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Original article

Design, synthesis and biological evaluation of novel arylpiperazine derivatives on human prostate cancer cell lines

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ABSTRACT

A series of novel arylpiperazine derivatives was synthesized. The *in vitro* cytotoxic activities of all synthesized compounds against three human prostate cancer cell lines (PC-3, LNCaP, and DU145) were evaluated by a CCK-8 assay. Compounds **8**, **10**, **13**, **17** and **20** exhibited strong cytotoxic activities against the tested cancer cell lines (IC_{50} <3 μmol/L). In addition, these compounds exhibited weak cytotoxic effects on human epithelial prostate normal cells WPMY-1. The structure–activity relationship (SAR) of these arylpiperazine derivatives was also discussed based on the obtained experimental data.

1. Introduction

Prostate cancer is the most common non-skin cancer in men and is the second-leading cause of cancer-related deaths in the US [1]. Generally, the incidence rate of prostate cancer in Western countries is higher than that in Asian countries [2,3]. Prostate cancer mortality typically results from metastasis to the bone and lymph nodes, as well as the progression from androgen-dependent to androgen-independent prostatic growth [4]. Although various chemotherapeutic agents are used solely or in combination with radiotherapy to treat advanced diseases, none of the conventional approaches to cancer therapy have been proven to be highly successful for prostate cancer [5]. Therefore, inventing and developing more effective, safe and selective anti-prostate cancer drugs are urgently needed. The selective targeting of tumor cells is the goal of modern cancer chemotherapy aimed at overcoming the nonspecific toxicity of most anticancer agents against normal cells [6]. At present, much of successful cancer chemotherapy probably lies in utilizing differences in cell kinetics between tumor and normal tissue, because most drugs can show some selective toxicity toward rapidly dividing cells compared to noncycling cells [7]. So, drugs designed are expected to have high affinity with the novel targets, and they not only inhibit the proliferation but also differentiation of tumor cells and speed up their death [8].

Studies have shown that compounds with arylpiperazine moieties have anti-proliferative properties [9–11]. Naftopidil, an arylpiperazine ether derivative, is a specific α_{1d}-adrenergic receptor antagonist [12,13], and it is one of the most widely used α_1-adrenergic receptor antagonists in Japan for the treatment of benign prostatic hyperplasia (BPH) [14,15]. Recent studies have shown that naftopidil could possibly exert an anticancer effect and inhibit prostate cancer cell growth by arresting the G1 cell cycle phase [16,17], as well as inducing apoptosis in malignant mesothelioma cell lines [18]. In our previous works [19,20], we reported anti-prostate cancer activities of a series of arylpiperazine ether derivatives. In this work, we report the synthesis of a series of novel arylpiperazine amide derivatives (Scheme 1) with the intention of identifying much more effective anti-prostate cancer drugs. All synthesized compounds were evaluated for their cytotoxic activities against three human prostate cancer cell lines PC-3, LNCaP and DU145 cell line, and human prostate epithelial cell line WPMY-1. The SAR was further discussed on the basis of the obtained experimental

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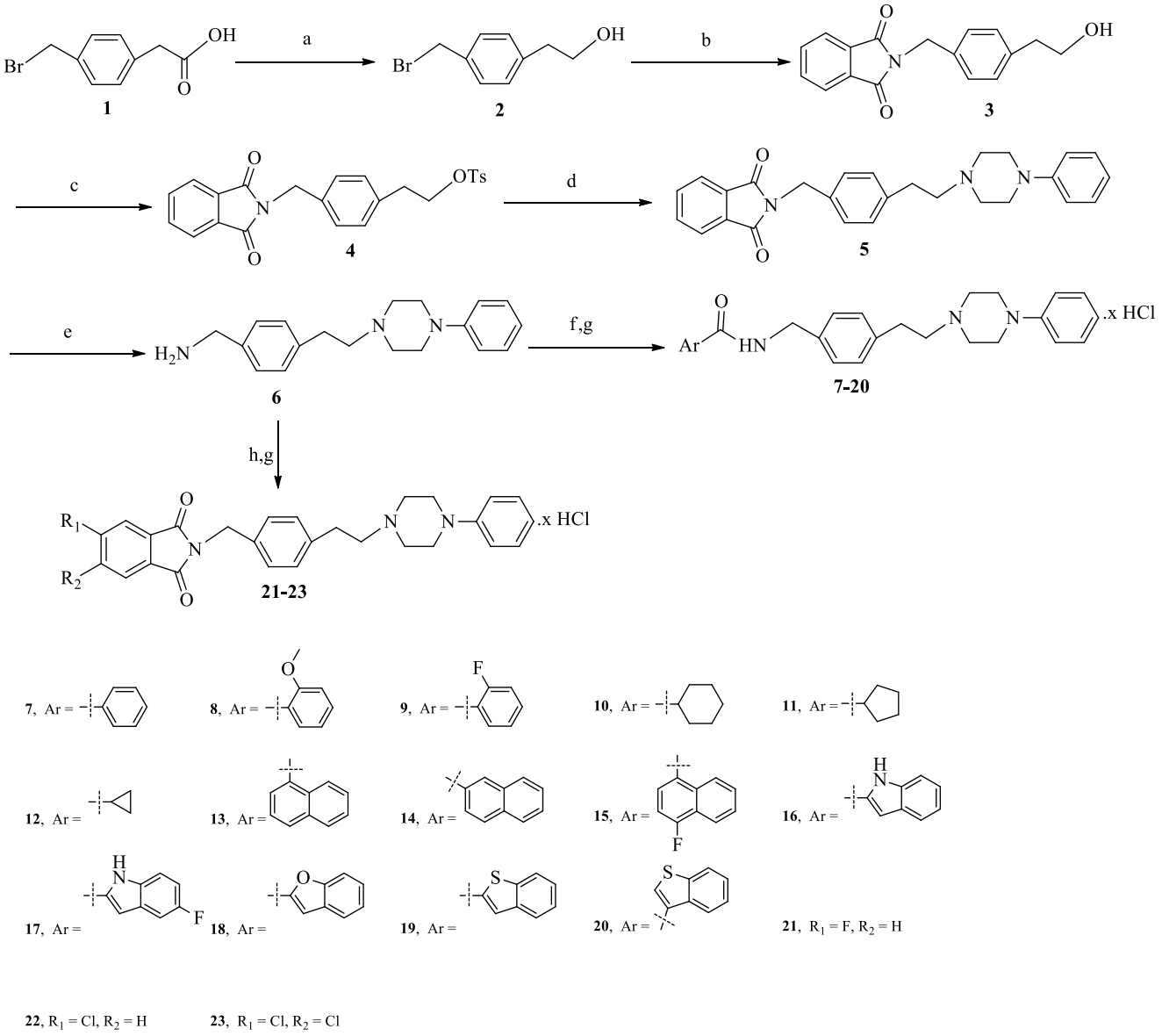

Scheme 1. Synthetic route of compounds **7–23**. Reagents and conditions: (a) $BH_3.S(CH_3)_2$, THF, 0 °C for 1 h, and then room temperature for 10 h; (b) phthalimide potassium salt, K_2CO_3, CH_3CN, reflux, 16 h; (c) TsCl, Et_3N and 4-dimethylaminopyridine, Cl_2CH_2, 0 °C, 16 h; (d) *N*-phenylpiperazine, K_2CO_3, CH_3CN, reflux, 16 h; (e) $N_2H_4.H_2O$, EtOH, room temperature, 16 h; (f) acids, DIPEA, HATU, Cl_2CH_2, room temperature, 16 h; (g) HCl, AcOEt, room temperature, 0.5 h; (h) acid anhydrides, toluene, reflux, 16 h.

data. As we expected, some arylpiperazine amide derivatives exhibited strong anti-prostate cancer activities against the tested cancer cells and potency superior to naftopidil.

2. Experimental

Reagents and solvents were commercially available. Solvents were dried and purified prior to use using standard procedures. Melting points were determined on SGW X-4 micro melting point apparatus (Shanghai Precision & Scientific Instrument Co., Ltd., Shanghai, China) and are uncorrected. NMR spectra were determined on a Bruker AV-400 NB spectrometer (Faellanden, Switzerland) or Bruker AVANCE-500 spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as internal standard, and coupling constants (*J*) are in Hz. EI mass spectra were recorded on a DSQ mass spectrometer. ESI mass spectra were recorded on an Agilent 6460 Triple Quadrupole mass spectrometer (Agilent Technologies, USA). HRMS spectra were recorded on LTQ Orbitrap LC–MS (Thermo, Rockford, IL, USA). Elemental analyses (C, H, N) were performed on an Elementar Vario EL elemental analyzer and the analytical results were within ±0.4% of the theoretical values for the formula given unless otherwise listed. Flash column chromatography was performed with silica gel (Qing Dao Ocean Chemical Factory, 300–400 mesh) eluted with petroleum ether–ethyl acetate.

2.1. Synthesis of 2-(4-(bromomethyl)phenyl)ethanol (*2*)

To a cooled (0 °C) solution of carboxylic acid **1** (5.5 g, 24 mmol) in dry tetrahydrofuran (THF, 100 mL) borane–dimethyl sulfide complex (24 mL, 0.048 mol, 2 mol/L in THF) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 10 h. Water (20 mL) was added slowly and extracted with ethyl acetate (3× 100 mL). The combined organic phase was successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The resulting residue was directly used without further purification in the following step.