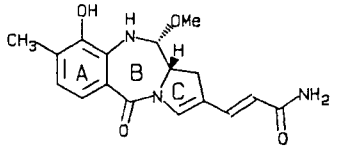
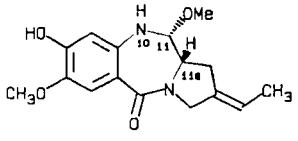
SYNTHESIS OF TOMANTHRAMYCIN, A NOVEL PYRROLO {2,1-C}{1,4}BENZO DIAZEPINE HYBRID OF ANTHRAMYCIN AND TOMAYMYCIN

A.S. Thompson, S.J. Morris, D.E. Thurston,
School of Pharmacy, Portsmouth Polytechnic PO1 2DZ.

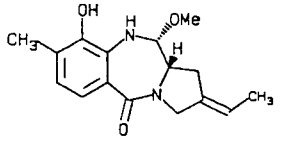
Anthramycin (**1**) and tomaymycin (**2**) are potent pyrrolo[2,1-c][1,4]benzodiazepine (PBD) antitumour antibiotics, known to exert their biological activity through the formation of an aminal linkage between the carbinolamine at N10-C11 and an exocyclic N2 of guanine in the minor groove of DNA (Hurley et al, 1984). Both anthramycin and tomaymycin have been extensively studied by footprinting and NMR which have shown that anthramycin binds unidirectionally on DNA whereas tomaymycin binds in both directions (Cheatham et al, 1988). Various considerations have been put forward to explain this phenomenon including substituent effects and ring twist between the A and C rings.



1

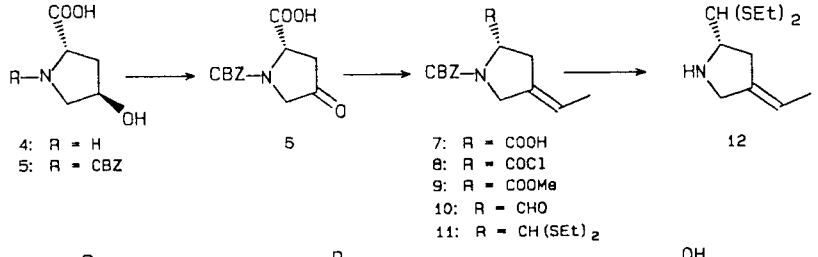


2



3

To investigate possible reasons for the different binding orientations, modelling studies have been carried out (Quanta, CHARMm) which indicate that the C-ring substituents are responsible for the overall twist of the molecule. The lesser twist of tomaymycin (anthramycin 45°, tomaymycin 9°) may explain why the planar N10-C11 imine species is easily formed in the case of tomaymycin but not anthramycin. In addition, a limited Hansch-type analysis on a larger series of PBDs has suggested that the type and pattern of substituents in the A-ring may modulate DNA-binding and biological activity. In order to study the effect of A-ring substituents versus ring twist, a fourteen-step convergent synthesis of tomanthramycin, an anthramycin-tomaymycin hybrid (**3**) has been carried out.

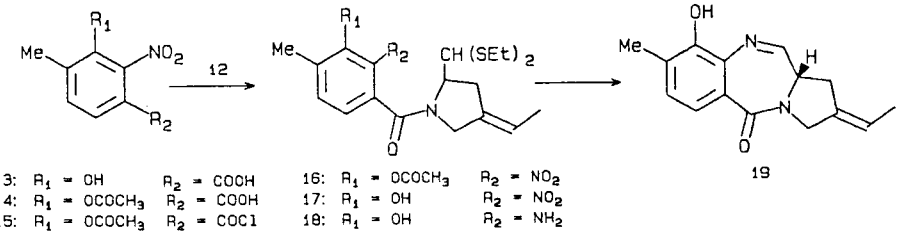


4: R = H
5: R = CBZ

5

7: R = COOH
8: R = COCl
9: R = COOMe
10: R = CHO
11: R = CH(SEt)$_2$

12



13: R_1 = OH R_2 = COOH
14: R_1 = OCOCH$_3$ R_2 = COOH
15: R_1 = OCOCH$_3$ R_2 = COCl

16: R_1 = OCOCH$_3$ R_2 = NO_2
17: R_1 = OH R_2 = NO_2
18: R_1 = OH R_2 = NH_2

19

Hydroxyproline (**4**) has been converted to the tomaymycin C-ring fragment (**12**) over seven steps and then coupled to the protected o-nitro benzoic acid (A-ring) fragment (**15**) to form the nitro thioacetal (**16**). After deacetylation and reduction of the nitro group, cyclisation with $HgCl_2/NaHCO_3$ afforded tomanthramycin imine (**19**) in 14% overall yield. The N10-C11 imine species formed spontaneously, supporting the view that the small degree of twist associated with the tomaymycin C-ring substitution pattern encourages imine formation. The structure of **19** was confirmed by ^{1}H- and ^{13}C-NMR and HR mass spectrometry (256.1186). Like other PBDs, tomanthramycin could be converted to the C11a-methyl ether (**3**) upon treatment with hot methanol.
Tomanthramycin should prove a useful tool in probing structural features important for controlling the DNA binding of PBDs. Preliminary studies indicate that the N10-C11 position is capable of reacting with nucleophiles and DNA binding studies are in progress.

Hurley, L.H., Thurston, D.E. (1984) Pharm. Res. 1: 52-59
Cheatham, S. et al (1988) J. Med. Chem. 31: 583-5901