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

**Dedicated to Professor Jan Bergman on the occasion of his 80th birthday**

Abstract

Imidazo[5,1-*d*][1,2,3,5]tetrazines related in structure to the anticancer drugs temozolomide and mitozolomide with modification of the 8-carboxamide group, have been synthesized, *N*-nitrocarboxamides by direct nitration of the corresponding carboxamides, and *N*-cyanomitozolomide by sodium cyanamide acylation. The NH groups in the *N*-nitro- and *N*-cyano-carboxamides were considerably more acidic than the parent carboxamide, and readily formed salts with morpholine and imidazole. X-Ray crystallography revealed that the *N*-nitro compound existed as such rather than the nitronic acid tautomer. Preliminary evaluation showed that enhancing the acidity of the carboxamide NH in mitozolomide analogues was detrimental to the growth inhibitory activity.

R = CH₃ or CH₂CH₂Cl
Z = H, NO₂, CN

DNA alkylation
Effect of modulation of carboxamide NH acidity
on growth inhibitory activity
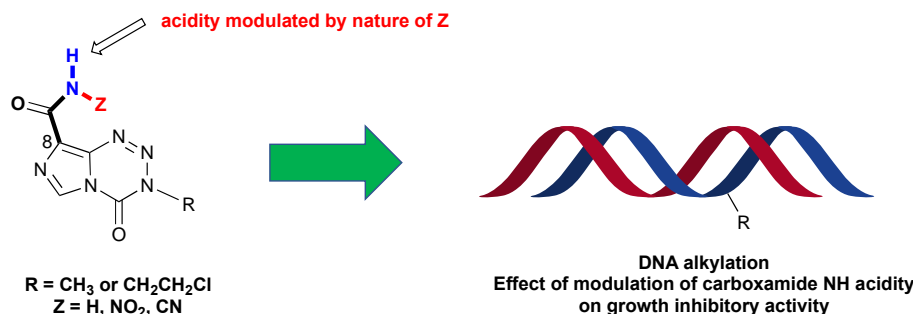
Keywords: Heterocyclic antitumor agents, imidazotetrazine, temozolomide, carboxamide acidity

[†]Part 45 in the series 'Antitumor Imidazotetrazines'. Part 44 is ref. 1.

Introduction

Remarkably, since the original synthesis in 1980[2] of the anticancer drugs temozolomide (**1**, TMZ) and mitozolomide (**2**, MTZ) (Figure 1) and the subsequent marketing of **1** in 1999, no closely related small molecule agents have competed in the treatment of *glioblastoma multiforme* (GBM), the most prevalent and aggressive adult primary brain tumor. This class of anticancer imidazo[5,1-*d*][1,2,3,5]tetrazines has been extensively reviewed from chemical, biological and clinical perspectives.[3,4] The clinical success of **1** was due, in part, to its synthetic tractability (the original two-step Stone synthesis),[2] or more recently via the trimethylsilylmethyl derivative **3** (Figure 1).[5] The compound was also free from metabolic liabilities and possessed robust pharmaceutical properties allowing convenient oral delivery to out-patients, with a surprisingly tolerable safety profile for what might be considered as a classical DNA-interactive 'cytotoxic' agent.

1 R = Me (temozolomide: TMZ)
2 R = CH₂CH₂Cl (mitozolomide: MTZ)
3 R = CH₂SiMe₃

4 R = CO₂H
5 R = CONHMe
6 R = CONHPh
7 R = CONMe₂
8 R = CONHOH
9 R = SO₂NH₂
10 R = SO₂NHMe
11 R = SO₂NMe₂

12 R = Me, Z = NO₂
13 R = CH₂CH₂Cl, Z = NO₂
14 R = CH₂SiMe₃, Z = NO₂
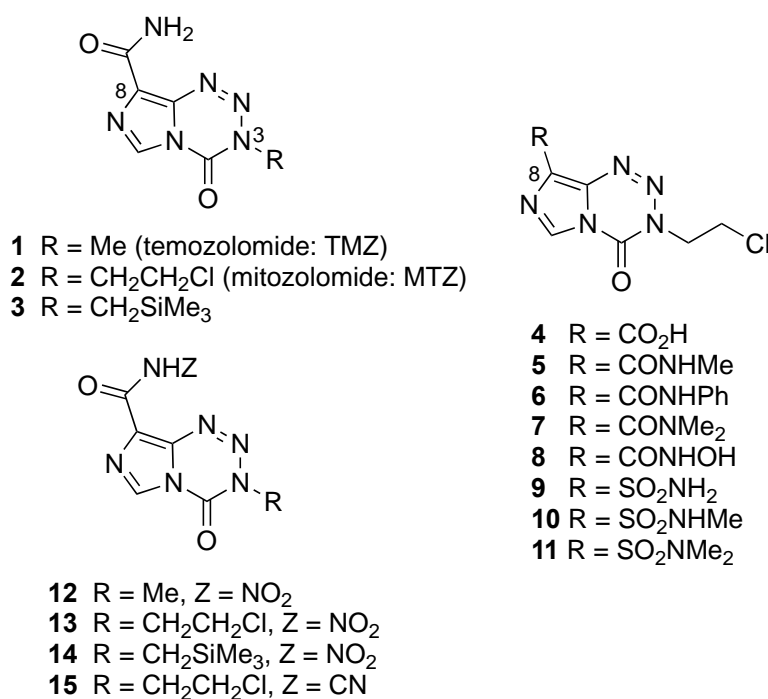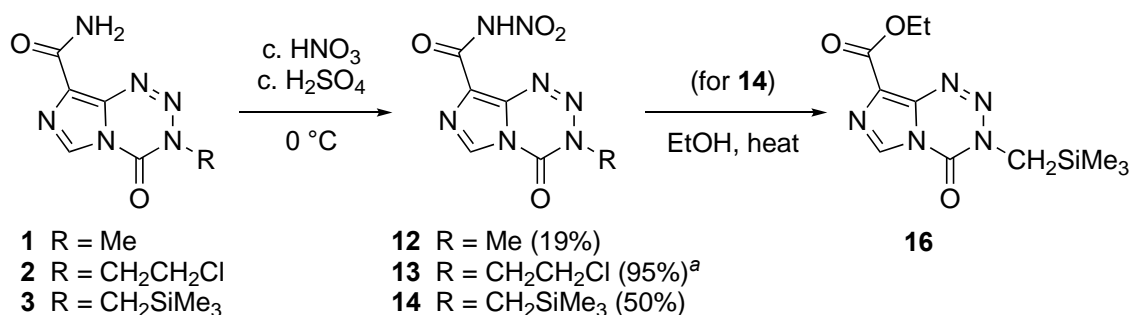**15** R = CH₂CH₂Cl, Z = CN

Figure 1. Structures of anticancer imidazo[5,1-*d*][1,2,3,5]tetrazines.

In the early phase of work on imidazotetrazines, the synthesis of a range of derivatives of MTZ, modified at the 8-position was carried out, and their growth-inhibitory activities were evaluated against murine tumors *in vitro* and *in vivo*, including leukemias P388 and L1210 and the TLX5 lymphoma.[6-9] Overall, it was concluded that a substituent at C-8 with a weakly acidic amide NH atom was apparently required for good inhibitory activity. Thus, although the parent carboxylic acid **4** (pK_a ~3) was poorly active, high potency was recorded for MTZ **2** itself (NH pK_a ~15), a range of *N*-alkyl- and -aryl carboxamides NH such as **5** and **6** (NH pK_a ~11-14), hydroxamic acid **8**, sulfonamide **9** (NH pK_a ~9), and *N*-methylsulfonamide **10** (Figure 1). The potently active dimethylcarboxamide **7**, which does not present an acidic hydrogen, apparently contradicts this conclusion: however, in separate experiments, we showed that this tertiary amide is metabolized in mice *in vivo* (89%) to the secondary monomethylcarboxamide **5** that does bear an acidic H-atom.[10] Presumably, the potency of the 8-dimethylsulfonamide **11** is also mediated *via* metabolism to the monomethylsulfonamide **10**. This early work has been reviewed.[11] We have now revisited the nature of the carboxamide substituent at C-8, and focused on

the modulation of NH acidity by incorporation of electron-withdrawing groups. We now report the synthesis and properties of the *N*-nitrocarboxamides **12 − 14** (NH pK_a ~3-4) and *N*-cyanocarboxamide **15** (NH pK_a ~6-7) (Figure 1).

Results and Discussion

Secondary *N*-nitrocarboxamides (RCONHNO$_2$) are a relatively rare class of compounds with fewer than 100 examples reported (as at December 2019). They are generally prepared by direct nitration of carboxamides using HNO$_3$/H$_2$SO$_4$,[7,12,13] or nitronium tetrafluoroborate,[14,15] or less commonly by acylation of nitramines.[16] In the imidazotetrazine series, we have reported previously that nitration of mitozolomide **2** in a nitric/sulfuric acid mixture gave the stable nitrocarboxamide **13** in 95% yield.[7] We now find that the reaction can be extended to TMZ **1** and the TMS-methyl analogue **3** to give the nitrocarboxamides **12** and **14** respectively (Scheme 1), albeit in lower yield. Interestingly attempts to crystallize the latter compound from ethanol led only to the growth of crystals of the corresponding ethyl ester **16**, presumably involving displacement of nitramine by the alcohol in a reaction analogous to trans-esterification reactions. Exploratory reactions treating **2** with nitronium tetrafluoroborate, nitronium acetate or nitronium trifluoroacetate in the presence of different bases gave complex mixtures from which the required nitrocarboxamide **13** could not be recovered. As expected on the basis of predicted pK_a and literature precedent,[13,17] the nitrocarboxamide **13** was sufficiently acidic to form salts readily with the bases morpholine (93%), imidazole (82%) as well as a sodium salt from sodium methoxide (75%), and the structures of the morpholine and imidazole salts, together with **13** itself were confirmed by X-ray crystallography (Figures 2, S2-S4). Likewise, the structure of ethyl ester **16** was confirmed by crystallography (Figure S6). The X-ray crystal structures are discussed in more detail below.

1 R = Me
2 R = CH$_2$CH$_2$Cl
3 R = CH$_2$SiMe$_3$

12 R = Me (19%)
13 R = CH$_2$CH$_2$Cl (95%)[a]
14 R = CH$_2$SiMe$_3$ (50%)

16

Scheme 1. Synthesis of *N*-nitrocarboxamides **12 − 14** (Reference 7).

In contrast to *N*-nitrocarboxamides, *N*-cyanocarboxamides are relatively well known. They are usually prepared by acylation of cyanamide or its sodium salt, most often with an acid chloride,[18] or by cyanation reactions with cyanogen bromide.[18] Therefore our attention then turned to the synthesis of the *N*-cyanocarboxamide **15** by acylation of cyanamide. As previously reported, reaction of MTZ **2** with nitrosylsulfuric acid (from a mixture of sodium nitrite and sulfuric acid) proceeded *via* the intermediate *N*-nitrosoamide, which was not isolated, to afford the carboxylic acid **4** (77%),[13] the structure being confirmed by X-ray crystallography (Figure S1). The acid chloride **17** had been prepared previously from the corresponding acid **4** and thionyl chloride/DMF.[7] In the present work, attempts to condense this unstable acid chloride with

sodium cyanamide gave only mixtures and none of the required *N*-cyanoamide **15** was recovered. More success was achieved by treating **4** with an oxalyl chloride/DMF mixture followed by sodium cyanamide which gave **15** in a useful 61% yield, presumably *via* its acid chloride **17** (Scheme 2**)**; the presence of an IR band at 2,200 cm^{-1} confirmed the cyano-carboxamide structure of **15**, and this was corroborated by an X-ray crystal structure determination (Figures 3, S5).
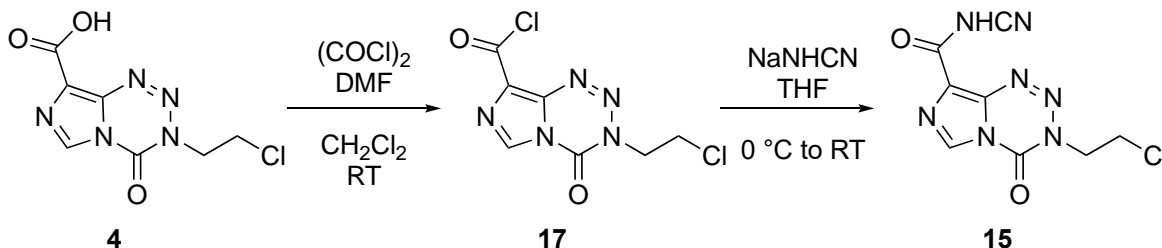
Scheme 2. Synthesis of the *N*-cyanocarboxamide **15.**

N-Nitro- and *N*–cyano-carboxamides are under-explored classes of compounds and an X-ray structure of **13** was determined from a single crystal grown from CHCl$_3$. The structure (Figure 2A) showed that the compound existed in the *N*–nitro rather than the nitronic acid tautomeric form with an N-N single bond length of 1.377 Å. Other *N*-nitrocarboxamides have very similar N-N bond lengths in the solid state (1.389Å and 1.380 Å).[19,20] In the unit cell of **13** there were intermolecular hydrogen bonds linking a nitrocarboxamide N-H to N(1) of another tetrazine ring, and a nitrocarboxamide carbonyl oxygen atom to an H atom on C(8) of a second molecule (Figure 2B). The *N*–nitro group was essentially coplanar with the imidazotetrazine nucleus (Figure 2C). A single crystal X-ray structure of the morpholinium salt of **13** (Figure 2D) confirmed that the N-N bond order (1.376 Å) was similar to **13** and existed in the *N*–nitro rather than the nitronic acid arrangement. The X-ray crystal structure of the imidazolium salt of **13** is shown in Figure S4 (SI).

Biological investigations

Preliminary biological investigation of the new compounds was carried out in three human cell lines: *glioblastoma multiforme* (GBM) U373V (vector control) and U373M (*MGMT*-transfected); colon HCT 116. The human GBM U373V line is relatively sensitive to TMZ and MTZ and gave GI$_{50}$ values of 51.9 and 11.3 μM, respectively. The isogenic line transfected with *MGMT* (U373M) showed approximately 6-fold and 3-fold resistance to TMZ (**1**) and MTZ (**2**) with GI$_{50}$ values of 302 and 33.9 μM, respectively. Conversion of the 8-carboxamide groups of TMZ and MTZ into the corresponding *N*-nitrocarboxamides (**12**) and (**13**) and the *N*-cyanocarboxamide (**15**) substantially increases the acidity of the carboxamide N-H. In earlier studies nitrocarboxamide analogue of MTZ (**13**) proved to be as active as MTZ (**2**) against the murine TLX5 lymphoma growing *in vivo,*[13] but this potency was not mirrored in activity against the human cancer cell lines *in vitro* when compared to that of the carboxamides (**1**) and (**2**), respectively, in the present study. The compounds (**12**, **13**, **15**) all were approximately equiactive against U373V and M and colon HCT 116 cell lines.
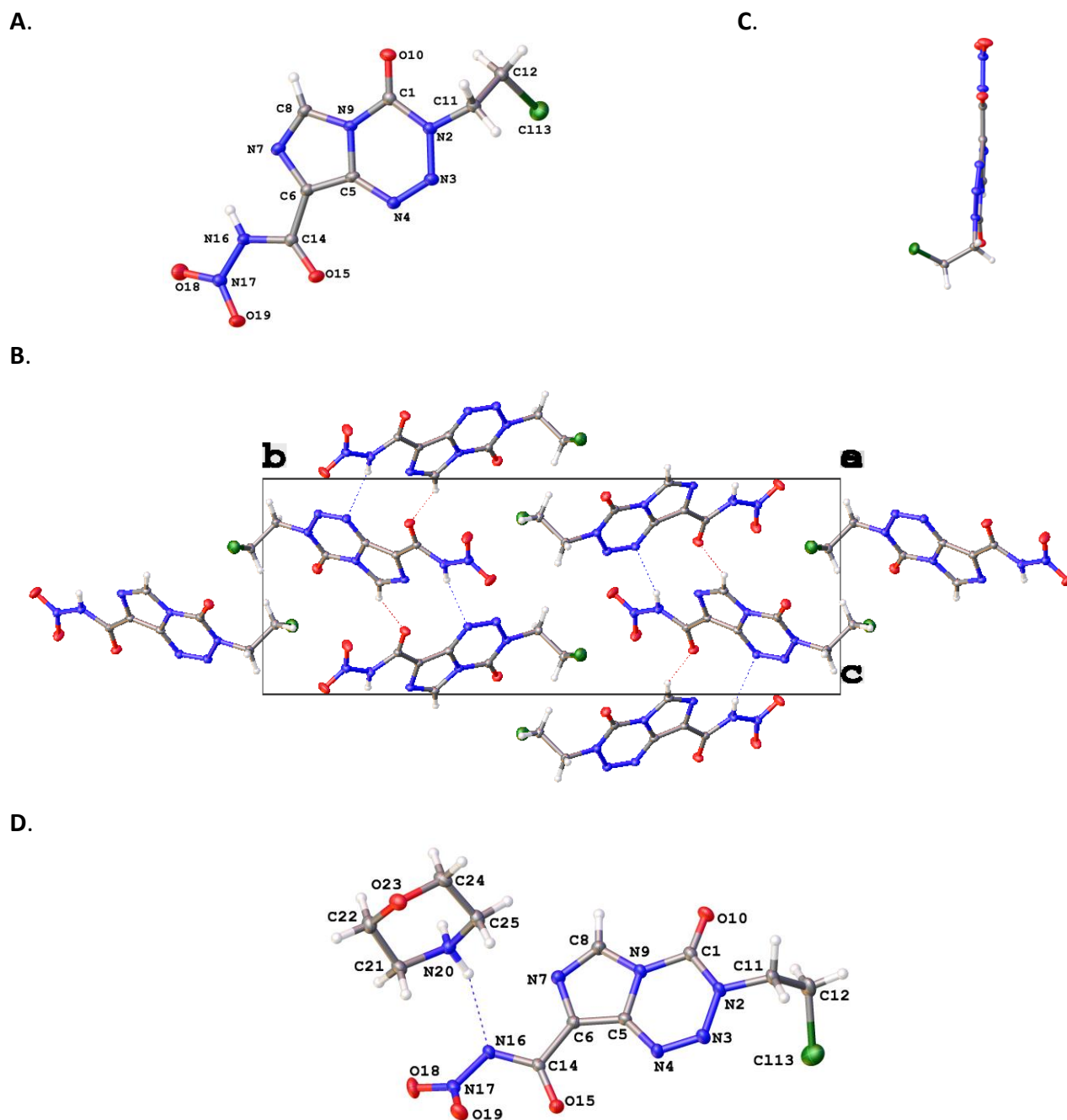
A.

B.

C.

D.

Figure 2. (A) X-Ray crystal structure of imidazotetrazine (**13**); (B) intermolecular H-bonding in the unit cell of (**13**); (C) coplanarity of nitrocarboxamide group and the bicyclic ring of (**13**); (D) structure of the morpholine salt of (**13**).
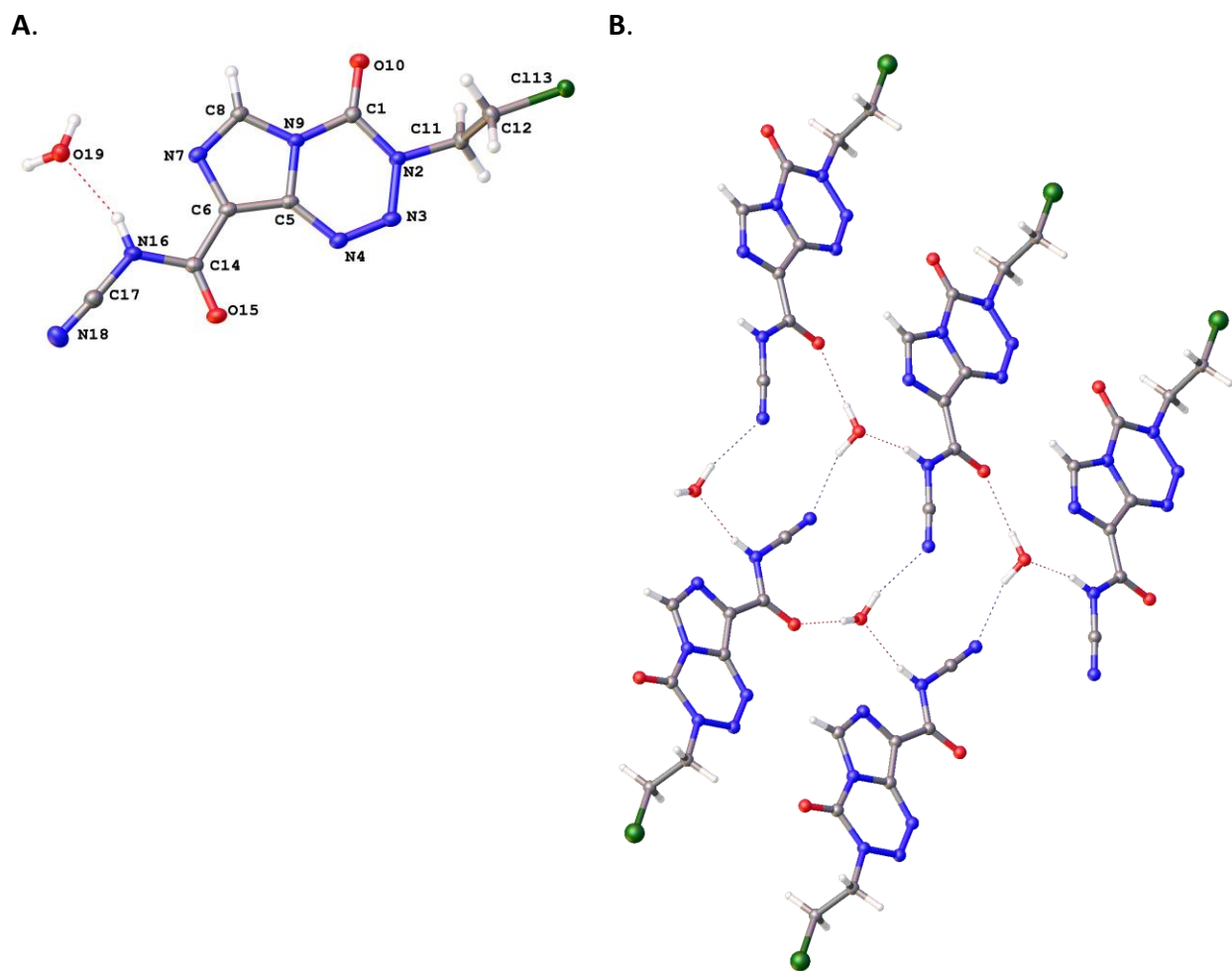
Figure 3. (A) Crystal structure of imidazotetrazine (**15**) hydrate; (B) intermolecular H-bonding between the cyanocarboxamide groups and water molecules.

Conclusions

Enhancing the acidity of the 8-carboxamide residue of MTZ (**1**) and TMZ (**2**) by conversion to *N*-nitro- (**12** and **13**) and an *N*-cyano-derivative (**15**), respectively, has a profound *dys*chemotherapeutic effect, showing that strongly acidic groups are not tolerated. Although these new biological results do not contradict our previous contention that a weakly acidic group at C-8 in imidazotetrazines leads to potent anticancer activity in the series, they do not confirm that such a group is essential. Indeed, our most recent studies have focused on incorporation of a range of cyclic modifications of the 8-carboxamide group in an effort to control the stabilities of the imidazotetrazine ring structures, and allow fine-tuning of the pharmaceutical properties of future drug candidates.

Experimental Section

General. Most imidazotetrazines decomposed in their melting ranges which varied according to the rate of heating. Melting points were not a reliable means to assess purity. Compounds were purified by crystallization or flash chromatography on Merck silica gel 60.

The following compounds were prepared as previously described: TMZ (**1**) and MTZ (**2**),[2] 8-carbamoyl-3-(trimethylsilylmethyl)imidazo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one　(**3**),[5]　3-(2-chloroethyl)-3,4-dihydro-4-oximid-azo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylic　acid　(**4**),[7]　3-(2-chloroethyl)-8-(*N*-nitrocarbamoyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (**13**).[7]

3-Methyl-8-(*N*-nitrocarbamoyl)imidazo[5,1-d][1,2,3,5]tetrazin-4(3*H*)-one (12). An ice-cold suspension of TMZ (**1**) (743 mg, 3.8 mmol) in concentrated sulfuric acid (8 mL) was treated dropwise with nitric acid (68%; 4.5 mL). The reaction mixture was stirred at 0 °C for 2 h then poured onto ice. The precipitate formed was filtered under vacuum and washed with water to give **12** as a colorless crystalline solid (172 mg, 19%); mp 180 °C; v_{max} (ATR)/cm^{-1} 3251, 3244, 3131, 1739, 1703, 1616, 1562, 1461, 1421, 1366, 1295, 1243, 1209, 1181, 1124, 1011; δ_H (400 MHz, DMSO-d_6) 8.91 (1 H, s, CH), 3.89 (3 H, s, CH$_3$); δ_C (100 MHz, DMSO-d_6) 161.8 (C), 139.0 (C), 136.4.3 (C), 129.0 (CH), 36.2 (CH$_3$); *m/z* (ESI) 262 [M+Na]$^+$, 29%). MS: *m/z* Found: [M+Na]$^+$, 262.0295. C$_6$H$_5$N$_7$O$_4$$^+Na^+$ requires 262.0284.

8-(*N*-Nitrocarbamoyl)-3-(trimethylsilylmethyl)imidazo[5,1-d][1,2,3,5]tetrazin-4(3*H*)-one　(14). An ice-cold suspension of the (trimethylsilylmethyl)imidazotetrazine (**3**) (500 mg, 1.88 mmol) in concentrated sulfuric acid (4.7 mL) was treated dropwise with nitric acid (68%; 1.9 mL). The reaction mixture was stirred at 0 °C for 1 h then poured onto ice. The precipitate formed was collected and washed with cold water to give **14** as a solid (289 mg, 50%); δ_H (400 MHz, DMSO-d_6) 8.92 (1 H, s, CH), 3.84 (2 H, s, CH$_2$), 0.17 (9 H, s, 3 x CH$_3$); δ_C (100 MHz, DMSO-d_6) 181.14, 156.35, 137.01, 129.02, 126.07, 40.28, -1.93. MS: *m/z* Found: [M+H]$^+$, 312.0871. C$_9$H$_{13}$N$_7$O$_4$Si$^+$+H$^+$ requires 312.0871.

Attempted crystallization from ethanol resulted in formation of crystals of ethyl 4-oxo-3-(trimethyl-silylmethyl)imidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**16**).

3-(2-Chloroethyl)-8-(*N*-cyanocarbamoyl)imidazo[5,1-d][1,2,3,5]tetrazin-4(3*H*)-one (15). To a suspension of 3-(2-chloroethyl)imidazo[5,1-*d*][1,2,3,5]tetrazin-4-oxo-8-carboxylic acid (**4**)[13] (0.5 g, 2.05 mmol) in dry DCM (3 mL) under argon at room temperature was added oxalyl chloride (0.58 mL, 10.3 mmol), followed by dry DMF (6 drops). The reaction mixture was stirred for 1 h, concentrated under vacuum, dissolved in THF (5 mL) and added dropwise to a suspension of sodium cyanamide (157 mg, 2.46 mmol) in dry THF (10 mL) in an ice bath under argon. The reaction mixture was stirred for 18 h at room temperature, then the precipitated formed was collected. The filtrate was diluted with water (20 mL), extracted with EtOAc (2 x 25 mL), acidified to pH 1 with hydrochloric acid (1 M) and the resulting precipitate was collected by vacuum filtration, washed with water and dried under vacuum to give **15** as a pink solid (total yield 337 mg, 61%); v_{max} (ATR)/cm^{-1} 2200 (CN); δ_H (400 MHz, DMSO-d_6) 9.06 (1 H, s, CH), 4.68 (2 H, t, *J* 6.0, CH$_2$), 4.04 (2 H, t, *J* 6.0, CH$_2$); δ_C (100 MHz, DMSO-d_6) 159.95, 138.69, 135.99, 130.01, 126.43, 108.59, 50.44, 41.34; LCMS: R$_f$ 1.918 min, MS: *m/z* [M+H] 268.0, [M+Na] 290.0.

Salt formation reactions

(a) Imidazole (0.9 eq, 0.1 g) was added to a suspension of *N*-nitromitozolomide **13** (1.738 mmol, 0.5 g) in acetonitrile (7 mL) and the mixture was stirred for 18 h at room temperature. As the reaction progressed, the

particles in a suspension of starting material became finer. The solids were filtered off and washed with more acetonitrile and diethyl ether, then dried *in vacuo*, to give (0.49 g, 82 %) of 3-(2-chloroethyl)-8-(*N*-nitrocarbamoyl)imidazo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one imidazole salt hydrate, δ_H (400 MHz, DMSO-d_6) 14.5 (1 H, br, NH), 9.06 (1 H, s, CH), 8.73 (1 H, s, CH), 7.69 (2 H, s), 2 x CH), 4.60 (2 H, t, *J* 6.0, CH$_2$), 4.02 (2 H, t, *J* 6.0, CH$_2$).

(b) By analogy to the above procedure, using morpholine (1 equivalent), the initial suspension dissolved completely with the addition of a base, and within minutes the precipitate appeared. This gave (0.24 g, 93%) of 3-(2-chloroethyl)-8-(*N*-nitrocarbamoyl)imidazo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one morpholine salt, δ_H (400 MHz, DMSO-d_6) 8.83 (1 H, br, NH), 8.72 (1 H, s, CH), 4.60 (2 H, t, *J* 6.0, CH$_2$), 4.02 (2 H, t, *J* 6.0, CH$_2$), 3.76 (4 H, m, 2 x CH$_2$), 3.12 (4 H, m. 2 x CH$_2$).

(c) Using *N*-cyanomitozolomide **15**, the corresponding imidazole salt was prepared in 89% yield; δ_H (400 MHz, DMSO-d_6) 8.97 (1 H, s, CH), 8.70 (1 H, s, CH), 7.64 (2 H, s), 2 x CH), 4.60 (2 H, t, *J* 6.0, CH$_2$), 4.02 (2 H, t, *J* 6.0, CH$_2$), NH not observed.

(d) Using *N*-cyanomitozolomide **15**, the corresponding morpholine salt was prepared in 61% yield; δ_H (400 MHz, DMSO-d_6) 8.84 (1 H, br, NH), 8.66 (1 H, s, CH), 4.58 (2 H, t, *J* 6.0, CH$_2$), 4.01 (2 H, t, *J* 6.0, CH$_2$), 3.77 (4 H, m, 2 x CH$_2$), 3.13 (4 H, m. 2 x CH$_2$).

Crystallography
Details of X-ray crystallography are given in the Supplementary Material.

Anti-proliferative assays
Stock solutions of test compounds listed in were prepared in DMSO (100 mM) and aliquots stored at -20 °C, protected from light. U373V and U373M were originally obtained from Schering-Plough Research Institute, USA and were verified as being mycoplasma free. Expression of MGMT in lysates prepared from U373M was verified by western blot. HCT 116 colorectal carcinoma cells were sourced from the American Type Culture Collection (ATCC). HCT 116 cells were maintained in RPMI 1640 nutrient medium supplemented with 10% fetal bovine serum (FBS), sub-cultivated twice weekly and incubated at 37 °C in an atmosphere containing 5% CO$_2$. For U373V and U373M cell lines, the medium was additionally supplemented with 1% non-essential amino acids, 50 µg/mL gentamicin and 400 µg/mL G418. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays were performed as reported previously.[21,22] Compound concentrations required to inhibit 50% growth (GI$_{50}$; µM) were calculated using non-linear regression analysis.

Supplementary Material

Supplementary material (SI) available: crystallographic data. CCDC 1894718, 1894720, 1894722, 1895634, 1896795, 1896797.

References

1. Cousin, D.; Hummersone, M. G.; Bradshaw, T. D.; Zhang, J.; Moody, C. J.; Foreiter, M. B.; Summers, H. S.; Lewis, W.; Wheelhouse, R. T.; Stevens, M. F. G. *Med. Chem. Commun.* **2018**, *9*, 545-553.

https://doi.org/10.1039/C7MD00554G

2. Stevens, M. F. G.; Hickman, J. A.; Stone, R.; Gibson, N. W.; Baig, G. U.; Lunt, E.; Newton, C. G. *J. Med. Chem.* **1984**, *27*, 196-201.
https://doi.org/10.1021/jm00368a016

3. Stevens, M. F. G. In *Cancer Drug Design and Discovery*; 2nd ed.; Neidle, S., Ed.; Elsevier Science: San Diego, 2014, p 145-164.
https://doi.org/10.1016/B978-0-12-396521-9.00005-X

4. Moody, C. L.; Wheelhouse, R. T. *Pharamaceuticals* **2014**, *7*, 797-838.
https://doi.org/10.3390/ph7070797

5. Wang, Y. F.; Stevens, M. F. G.; Thomson, W. T.; Shutts, B. P. *J. Chem. Soc.-Perkin Trans. 1* **1995**, 2783-2787.
https://doi.org/10.1039/P19950002783

6. Lunt, E.; Newton, C. G.; Smith, C.; Stevens, G. P.; Stevens, M. F. G.; Straw, C. G.; Walsh, R. J. A.; Warren, P. J.; Fizames, C.; Lavelle, F.; Langdon, S. P.; Vickers, L. M. *J. Med. Chem.* **1987**, *30*, 357-366.
https://doi.org/10.1021/jm00385a018

7. Horspool, K. R.; Stevens, M. F. G.; Newton, C. G.; Lunt, E.; Walsh, R. J. A.; Pedgrift, B. L.; Baig, G. U.; Lavelle, F.; Fizames, C. *J. Med. Chem.* **1990**, *33*, 1393-1399.
https://doi.org/10.1021/jm00167a018

8. Clark, A. S.; Deans, B.; Stevens, M. F. G.; Tisdale, M. J.; Wheelhouse, R. T.; Denny, B. J.; Hartley, J. A. *J. Med. Chem.* **1995**, *38*, 1493-1504.
https://doi.org/10.1021/jm00009a010

9. Langnel, D. A. F.; Arrowsmith, J.; Stevens, M. F. G. *Arkivoc* **2000** (*iii*), 421-437.

10. Horspool, K. R.; Quarterman, C. P.; Slack, J. A.; Gescher, A.; Stevens, M. F. G.; Lunt, E. *Cancer Res.* **1989**, *49*, 5023-5026.

11. Stevens, M. F. G. In *New Avenues in Developmental Cancer Chemotherapy*; Academic Press: 1987, p 335-353.

12. Campbell, R.; Peterson, C. J. *J. Org. Chem.* **1963**, *28*, 2294-2298.
https://doi.org/10.1021/jo01044a033

13. Axthammer, Q. J.; Krumm, B.; Klapotke, T. M. *Eur. J. Org. Chem.* **2015**, 723-729.
https://doi.org/10.1002/ejoc.201403265

14. Olah, G. A.; Narang, S. C.; Olah, J. A.; Lammertsma, K. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 4487-4494.
https://doi.org/10.1073/pnas.79.14.4487

15. Romea, P.; Aragones, M.; Garcia, J.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 7038-7042.
https://doi.org/10.1021/jo00025a017

16. Bohle, D. S.; Chua, Z. J. *Inorg. Chem.* **2014**, *53*, 11160-11172.
https://doi.org/10.1021/ic5017033

17. Groziak, M. P.; Huan, Z. W.; Ding, H.; Meng, Z. Y.; Stevens, W. C.; Robinson, P. D. *J. Med. Chem.* **1997**, *40*, 3336-3345.
https://doi.org/10.1021/jm970301s

18. Larraufie, M. H.; Courillon, C.; Ollivier, C.; Lacote, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, *132*, 4381-4387.
https://doi.org/10.1021/ja910653k

19. Liu, L.; He, C. L.; Li, Z. X.; Li, C. S.; Zhang, X. P.; Zhang, S. J. *Acta Cryst. Sect. E-***2011**, *67*, O479-U1612.
https://doi.org/10.1107/S1600536811002455

20. Klenov, M. S.; Churakov, A. M.; Fedyanin, I. V.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2016**, *65*, 2682-2685.
    https://doi.org/10.1007/s11172-016-1636-0
21. Zhang, J.; Stevens, M. F. G.; Bradshaw, T. D. *Curr. Mol. Pharmacol.* **2012**, *5*, 102-114.
    https://doi.org/10.2174/1874467211205010102
22. Zhang, J. H.; Hummersone, M.; Matthews, C. S.; Stevens, M. F. G.; Bradshaw, T. D. *Oncology* **2015**, *88*, 28-48.
    https://doi.org/10.1159/000366131