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.

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 C₇H₈ClN₂O₄
Formula weight 261.63
Temperature/K 120(2)
Crystal system monoclinic
Space group P2₁/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
ρcalcd/g/cm³ 1.721
μ/mm¹ 3.548
F(000) 536.0
Crystal size/mm³ 0.2112 × 0.1300 × 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 [Rint = 0.0222, Rsigma = 0.0217]
Data/restraints/parameters 1982/0/164
Goodness-of-fit on F² 1.061
Final R indexes [I>2σ(I)] R₁ = 0.0270, wR₂ = 0.0674
Final R indexes [all data] R₁ = 0.0288, wR₂ = 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(3H)-one (13) [CCDC 1894718].

Crystal data

| Property                      | Value                                      |
|-------------------------------|--------------------------------------------|
| Identification code           | MBFCMD                                     |
| Empirical formula             | C₇H₅ClN₆O₄                                 |
| 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/mm³                         | 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, Rmerge = 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 Å³ | 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**

| Property                  | Value                          |
|---------------------------|-------------------------------|
| 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_{calc}/cm³              | 1.612                         |
| μ/mm⁻¹                    | 2.627                         |
| F(000)                    | 7760                          |
| Crystal 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-nitrocarbamoyl)imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one imidazole salt hydrate [CCDC 1894722].

Crystal data

| Property                      | Value                        |
|-------------------------------|------------------------------|
| Identification code           | MBFCMP                       |
| Empirical formula             | C_{16}H_{11}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/Å³                     | 763.28(8)                    |
| Z                             | 2                            |
| ρ_{oxygen}/cm³                | 1.626                        |
| μ/mm⁻¹                        | 2.679                        |
| F(000)                        | 384.0                        |
| Crystal size/mm³              | 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 F²         | 1.036                        |
| Final R indexes [I>2σ(I)]     | R₁ = 0.0371, wR₂ = 0.0966   |
| Final R indexes [all data]    | R₁ = 0.0429, wR₂ = 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(3H)-one hydrate (15) [CCDC 1895634].

**Crystal data**
- **Identification code**: MBFCMK
- **Empirical formula**: C₃H₅ClN₅O₃
- **Formula weight**: 285.66
- **Temperature/K**: 120(2)
- **Crystal system**: monoclinic
- **Space group**: P2₁/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
- **ρcalc/g/cm³**: 1.070
- **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 146.802
- **Index ranges**: -14 ≤ h ≤ 13, -7 ≤ k ≤ 8, -18 ≤ l ≤ 13
- **Reflections collected**: 6446
- **Independent reflections**: 2234 [Rint = 0.0194, Rsigma = 0.0160]
- **Data/restraints/parameters**: 2234/0/181
- **Goodness-of-fit on F²**: 1.063
- **Final R indexes [I>2σ (I)]**: R₁ = 0.0284, wR₂ = 0.0796
- **Final R indexes [all data]**: R₁ = 0.0302, wR₂ = 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

| Property                  | Value                                |
|---------------------------|--------------------------------------|
| Identification code       | MBFCMN                               |
| Empirical formula         | C_{12}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/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)] | R₁ = 0.0508, wR₂ = 0.1226         |
| Final R indexes [all data]| R₁ = 0.0701, wR₂ = 0.1334           |
| Largest diff. peak/hole / e Å⁻³ | 0.31/-0.27                       |