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Exploitation of a New Route to Fused Pyrroles: Synthesis of TNP-351, Homo-MTA and 5-Arylpyrrolo[2,3-d]pyrimidines

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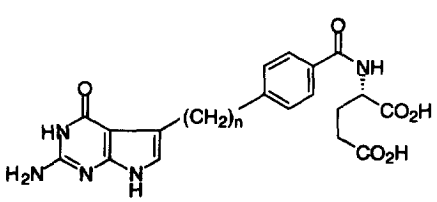
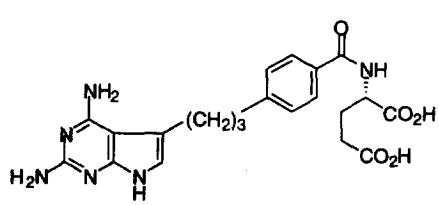
Abstract: We have developed a new methodology for the construction of pyrrolo[2,3-d]pyrimidines that involves Michael addition of 2,6-diamino-4(3H)-pyrimidinone or 2,4,6-triaminopyrimidines to nitroolefins, followed by a Nef reaction of the resulting adduct to form an intermediate aldehyde that spontaneously cyclizes to the fused pyrrole ring, This methodology has been exploited in a new synthesis of TNP-351, and for the first reported preparation of homo-MTA and of a series of 5-arylpyrrolo[2,3-d]pyrimidines.

Keywords:cyclisation; Michael reactions; nitrogen heterocycles; sonochemistry

As summarized in the preceding Communication,[1] N-[4-[2-(2-amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid (**1**, LY231514, MTA)[2] has been found to be extraordinarily effective in the treatment of a wide range of solid tumors.[3] This activity has been ascribed to the ability of **1** to inhibit at least five of the folate-dependent enzymes involved in cellular metabolism.[4] We described in the above Communication a new synthesis which involved, as its fundamental strategy for construction of the bicyclic pyrrolo[2,3-d]pyrimidine ring system, Michael addition of 2,6-diamino-4(3H)-pyrimidinone to a nitroolefin, and a one-pot conversion of the resulting adduct via a Nef reaction to an intermediate aldehyde which cyclized and aromatized to the above bicyclic ring system. The present Communication describes exploitation of this methodology for a new and abbreviated synthesis of the dihydrofolate reductase (DHFR) inhibitor TNP-351 (**2**),[5] the previously undescribed homolog **3**, and the non-bridged (5-aryl) analog **4** of MTA. In addition, this methodology provides ready access to a broad series of previously unknown pyrrolo[2,3-d]pyrimidine derivatives carrying an aryl substituent at position 5.



1, n = 2, LY231514, MTA
3, n = 3, homoLY231514
4, n = 0



2, TNP-351

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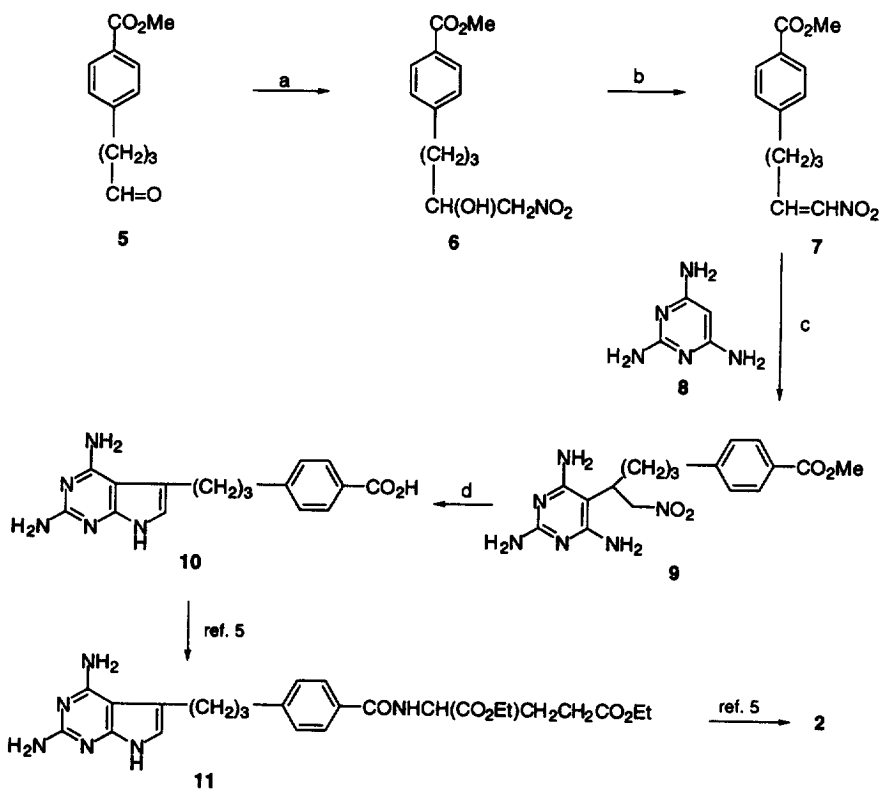
TNP-351 (**2**) was readily prepared from the known 4-arylbutyraldehyde **5**[6] by the following sequence of reactions: (a) aldol reaction with nitromethane to give the nitroalcohol,**6**, followed by dehydration with mesylation and subsequent treatment with triethylamine; (b) Michael addition of the resulting nitroolefin **7** with 2,4,6-triaminopyrimidine (**8**) at 50 °C in aqueous ethyl acetate; (c) subjection of the adduct **9** to a Nef reaction by initial treatment by sodium hydroxide at room temperature followed by acidification at 0 °C, resulting in formation of the pyrrolo[2,3-d]pyrimidine **10** and (d) coupling with diethyl L-glutamate to **11** followed by saponification (Scheme 1).

Scheme 1



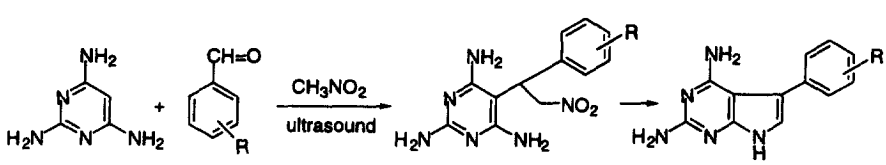
[a] CH_3NO_2, NaOH, EtOH, 38 °C (61% yield); [b] MsCl, CH_2Cl_2, then Et_3N, 0 °C (96% yield); [c] EtOAc/H_2O 1:1, 50 °C (84% yield); [d] (i) aq. NaOH, rt; (ii) add to aq. H_2SO_4 at O °C; (iii) aq. NaOH to pH 7, rt; (iv) HOAc, then filter (overall yield 51% yield)

Homo-MTA (**3**) was analogously prepared from the above nitroolefin **7** by reaction with 2,6-diamino-4(3H)-pyrimidinone to give the analogous Michael adduct which was then converted to **3** through the above sequence of reactions (Nef conversion to the intermediate aldehyde that cyclizes and aromatizes, glutamate coupling and saponification). Interestingly, homo-MTA proved in initial cell growth inhibition studies to be approximately as active as MTA itself.[7]

The non-bridged analog **4** was very readily prepared from methyl 4-formylbenzoate through an analogous sequence of reactions. This analog proved to be completely inactive as a cell growth inhibitor.

We were surprised to find that 5-aryl substituted pyrrolo[2,3-d]pyrimidines, as a class, appear to be virtually unknown.[8] We have prepared some representative examples by exploitation of a modification of the above methodology. It was recently reported that nitrostyrenes bearing electron-donating substituents in the aromatic ring can be obtained in a single step by ultrasound-promoted reaction of the corresponding arylaldehyde with nitromethane.[9] Arylaldehydes bearing electron-withdrawing substituents gave only the intermediate nitro alcohols. We have found not only that both classes of nitrostyrenes can be obtained in a single step by sonication of the nitromethane/arylaldehyde mixture at 60-65 °C, but that a mixture of 2,4,6-triaminopyrimidine (**8**), the arylaldehyde and nitromethane in acetic acid containing ammonium acetate, upon sonication at 60-65 °C, led in one smooth step to the Michael adduct **12** of the in situ-produced nitrostyrene. These Michael adducts were then converted, again in a single step, to the corresponding 5-arylpyrrolo[2,3-d]pyrimidines **13** under the above conditions for the Nef reaction (Scheme 2). The same sequence of reactions can be carried out starting with 2,6-diamino-4(3H)-pyrimidinone, leading to 2-amino-4(H)-oxo-5-arylpyrrolo[2,3-d]pyrimidines. An investigation of these novel compounds as "non-classical antifolates" for possible inhibition of *P. carinii* DHFR is currently underway.

Scheme 2



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REFERENCES

1. Taylor, E. C.; Liu, B. *Tetrahedron Lett.* **1999**, *40*, preceding paper in this issue.
2. Taylor, E. C.; Kuhnt, D.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatipour, M.; Moran, R. G. *J. Med. Chem.* **1992**, *35*, 4450.
3. For example, see (a) Rinaldi, D. A.; Burris, H. A.; Dorr, F. A.; Woodworth, J. R.; Kuhn, J. G.; Eckardt, J. R.; Rodriguez, G.; Corso, S. W.; Fields, S. M.; Langley, C.; Clark, G.; Faries, D.; Lu, P.; Van Hoff, D. D. *J. Clin. Oncol.* **1995**, *13*, 2842. (b) Calvert, A. H.; Walling, J. M. *British J. Cancer* **1998**, *78* (Suppl), 35. (c) Hammond, L.; Baker, S. D.; Villalona-Calero, M.; Eckhardt, S. G.; Drengler, R.; Aylesworth, C.; Johnson, T.; Hidalgo, M.; Rodriguez, G.; Diab, S.; Monroe, P.; Thornton, D.; Johnson, R.; Von Hoff, D.; Rowinsky, E. *Ann. Oncol.* **1998**, *9* (Suppl), 160. (d) Johnson, T.; Schwartz, G.; McCune, D.; Stephenson, J.; Aylesworth, C.; Hammond, L.; Monroe, P.; Thornton, D.; Von Hoff, D.; Rowinsky, E. *Ann. Oncol.* **1998**, *9* (Suppl), 160. (e) John, W.; Clark, J.; Burris, H.; Picus, J.; Schulman, L.; Thornton, D.; Lochrer, P. *Proc. Am. Soc. Clin. Oncol.* **1997**, *16*, 292a-A1038. (f) Cripps, M. C.; Burnell, M.; Jolivet, J.; Lofters, W.; Fischer, B.; Panasci, L.; Iglesias, J.; Eisenhauer, E. *Eur. J. Cancer*, **1997**, *33* (Suppl. 8), S172-a768. (g) Rusthoven, J.; Eisenhauer, E.; Butts, C.; Gregg, R.; Dancey, J.; Fisher, B.; Iglesias, J. *Eur. J. Cancer* **1997**, *33* (Suppl. 8), S231-a1045. (h) Thoedtmann, R.; Kemmerich, M.; Depenbrock, H.; Blatter, J.; Ohnmacht, U.; Rastetter, J.; Hanauske, A. R. *Eur. J. Cancer* **1997**, 33 (Suppl. 8), S247-a1116.
4. (a) For the original synthesis of DDATHF, see Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. *J. Med. Chem.* **1985**, 28, 914. (b) Beardsley, G. P.; Moroson, B. A.; Taylor, E. C.; Moran, R. G. *J. Biol. Chem.* **1989**, 264, 328. (c) Moran, R.G.; Baldwin, S.W.; Taylor, E.C.; Shih, C. *J. Biol. Chem.* **1989**, 264, 21042. (d) Baldwin, S. W.; Tse, A.; Gossett, L. S.; Taylor, E. C., Rosowsky, A.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatapour, M.; Moran, R. G. *J. Med. Chem.* **1992**, 35, 4450. (e) For reviews, see Taylor, E. C. *J. Heterocycl. Chem.* **1990**, 27, 1; Taylor, E. C. *Chemistry and Biology of Pteridines and Folates*, Ayling, J. E.; Nair, M. G.; Baugh, C. M., eds, Plenum Press, **1993**, pp. 387.
5. (a) Miwa, T.; Hitaka, T.; Akimoto, H.; Nomura, H. *J. Med. Chem.* **1991**, *34*, 555; (b) Taylor, E. C.; Patel, H. H.; Jun, J.-G. *J. Org. Chem.* **1995**, *60*, 6684; (c) Taylor, E. C.; Mao, Z. *J. Org. Chem.* **1996**, *61*, 7973.
6. Taylor, E. C.; Harrington, P. M. *J. Org. Chem.* **1990**, *55*, 3222.
7. We are indebted to Eli Lilly & Co. for the *in vitro* cell growth inhibition studies [IC_{50} (μg/ml): MTA 0.007; homo-MTA (**3**) 0.0084].
8. Several 5-(4-benzyloxyphenyl)pyrrolo[2,3-d]pyrimidines were prepared from the corresponding 5-triflates and [p-(benzyloxy)phenyl]tri-n-butyltin with $ZnCl_2$, tris-2-furylphosphine and Pd_2bda_3 [Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1993**, *58*, 403: **1995**, *60*, 5069].
9. McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 8013.