Synthesis of Polyamides Containing N-Methylpyrrole and N-Methylimidazole and Their Anticancer Activity

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Three hairpin polyamides were designed and synthesized by a haloform reaction and DCC/HOBt coupling reaction without amino protection and deprotection. Their anticancer activity were investigated with three kinds of cell lines-hepatic carcinoma, lung carcinoma and gastric carcinoma, and the values of IC50 were at range of 10⁻⁷~10⁻⁸ M.

Key words: Polyamides, Haloform reaction, Anticancer activity

INTRODUCTION

Polyamides containing N-methylpyrrole (Py) and N-methylimidazole (Im) are a type of artificial DNA-binding molecules (Mrksich et al., 1994; Tao et al., 1999), which have been proven to permeate the cell membrane and regulate gene expression (Gottesfeld et al., 1997). In recent years, polyamides became the focus of chemical, biological and medical research and inspired considerable work in molecular design, DNA-recognition (Mrksich et al., 1992; Geierstanger et al., 1994; Kielkopf et al., 1998), synthetic chemistry (Baird et al., 1996; Xiao et al., 2000) and gene regulation (Dickinson et al., 1998; Szewczyk et al., 1996). Our interest in discovery and design of new anticancer drug had led us to study on the possibility for the polyamide as the candidate of anticancer compound. Here we report the synthesis of three polyamides (Fig. 1) in solution and their anticancer activity. In the polyamides, the γ-aminobutyric acid facilitate the formation of γ-turn, the β-alanine increase polyamide-DNA binding affinity, and N, N-dimethylpropyldiamine increase the polarity of the polyamides (Mrksich et al., 1992; Xiao et al., 2000).

RESULTS AND DISCUSSION

To synthesize three polyamides [PyPyPy · PyImImDp · (1), NO₂PyPy · PyImImPy · Dp(2), PyPyPyPy · PyImImPy · Dp (3)]; where Py = N-methylpyrrole, Im = N-methylimidazole, β = β-alanine, γ = γ-aminobutyric acid, Dp = N, N-dimethylpropyldiamine, 4-nitro-N-methyl-2-trichloroacetate-
tylpyrrole, 4-nitro-N-methyl-2-trichloroacetylimidazole were used as key intermediates, which were easily prepared from commercially available N-methylpyrrole and N-methylimidazole through trichloroacetylation and nitration (Baird et al., 1996; Xiao et al., 2000).

There are two subchains in the polyamides. For example, one is PyPyPy·OEt, and another is PylmlmOEt for PyPyPy·Pylmlm·Dp (1). Being different from the former step-by-step linear synthetic strategy (Baird et al., 1996), a converging synthetic strategy of the subchains condensation was employed to prepare the novel polyamides without amino protection and deprotection in a simple way.

In this research, a haloform reaction was used to synthesize the building blocks containing one or two heterocycles without column chromatography purification (Scheme 1). Then the building blocks prepared were effectively connected to synthesize the subchains by use of the DCC/HOBOT coupling reaction (Xiao et al., 2000) (Scheme 2).

After the hydrogenation of 6, which was coupled with 8 to construct containing six heterocycles 9 (1.2 g, 60% yield) in one step in the presence of DCC/HOBOT. After saponification with NaOH/ethanol solution and neutralization with 6N HCl of 9, acid 10 was obtained (0.73 g, 94% yield). The final N,N-dimethylpropyldiamine was introduced to acid 10 to give the desired polyamide 1 (45 mg, 65% yield) by the DCC/HOBOT mediated coupling reaction. The structure of the polyamide was confirmed by IR, NMR and HRMS. Polyamide 2 and 3 were prepared in the similar way.

The polyamides synthesized were tested for cytotoxicity against three kinds of cell lines - hepatic carcinoma, lung carcinoma and gastric carcinoma to assess antitumor activity by the standard assay (Lee, 1991). The in vitro antitumor activities of the polyamide 1, 2, 3 against tumor cell lines are shown in Table I.

The results of this experiment revealed high inhibition potencies of the polyamides against tumor cell, and the values of IC₅₀ were at range of 10⁻⁶–10⁻⁸ M. It has proven that the polyamides 1, 2, 3 possessed significant anticaner activity. The action of mode between the polyamides and DNA of tumor cell is through non-covalent interaction, such as hydrogen bond, van der waals and electrostatic (Mrksich et al., 1992; Kielkopf et al., 1998). Binding of the polyamides in the minor groove of the tumor cell DNA inhibits the expression of the specific gene (Gottesfeld et al., 1997; Dickinson et al., 1998) and then impedes the cell growth. The study of the exact mechanism of the action-mode for the polyamides against tumor cell is in the due course.

In conclusion, the polyamides containing N-methylpyrrole and N-methylimidazole are a new class of DNA-bind-