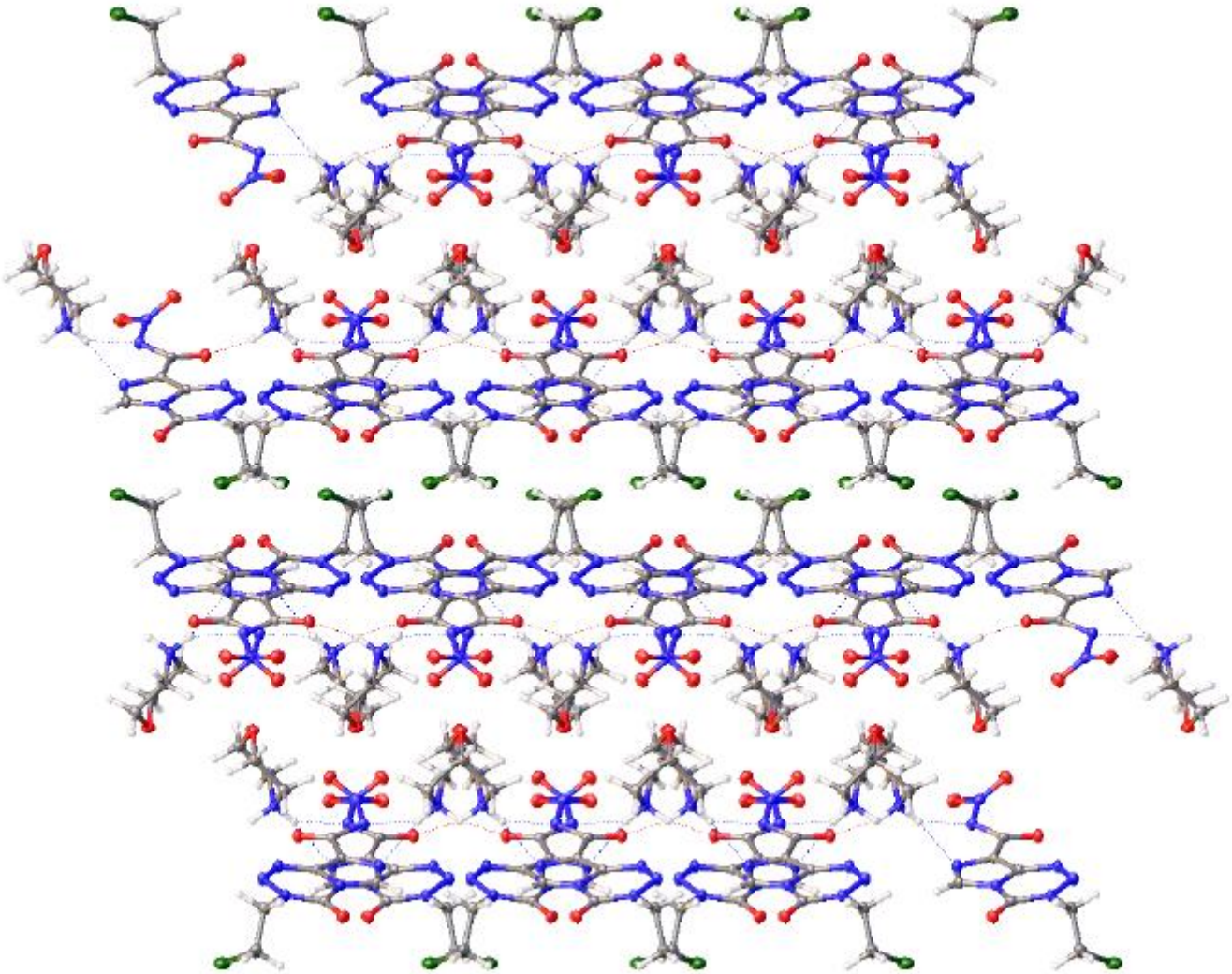
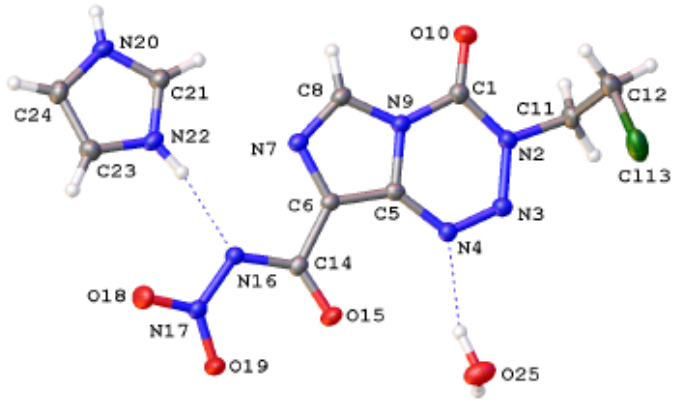


Figure S4. 3-(2-Chloroethyl)-8-(*N*-nitrocarbamoyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one imidazole salt hydrate [CCDC 1894722].



Crystal data

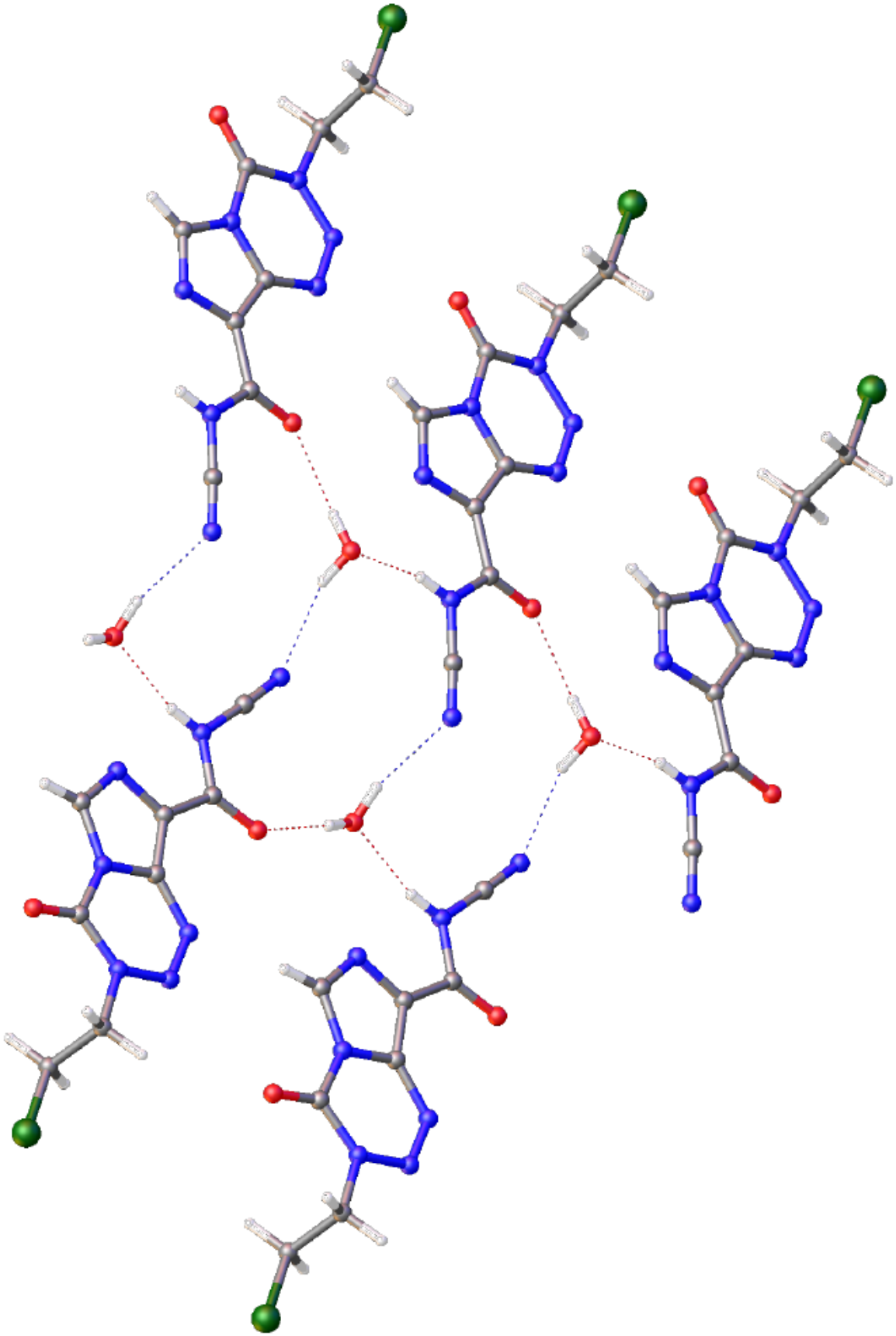
Identification code	MBFCMP
Empirical formula	$C_{10}H_{12}ClN_9O_5$
Formula weight	373.74
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	6.5419(3)
b/Å	9.2833(5)
c/Å	13.3123(8)
α/°	95.869(5)
β/°	94.373(5)
γ/°	107.232(5)
Volume/Å^3	763.28(8)
Z	2
ρ_{calc}g/cm^3	1.626
μ/mm^{-1}	2.679
F(000)	384.0
Crystal size/mm^3	0.237 × 0.132 × 0.036
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.718 to 148.468
Index ranges	$-6 \le h \le 7$, $-11 \le k \le 11$, $-16 \le l \le 16$
Reflections collected	5207
Independent reflections	2980 [R_{int} = 0.0209, R_{sigma} = 0.0299]
Data/restraints/parameters	2980/2/238
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0371, wR_2 = 0.0966
Final R indexes [all data]	R_1 = 0.0429, wR_2 = 0.1018
Largest diff. peak/hole / e Å^{-3}	0.29/-0.42

Figure S5. 3-(2-Chloroethyl)-8-(*N*-cyanocarbamoylimidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one hydrate (15) [CCDC 1895634].

Crystal data

Identification code	MBFCMK
Empirical formula	$C_8H_8ClN_7O_3$
Formula weight	285.66
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.0534(6)
b/Å	6.7162(2)
c/Å	14.8646(7)
α/°	90
β/°	109.249(5)
γ/°	90
Volume/Å³	1136.06(9)
Z	4
ϱ_{calc}g/cm³	1.670
μ/mm⁻¹	3.200
F(000)	584.0
Crystal size/mm³	0.4141 × 0.0386 × 0.0281
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.234 to 146.862
Index ranges	-14 ≤ h ≤ 13, -7 ≤ k ≤ 8, -18 ≤ l ≤ 13
Reflections collected	6446
Independent reflections	2234 [R_{int} = 0.0194, R_{sigma} = 0.0160]
Data/restraints/parameters	2234/0/181
Goodness-of-fit on F²	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0284, wR_2 = 0.0796
Final R indexes [all data]	R_1 = 0.0302, wR_2 = 0.0811
Largest diff. peak/hole / e Å⁻³	0.29/-0.34

H-bonding interactions



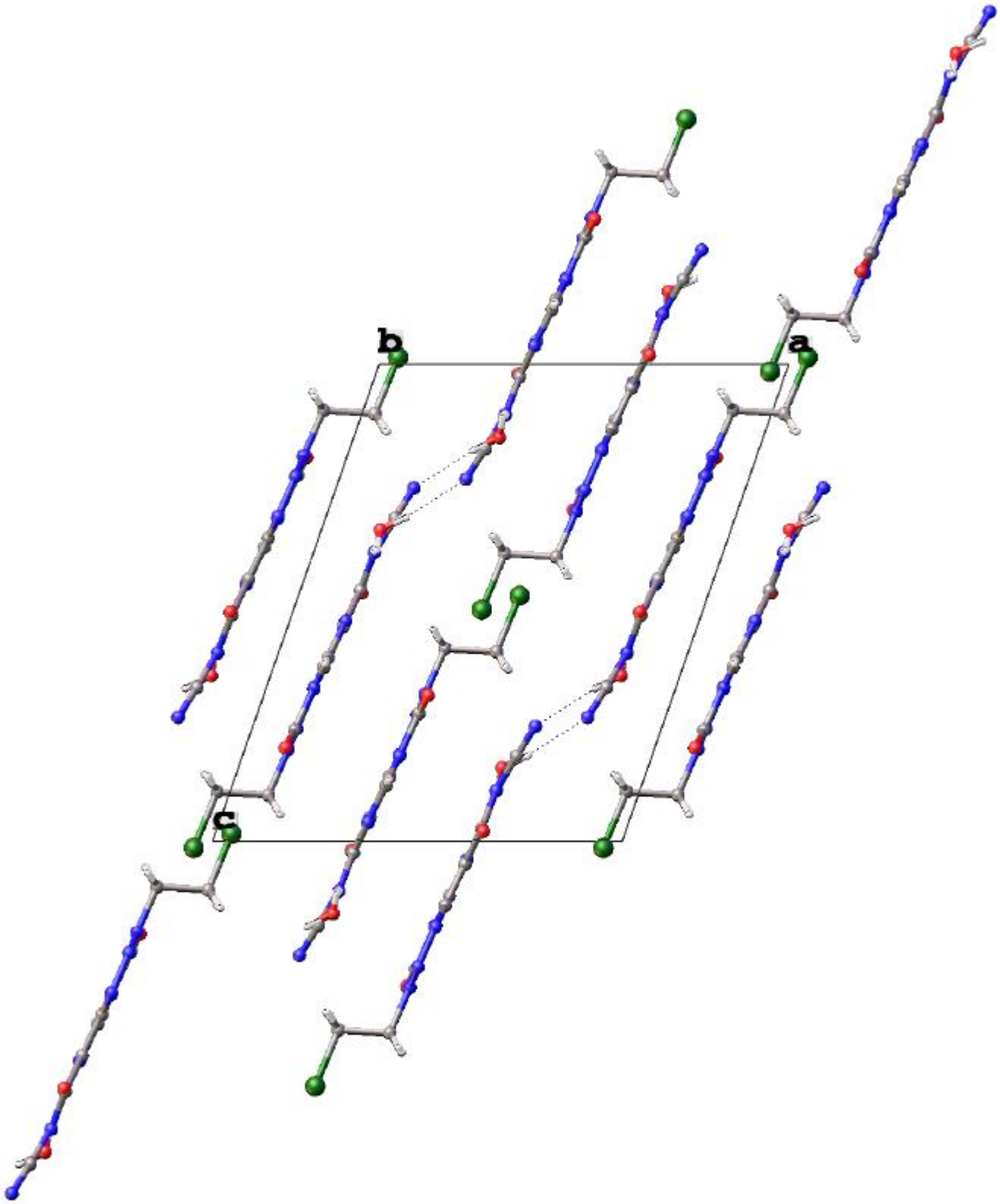
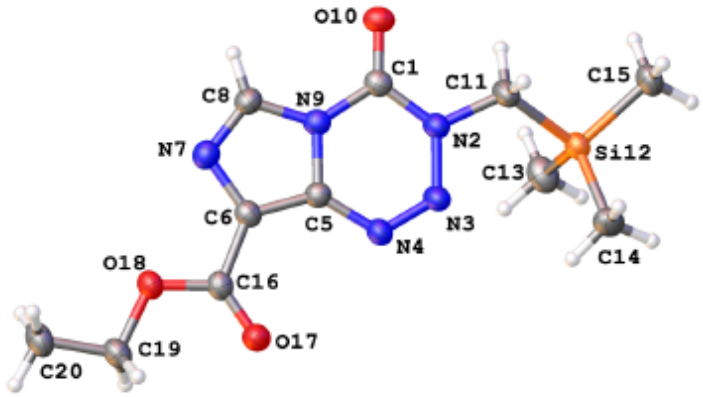


Figure S6. Ethyl 4-oxo-3-(trimethylsilylmethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazine-8-carboxylate (16) [CCDC 1896797].



Crystal data

Identification code	MBFCMN
Empirical formula	$C_{11}H_{17}N_5O_3Si$
Formula weight	295.38
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	14.9476(12)
b/Å	6.1486(6)
c/Å	16.0161(15)
α/°	90
β/°	95.442(8)
γ/°	90
Volume/Å³	1465.3(2)
Z	4
ϱ_{calc}g/cm³	1.339
μ/mm⁻¹	1.569
F(000)	624.0
Crystal size/mm³	0.192 × 0.162 × 0.021
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.732 to 151.912
Index ranges	-18 ≤ h ≤ 17, -6 ≤ k ≤ 7, -20 ≤ l ≤ 17
Reflections collected	12214
Independent reflections	2991 [R_{int} = 0.0517, R_{sigma} = 0.0411]
Data/restraints/parameters	2991/0/185
Goodness-of-fit on F²	1.094
Final R indexes [I>=2σ (I)]	R_1 = 0.0508, wR_2 = 0.1226
Final R indexes [all data]	R_1 = 0.0701, wR_2 = 0.1334
Largest diff. peak/hole / e Å⁻³	0.31/-0.27