

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[†]

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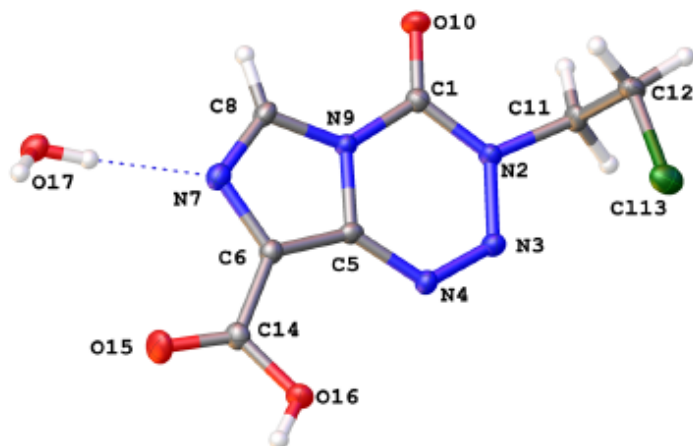
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Crystallography

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.

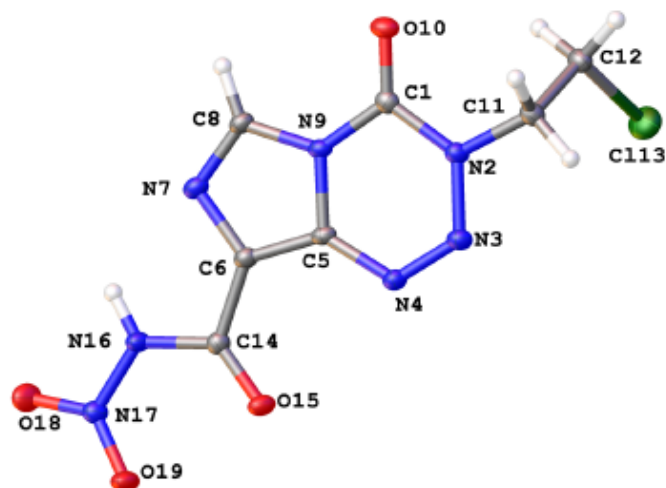
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. and Puschmann, H. *J. Appl. Cryst.* 2009, **42**, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. *Acta Cryst.* 2015, **A71**, 59-75.
3. Sheldrick, G.M. *Acta Cryst.* 2008, **A64**, 112-122.

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 ₇ H ₈ ClN ₅ O 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/Å ³	1009.56(7)
Z	4
ρ _{calc} /cm ³	1.721
μ/mm ⁻¹	3.548
F(000)	536.0
Crystal size/mm ³	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 F ²	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*-nitrocarbomoyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (13) [CCDC 1894718].

Crystal data

Identification code	MBFCMD
Empirical formula	C ₇ H ₆ ClN ₇ O 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} /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 ≤ h ≤ 4, -29 ≤ k ≤ 20, -11 ≤ l ≤ 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

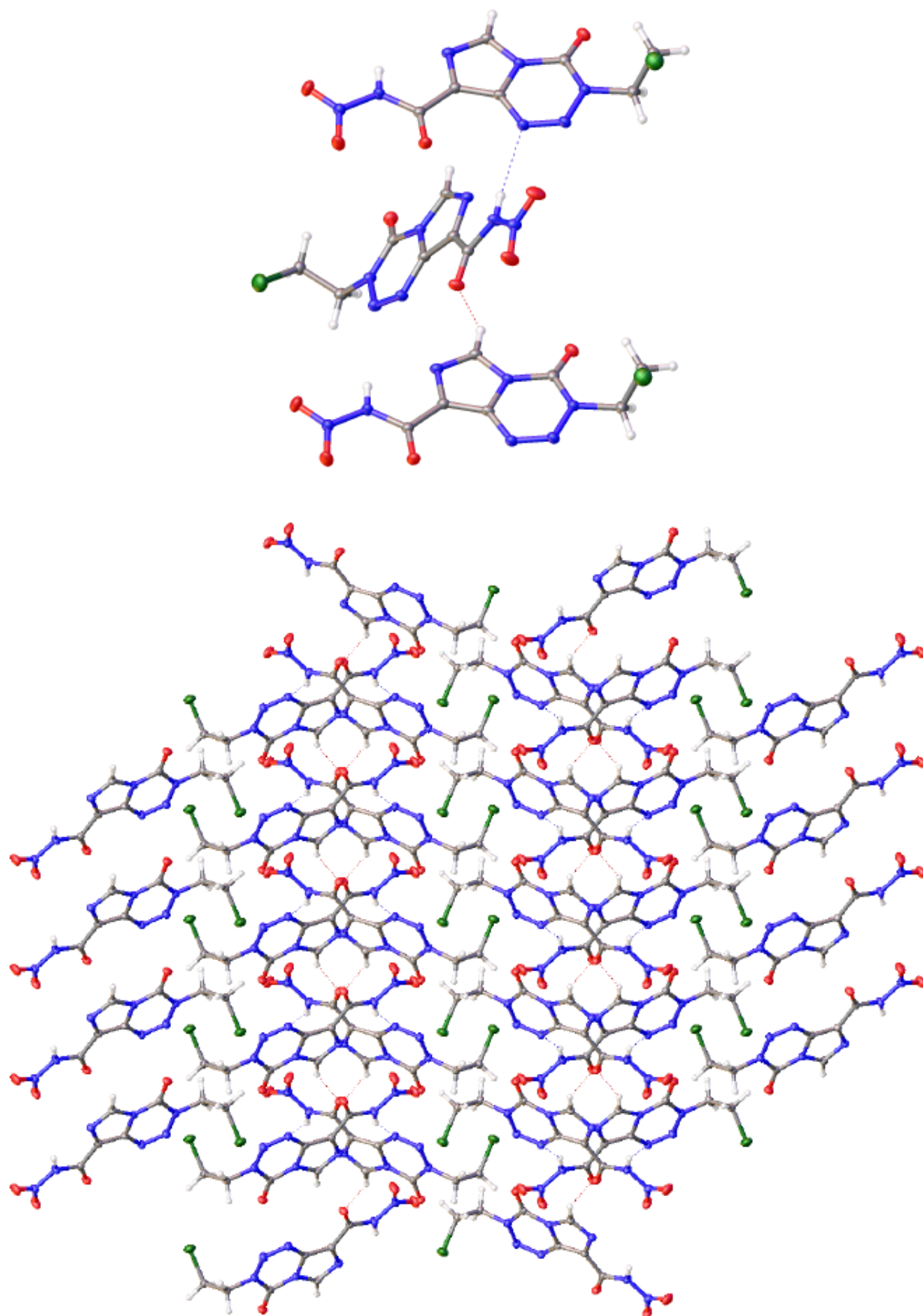
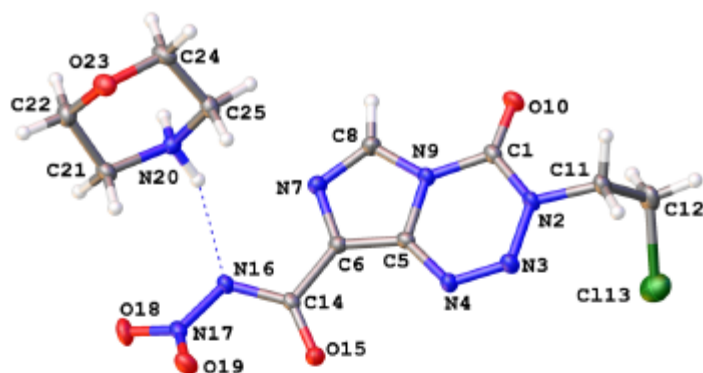


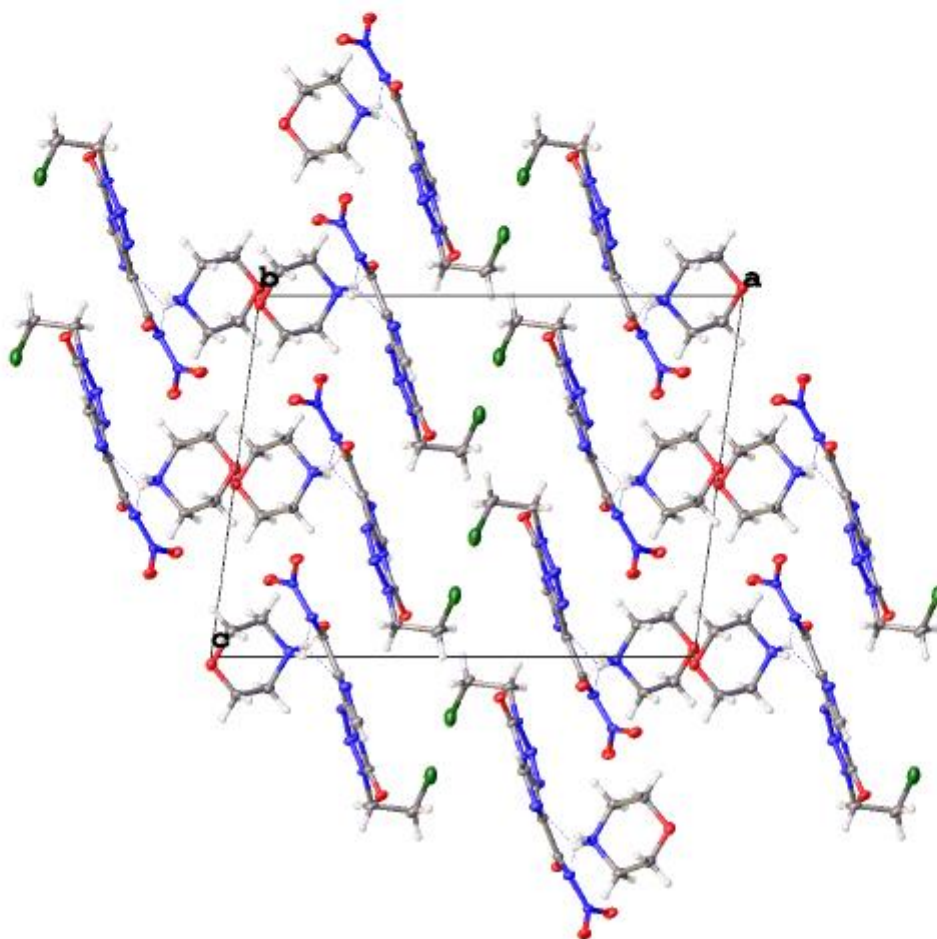
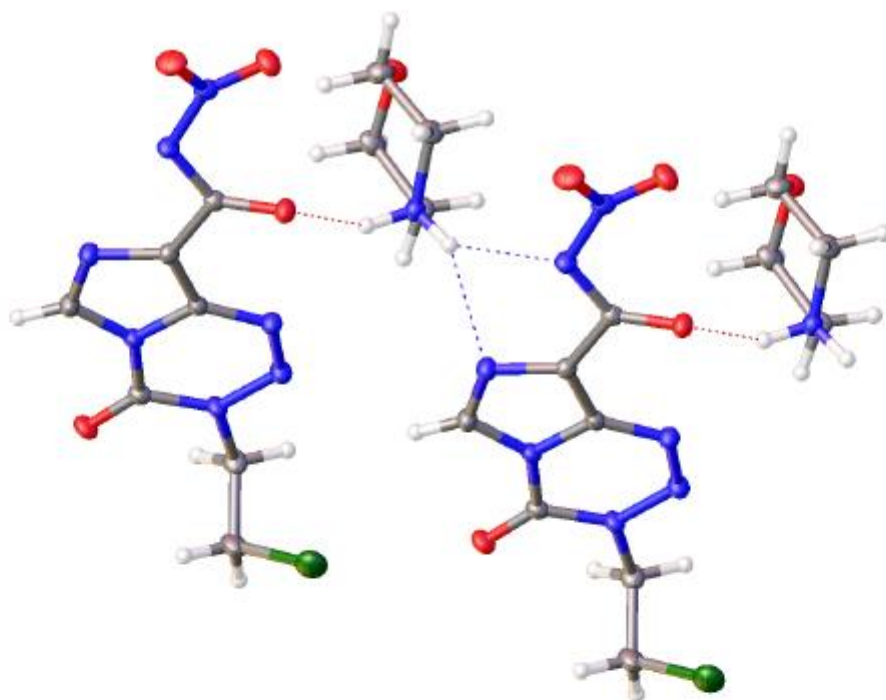
Figure S3. 3-(2-Chloroethyl)-8-(*N*-nitrocarbomoyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one morpholine salt [CCDC 1894720].



Crystal data

Identification code	MBFCMF
Empirical formula	C ₁₁ H ₁₅ ClN ₈ O 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} /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 ≤ h ≤ 20, -8 ≤ k ≤ 6, -15 ≤ l ≤ 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



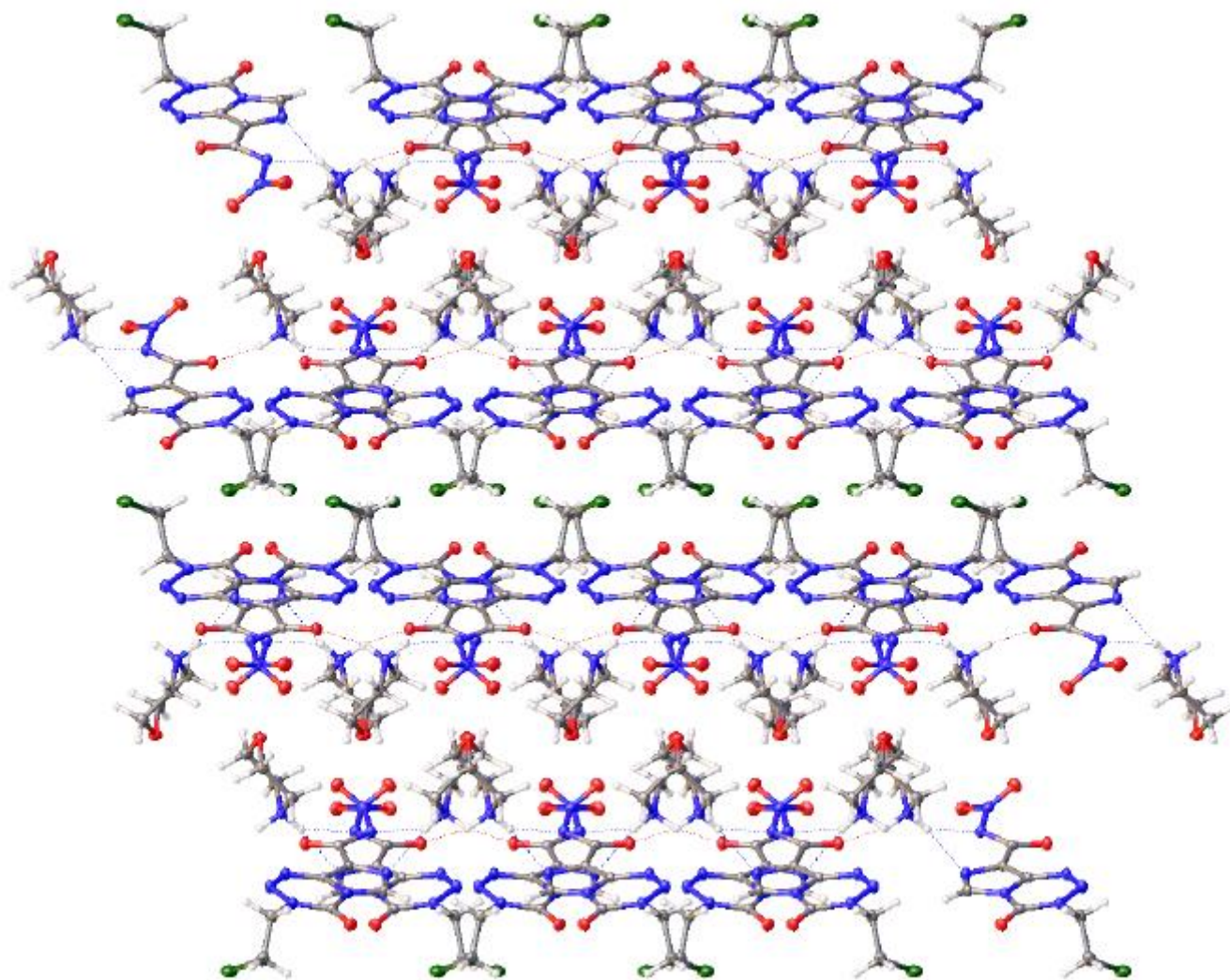
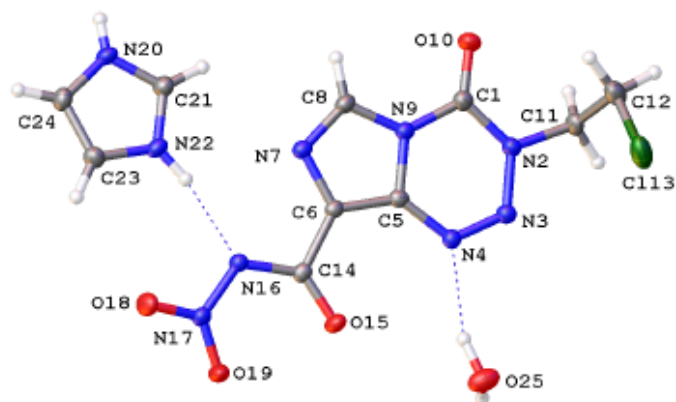
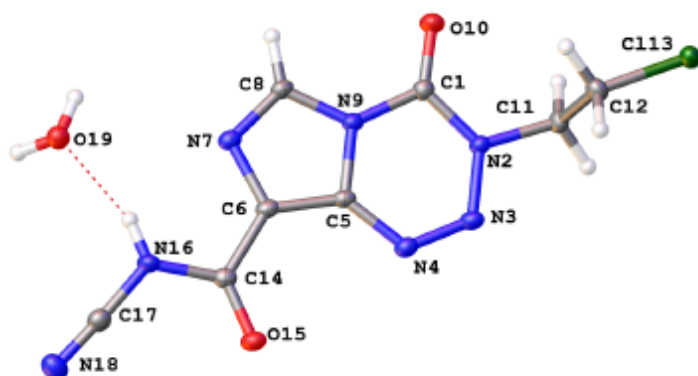


Figure S4. 3-(2-Chloroethyl)-8-(*N*-nitrocarbomyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one imidazole salt hydrate [CCDC 1894722].



Crystal data

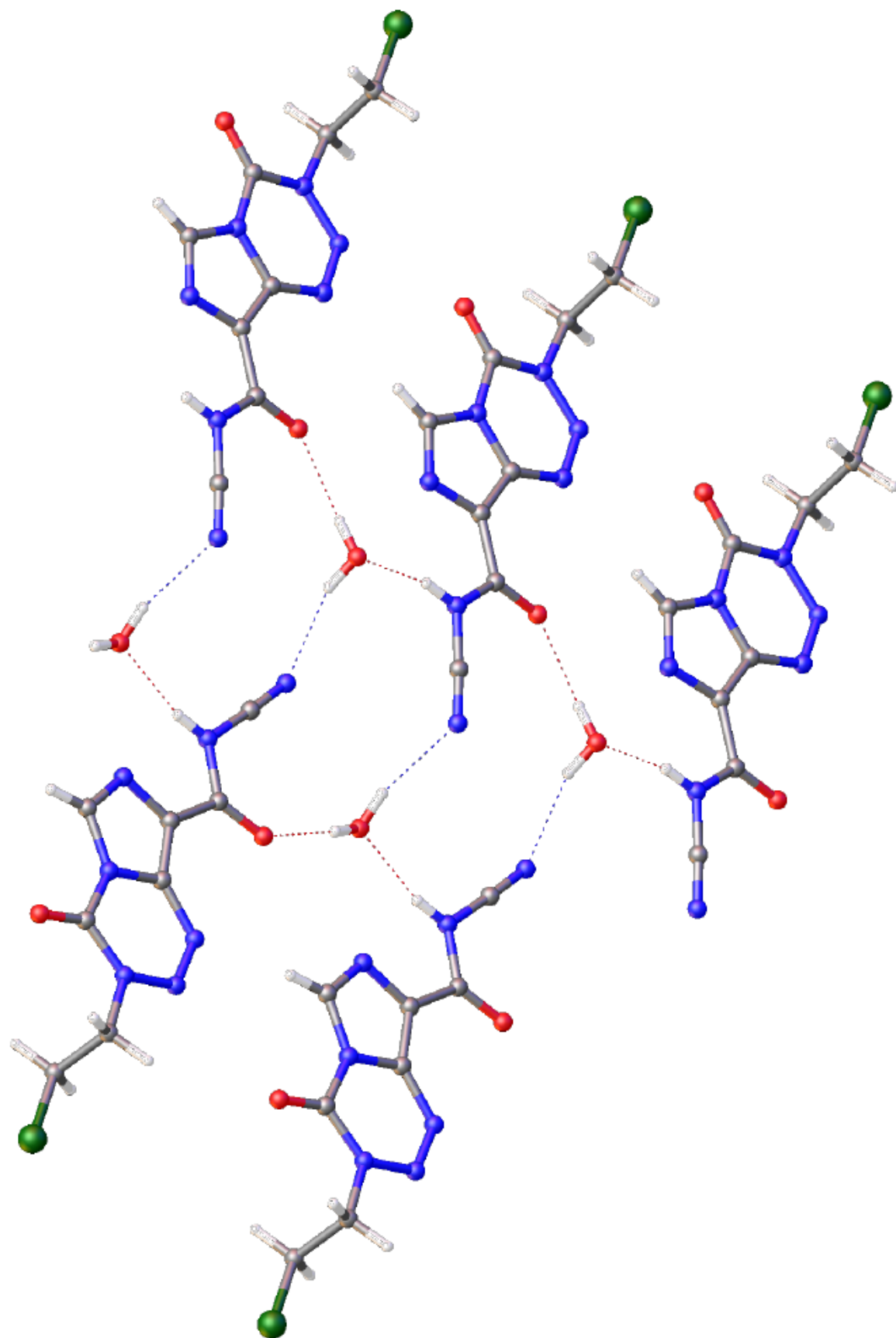
Identification code	MBFCMP
Empirical formula	C ₁₀ H ₁₂ ClN ₉ O ₅
Formula weight	373.74
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	6.5419(3)
b/Å	9.2833(5)
c/Å	13.3123(8)
α/°	95.869(5)
β/°	94.373(5)
γ/°	107.232(5)
Volume/Å ³	763.28(8)
Z	2
ρ _{calc} /cm ³	1.626
μ/mm ⁻¹	2.679
F(000)	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 ≤ h ≤ 7, -11 ≤ k ≤ 11, -16 ≤ l ≤ 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 ₈ H ₈ ClN ₇ O 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/Å ³	1136.06(9)
Z	4
ρ _{calc} /cm ³	1.670
μ/mm ⁻¹	3.200
F(000)	584.0
Crystal size/mm ³	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 F ²	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



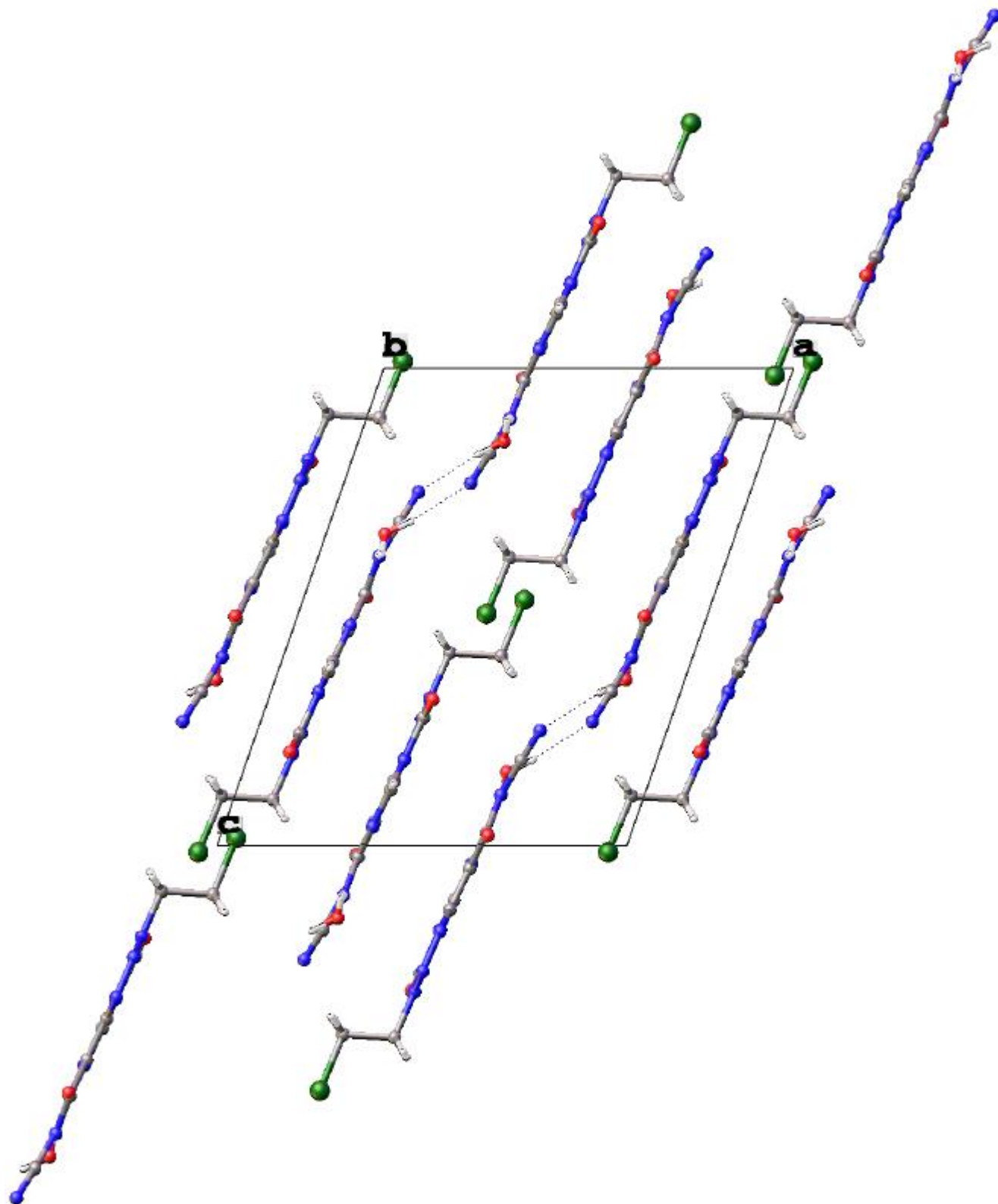
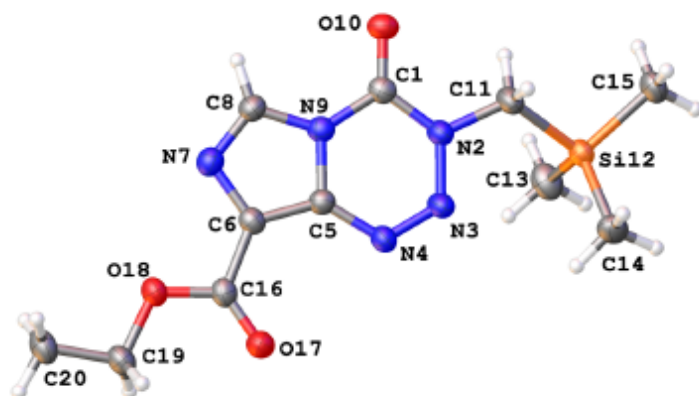


Figure S6. Ethyl 4-oxo-3-(trimethylsilylmethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazine-8-carboxylate (16) [CCDC 1896797].



Crystal data

Identification code	MBFCMN
Empirical formula	C ₁₁ H ₁₇ N ₅ O ₃ Si
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/Å ³	1465.3(2)
Z	4
ρ _{calc} /cm ³	1.339
μ/mm ⁻¹	1.569
F(000)	624.0
Crystal size/mm ³	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 F ²	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