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A Convenient Method for the Synthesis of Distamycin Analogue

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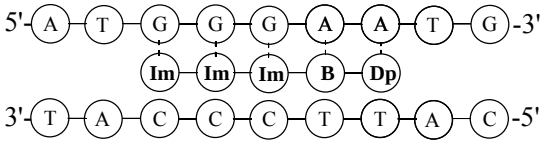
Abstract: A novel distamycin analogue was synthesized by chloroform reaction and DCC / HOBT coupling reaction without using amino protection and deprotection.

Keywords: Distamycin analogue, polyamide, chloroform reaction.

The natural distamycin is a well known antibiotic, which contains three pyrrole rings and can selectively recognize AT region in DNA minor groove[1]. However, many parts of DNA are rich of GC base pairs. For example, the telomere of DNA in cancer cell, which has repeatability GGG sequence. In this paper, 5′-GGGAA-3′ was chosen as the target site, thus we substitute pyrrole rings for imidazoles to get high affinity to GC regions according to Dervan's recognizing rules[2].

Scheme 1 Binding model of ImImImβDp designed with 5′-GGGAA-3′



Im= *N*-methylimidazole, β=β-alanine, Dp=*N, N*-dimethylaminopropylamine.

In the synthesis of ImImImβDp, the key point is that a novel chloroform reaction[3] was introduced for the construction of amide bond in a simple way that amino protection and deprotection can be avoided. Compound **1** was used as a key intermediate, which was easily prepared from commercial *N*-methylimidazole through trichloroacetylization and nitration. In the synthesis of compound **2**, **3**, **4,** amide bond was constructed by a chloroform reaction conveniently and the product **2**, **3** can precipitate from the solution avoiding separation by column chromatography. *N, N*- Dimethylaminopropylamine was introduced to increase the hydrophilicity of ImImImβDp (**5**) in the last step.

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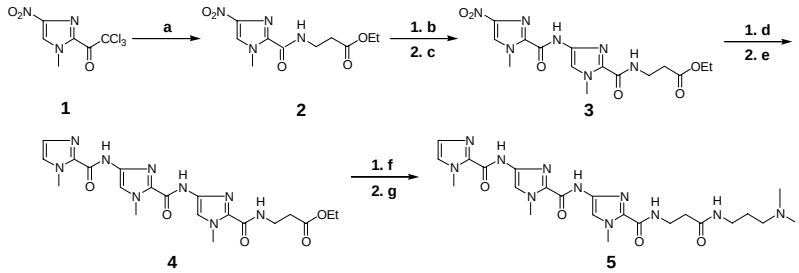
Scheme 2 The synthetic route of ImImImβDp



Reagents: **a**=$NH_2CH_2CH_2COOEt$/EtOAc; **b**=H_2, Pd-C/EtOAc; **c**=$NO_2ImCOCCl_3$; **d**=H_2, Pd-C/DMF; **e**=$ImCOCCl_3$; **f**=NaOH/H_2O; **g**=DMF, DCC/HOBT, $H_2N(CH_2)_3N(CH_3)_2$.

Experimental

ImImImβDp 5:

0.20 g (0.45 mmol) ImImImβCOOH was dissolved in 4 mL DMF. 0.07 g (0.50 mmol) HOBT and 0.11 g (0.50 mmol) DCC was added to the solution sequentially and stirred for 12 hr. Then, 0.06 mL (0.45 mmol) *N, N*-dimethylaminopropylamine was added and stirred for 12 hr. The reaction mixture was filtered and evaporated to remove DCU and DMF in vacuum, respectively. After purification by flash chromatography, 0.18 g slight yellow solid **5** was obtained (75% yield). ^{1}H-NMR($CDCl_3$, δppm): 1.66(m, 2H, CH_2), 2.20(s, 6H, $2NCH_3$), 2.37(t, 2H, J=6.5 Hz, CH_2), 2.47(t, 2H, J=6.2 Hz, CH_2), 3.37(m, 2H, CH_2), 3.68(m, 2H, CH_2), 4.03(s, 3H, NCH_3), 4.08(s, 3H, NCH_3), 4.10(s, 3H, NCH_3), 7.04(d, 1H, J=1.0 Hz, ArH), 7.09(d, 1H, J=1.0 Hz, ArH), 7.16(t, 1H, J=6.2 Hz, CONH), 7.41(s, 1H, ArH), 7.50(s, 1H, ArH), 7.82(t, 1H, J=6.2 Hz, CONH), 9.33(s, 1H, ArCONH), 9.58(s, 1H, ArCONH). FAB-MS: calcd for $C_{23}H_{34}N_{11}O_4$ (MH^+) 528, found 528.

Acknowledgments

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