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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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.

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

Crystal data

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

Crystal data

Identification code MBFCMD
Empirical formula C₇H₇ClN₇O₄
Formula weight 287.64
Temperature/K 120(2)
Crystal system monoclinic
Space group P2₁/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/Å³ 1100.79(11)
Z 4
ρcalc/cm³ 1.736
μ/mm⁻¹ 3.379
F(000) 584.0
Crystal size/mm³ 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 [Rint = 0.0294, Ringerprint = 0.0373]
Data/restraints/parameters 2151/0/172
Goodness-of-fit on F² 1.070
Final R indexes [I=2σ(I)] R₁ = 0.0410, wR₂ = 0.1059
Final R indexes [all data] R₁ = 0.0462, wR₂ = 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(3H)-one morpholine salt [CCDC 1894720].

Crystal data

- **Identification code**: MBFCMF
- **Empirical formula**: C_{11}H_{13}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/Å³**: 1544.6(2)
- **Z**: 4
- **ρ_{calcd}/cm³**: 1.612
- **μ/μm⁻¹**: 2.027
- **F(000)**: 776.0
- **Crystall size/mm³**: 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 F²**: 1.058
- **Final R indexes [I=2σ (I)]**: R₁ = 0.0401, wR₂ = 0.1095
- **Final R indexes [all data]**: R₁ = 0.0422, wR₂ = 0.1112
- **Largest diff. peak/hole / e Å⁻³**: 0.35/ -0.40
H-bonding interactions
Figure S4. 3-(2-Chloroethyl)-8-(N-nitrocarbamoylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one imidazole salt hydrate [CCDC 1894722].

Crystal data

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

Crystal data
Identification code MBFCMK
Empirical formula C$_8$H$_5$ClN$_5$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
$\rho_{calc}$/g/cm$^3$ 1.070
μ/mm$^{-1}$ 3.200
F(000) 584.0
Crystal size/mm$^3$ 0.4141 × 0.0386 × 0.0281
Radiation CuKα ($\lambda = 1.54184$)
2Θ range for data collection/° 8.234 to 146.802
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].

![Chemical Structure](image)

**Crystal data**

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