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TOTAL SYNTHESIS OF A NEW TOPOISOMERASE II INHIBITOR BE 10988

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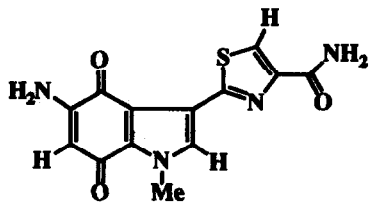
Summary: The total synthesis of a new topoisomerase II inhibitor BE 10988 is described. And the structure was unambiguously established by this synthesis.

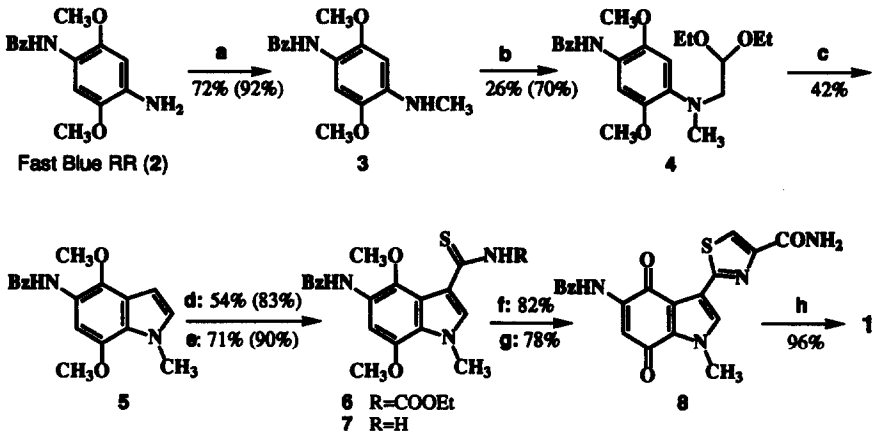
The structure of a new topoisomerase II inhibitor BE 10988 (1) isolated by our group has been determined on the basis of spectral and some chemical evidences.[1,2] Due to the fact that BE 10988 showed only six singlets in the ^{1}H NMR spectrum and almost no information about the adjacent carbon atoms to these protons has been obtained from its spectrum, the proposed structure of this unique antibiotic had some ambiguity. Furthermore, productivity of this antibiotic by micro-organism is quite low, giving us some difficulty to develop antitumor drugs. Thus, we have been trying to develope a short-step, versatile route for the synthesis of 1. Quite recently, an elegant total synthesis of 1 starting from 4-benzyloxy-5-methoxyindole-2-carboxaldehyde, the key intermediate in their work on the synthesis of mitomycin analogues, was reported by Moody and Swann, without direct comparison with natural antibiotic.[3,4] We report herein the second and short step synthesis of BE 10988, establishing the reported structure.



BE 10988 (1)

The starting material for our synthesis was commercially available Fast Blue RR (2), nicely functionalized for the construction of the indolequinone part of 1. The compound 2 was monomethylated[5] with paraformaldehyde / NaOMe / $NaBH_4$ in MeOH-THF to give 3 in 72 % yield (92 % based on reacted 2). On alkylation with bromoacetaldehyde diethylacetal, 3 produced the acetal 4[6] in 26 % yield (70 % based on reacted 3), Lewis acid

catalyzed cyclization of which afforded the indole 5[7] in 42% yield. A side chain was introduced into the 3-position of indole using ethoxycarbonyl isothiocyanate to give the ethoxycarbonyl thioamide 6[6] in 54% yield (83% based on consumed 5). Hydrolytic removal of ethoxycarbonyl group resulted in the formation of the desired thioamide 7[6] in 71% yield (90% based on reacted 6).



Scheme a) $(CH_2O)_3$ / NaOMe / $NaBH_4$ b) $(EtO)_2CHCH_2Br$ / K_2CO_3 / $MeOCH_2CH_2OH$
c) $ZnCl_2$ / DMF d) EtOOCN=C=S / Toluene e) KOH / EtOH f) $BrCH_2COCONH_2$
g) CAN / MeOH h) NH_4OH / MeOH

A thiazole ring was easily constructed by a modified Hantzsch reaction of the thioamide 7 with bromopyruvamide in high yield. The dimethoxy indole was oxidized with CAN to the quinone 8.[6] Finally, benzamide group was successfully displaced with amino group by addition-elimination reaction to give BE 10988 (1), the spectral data of which were completely identical with those of natural one. Further studies on the formation of antitumor agents derived from BE 10988 are in progress.

Footnotes and references

1) Oka, H.; Yoshinari, T.; Murai, T,; Kawamura, K.; Satoh, F.; Funaishi, K.; Okura, A.; Suda, H.; Okanishi, M.; Shizuri, Y. *J. Antibiotics*, **1991**, *44*, 486.
2) Suda, H.; Matsunaga K.; Yamamura, S.; Shizuri, Y. *Tetrahedron Letters*, **1991**, *32* , 2791.
3) Moody, C. J.; Swann, E. *Tetrahedron Letters*, **1993**, *34*, 1989.
4) Jones, G. B.; Moody, C. J. *J. Chem. Soc., Perkin Trans. I*, **1989**, 2455.
5) Barluenga, J.; Bayon, A. M.; Asencio, G. *J. Chem. Soc. Chem. Commun.*, **1984**, 1334.
6) Spectral data of these compounds are in good agreement with the structures.
7) 5: red amorphous powder; FTIR (film) 3422, 3316, 1672 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.97 (3H, s), 4.00 (3H, s), 4.03 (3H, s), 6.48 (1H, d, J = 3.1 Hz), 6.90 (1H, d, J = 3.2 Hz), 7.48~7.57 (3H, m), 7.90~7.96 (3H, m), 8.54 (1H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 36.0q, 55.6q, 60.5q, 96.9d, 97.8d, 121.6s, 122.0s, 124.6 s, 126.7 d x 2, 128.5 d x 2, 129.7d, 131.2d, 135.2s, 135.4s, 143.3s, 164.8s; HRMS found; 310.1319, calcd. 310.1317 for $C_{18}H_{18}O_3N_2$

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