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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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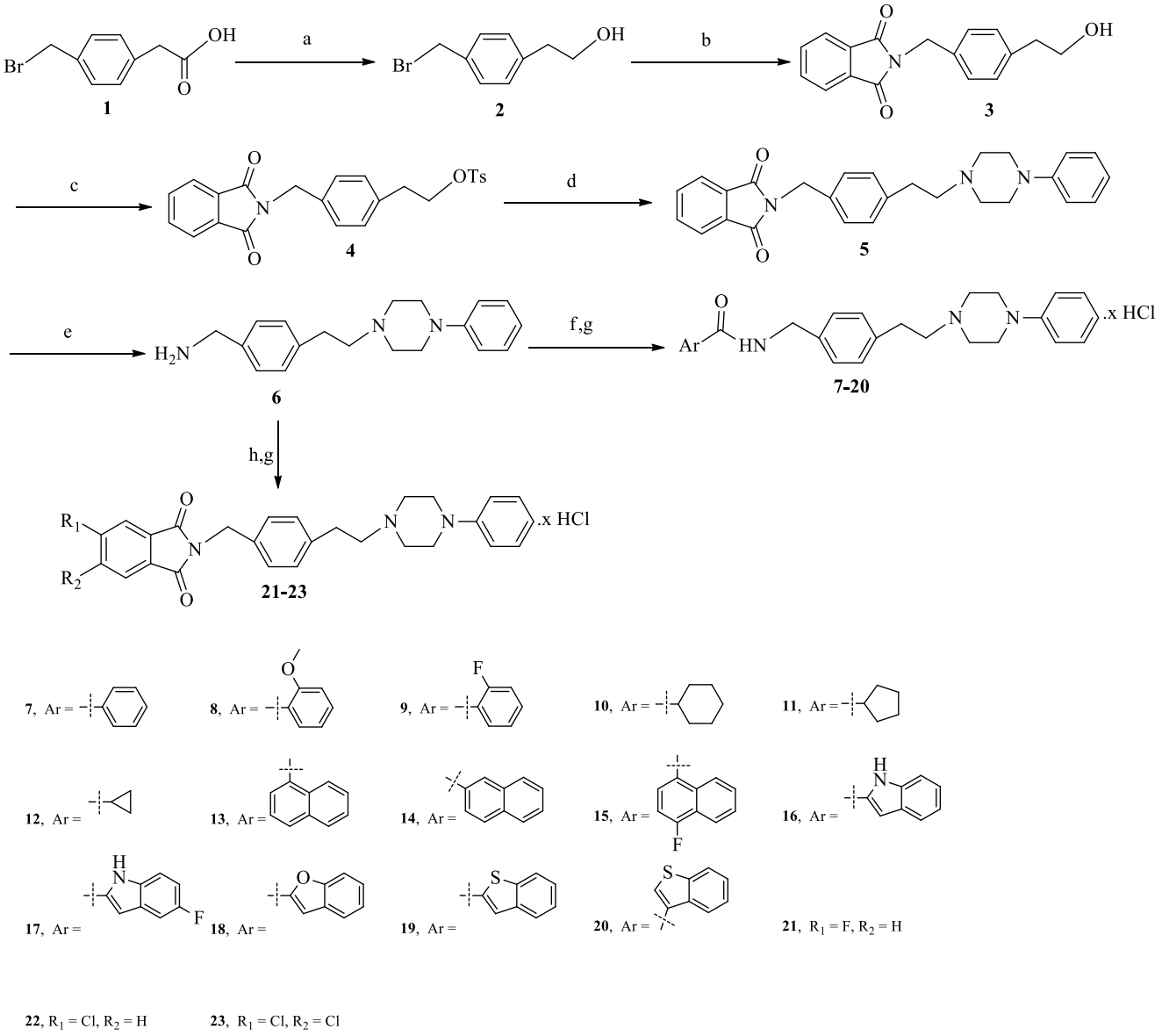

Scheme 1. Synthetic route of compounds **7–23**. Reagents and conditions: (a) $BH_3.S(CH_3)_2$, THF, 0 °C for 1 h, and then room temperature for 10 h; (b) phthalimide potassium salt, K_2CO_3, CH_3CN, reflux, 16 h; (c) TsCl, Et_3N and 4-dimethylaminopyridine, Cl_2CH_2, 0 °C, 16 h; (d) *N*-phenylpiperazine, 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.

2.2. Synthesis of 2-(4-(2-hydroxyethyl)benzyl)isoindoline-1,3-dione (**3**)

To a solution of compound **2** (4.7 g, 22 mmol) in CH_3CN (100 mL), phthalimide potassium salt (4.06 g, 22 mmol) and potassium carbonate (18.2 g, 132 mmol) were added, and the reaction mixture was stirred at reflux for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through a Buchner funnel. After filtration the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1/8, v/v) as eluent to afford 4.72 g of compound **3** (70% from compound **1**) as a white solid. Mp 101–102 °C; MS (EI, *m*/*z*): 281 (M^+), 236, 251 (100%), 232, 204, 192, 178, 160; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.70 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.38 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 4.82 (s, 2H), 3.82 (t, 2H, *J* = 6.5 Hz), 2.83 (t, 2H, *J* = 6.5 Hz), 1.44 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 138.6, 135.0, 134.4, 132.6, 129.7, 129.3, 123.7, 64.0, 41.7, 39.3.

2.3. Synthesis of 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)phenyl)ethyl 4-methylbenzenesulfonate (**4**)

To a solution of compound **3** (4.72 g, 16.8 mmol), triethylamine (6.79 g, 67.2 mmol) and 4-dimethylaminopyridine (0.13 g, 1.05 mmol) in dry dichloromethane (CH_2Cl_2, 80 mL) at 0 °C was added dropwise a solution of 4-toluene sulfonyl chloride (4.79 g, 25.2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 °C for 16 h. Water (20 mL) was added slowly and the reaction mixture was extracted with CH_2Cl_2 (2× 50 mL). The combined organic phase was successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1/10, v/v) as eluent to afford 6.9 g (95%) of compound **4** as a white solid. Mp 108–109 °C; MS (EI, *m*/*z*): 435 (M^+), 363, 250 (100%), 235, 204, 178, 148; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.71 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.66 (d, 2H, *J* = 8.3 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.3 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 4.81 (s, 2H), 4.16 (t, 2H, *J* = 7.0 Hz), 2.91 (t, 2H, *J* = 7.0 Hz), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 145.1, 136.3, 135.5, 134.4, 133.4, 132.6, 130.2, 129.6, 129.2, 128.3, 123.8, 70.8, 41.6, 35.4, 22.0.

2.4. Synthesis of 2-(4-(2-(4-phenylpiperazin-1-yl)ethyl)benzyl) isoindoline-1,3-dione (**5**)

To a solution of **4** (6.9 g, 15.9 mmol) in acetonitrile (CH_3CN, 50 mL) *N*-phenylpiperazine (3.09 g, 19.08 mmol) and potassium carbonate (13.16 g, 95.4 mmol) were added. The reaction mixture was stirred at reflux for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through a Buchner funnel. After filtration the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1/8, v/v) as eluent to afford 5.0 g (74%) of compound **5** as a white solid. Mp 130–131 °C; HRMS (ESI): calcd for $C_{27}H_{27}N_3O_2$, 426.2176 $[M+1]^+$, found, 426.2169 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.70 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 7.28–7.24 (m, 2H), 7.18 (d, 2H, *J* = 8.1 Hz), 6.93 (d, 2H, *J* = 7.9 Hz), 6.85 (t, 1H, *J* = 7.3 Hz), 4.82 (s, 2H), 3.22 (t, 4H, *J* = 5.0 Hz), 2.81 (dd, 2H, *J* = 9.8, 6.3 Hz), 2.67 (t, 4H, *J* = 5.0 Hz), 2.62 (dd, 2H, *J* = 9.8, 6.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 151.4, 140.0, 134.3, 134.0, 132.3, 129.2, 129.1, 128.9, 123.4, 119.8, 116.2, 60.4, 53.3, 49.3, 41.4, 33.3.

2.5. Synthesis of (4-(2-(4-phenylpiperazin-1-yl)ethyl)phenyl) methanamine (**6**)

To a solution of **5** (5.0 g, 11.8 mmol) in ethanol hydrazine hydrate (5.9 g, 118 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a Buchner funnel. After filtration the filtrate was concentrated *in vacuo* to afforded 3 g crude product **6**. The resulting crude product was directly used without further purification in the following step.

2.6. General procedure for the preparation of arylpiperazine derivative hydrochloride salts **7**–**20**

To a solution of **6** (100 mg, 3.39 mmol) in CH_2Cl_2 (20 mL) was added the corresponding acid (1.2 equiv.), *N*,*N*-diisopropylethylamine (DIPEA, 4 equiv.) and 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU, 1 equiv.). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a Buchner funnel. After filtration the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1/7, v/v) as eluent to afford the corresponding products (**7**–**20**). To a solution of the above corresponding products in ethyl acetate was added dropwise 4 mol/L HCl solution in ethyl acetate (50 mL), while maintaining stirring for 0.5 h. Then the resulting solid was collected by filtration to give corresponding hydrochloride salts as a white solid.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzamide dihydrochloride (**7**): White solid; Yield: 45%; Mp 152–153 °C (HCl salt); MS (ESI, *m*/*z*): 400.2 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.51 (s, 1H), 8.68 (t, 1H, *J* = 6.0 Hz), 7.68–7.54 (m, 2H), 7.35–7.20 (m, 7H), 7.14 (d, 1H, *J* = 8.3 Hz), 7.05 (t, 3H, *J* = 7.6 Hz), 6.77 (t, 1H, *J* = 7.3 Hz), 4.46 (d, 2H, *J* = 6.0 Hz), 3.81 (d, 2H, *J* = 11.0 Hz), 3.64 (d, 2H, *J* = 11.0 Hz), 3.41–3.02 (m, 8H); Anal. Calcd. for $C_{26}H_{29}N_3O.2HCl$: C, 66.10; H, 6.61; N, 8.89. Found: C, 66.25; H, 6.67; N, 8.78.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-2-methoxybenzamide hydrochloride dihydrochloride (**8**): White solid; Yield: 52%; Mp 168–169 °C (HCl salt); MS (ESI, *m*/*z*): 430.2 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.58 (s, 1H), 8.66 (t, 1H, *J* = 6.0 Hz), 7.74 (dd, 1H, *J* = 7.6, 1.7 Hz), 7.52–7.41 (m, 1H), 7.35–7.20 (m, 6H), 7.14 (d, 1H, *J* = 8.3 Hz), 7.03 (t, 3H, *J* = 7.6 Hz), 6.87 (t, 1H, *J* = 7.3 Hz), 4.48 (d, 2H, *J* = 6.0 Hz), 3.89 (s, 3H), 3.82 (d, 2H, *J* = 11.0 Hz), 3.62 (d, 2H, *J* = 11.0 Hz), 3.41–3.02 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.3, 157.1, 149.6, 138.4, 135.6, 132.3, 130.5, 129.3, 128.7, 127.5, 123.4, 120.6, 120.2, 116.2, 112.2, 56.2, 56.0, 50.6, 45.6, 42.4, 40.3, 29.0; Anal. Calcd. for $C_{27}H_{31}N_3O_2.2HCl$: C, 64.54; H, 6.62; N, 8.36. Found: C, 64.12; H, 6.67; N, 8.19.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-2-fluorobenzamide dihydrochloride (**9**): White solid; Yield: 46%; Mp 177–178 °C (HCl salt); MS (ESI, *m*/*z*): 418.2 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 8.86 (t, 1H, *J* = 6.0 Hz), 7.64 (td, 1H, *J* = 7.5, 1.5 Hz), 7.57–7.48 (m, 1H), 7.32–7.25 (m, 8H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.3 Hz), 4.45 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 11.0 Hz), 3.62 (d, 2H, *J* = 11.0 Hz), 3.41–3.06 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.9, 160.5, 158.0, 149.6, 138.0, 135.7, 132.5, 132.5, 130.2, 129.3, 128.7, 127.6, 124.6, 124.3, 124.1, 120.2, 116.3, 116.2, 56.2, 50.7, 45.6, 42.5, 29.0; Anal. Calcd. for $C_{26}H_{28}FN_3O.2HCl$: C, 63.67; H, 6.17; N, 8.57. Found: C, 63.36; H, 6.41; N, 8.23.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)cyclohexanecarboxamide dihydrochloride (**10**): White solid; Yield: 40%; Mp 192–193 °C(HCl salt); MS (ESI, *m*/*z*): 406.2 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (s, 1H), 8.21 (t, 1H, *J* = 6.0 Hz), 7.31–7.16 (m, 7H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 4.22

(d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.6 Hz), 3.62 (d, 2H, *J* = 10.6 Hz), 3.41–3.02 (m, 8H), 2.24–2.07 (m, 1H), 1.70 (d, 4H, *J* = 11.2 Hz), 1.61 (d, 1H, *J* = 10.1 Hz), 1.46–1.08 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.2, 149.6, 138.6, 135.5, 129.2, 128.7, 127.4, 120.2, 116.1, 56.2, 50.7, 45.6, 44.1, 41.62, 29.4, 29.0, 25.6, 25.4; Anal. Calcd. for $C_{26}H_{33}N_3O.2HCl$: C, 65.26; H, 7.79; N, 8.78. Found: C, 64.91; H, 7.60; N, 8.50.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)cyclopentanecarboxamide dihydrochloride (**11**): White solid; Yield: 44%; Mp 161–162 °C (HCl salt); MS (ESI, *m*/*z*): 392.2 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 8.28 (t, 1H, *J* = 6.0 Hz), 7.37–7.16 (m, 6H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 4.23 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.6 Hz), 3.62 (d, 2H, *J* = 10.6 Hz), 3.42–3.00 (m, 8H), 2.78–2.54 (m, 1H), 1.78–1.50 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.1, 149.4, 138.4, 135.3, 129.0, 128.5, 127.3, 120.0, 115.9, 56.0, 50.4, 45.3, 44.2, 41.6, 29.9, 28.8, 25.5; Anal. Calcd. for $C_{25}H_{33}N_3O.2HCl$: C, 64.65; H, 7.60; N, 9.05. Found: C, 64.58; H, 7.74; N, 8.85.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)cyclopropanecarboxamide dihydrochloride (**12**): White solid; Yield: 39%; Mp 172–173 °C (HCl salt); MS (ESI, *m*/*z*): 364.2 [M+1]$^+$; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.58 (t, 1H, *J* = 6.0 Hz), 7.36–7.15 (m, 6H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 4.25 (d, 2H, *J* = 6.0 Hz), 3.84 (d, 2H, *J* = 10.6 Hz), 3.63 (d, 2H, *J* = 10.6 Hz), 3.44–2.98 (m, 8H), 1.72–1.35 (m, 1H), 0.78–0.54 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 172.8, 149.8, 138.6, 135.7, 129.4, 128.9, 127.9, 120.3, 116.2, 56.3, 50.8, 45.7, 42.1, 29.2, 13.8, 6.5; Anal. Calcd. for $C_{23}H_{29}N_3O.2HCl$: C, 63.30; H, 7.16; N, 9.63. Found: C, 62.97; H, 6.39; N, 9.57.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-1-naphthamide dihydrochloride (**13**): White solid; Yield: 59%; Mp 191–192 °C (HCl salt); MS (ESI, *m*/*z*): 450.2 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 9.09 (t, 1H, *J* = 6.0 Hz), 8.23–8.18 (m, 1H), 8.02 (d, 1H, *J* = 8.2 Hz), 8.00–7.96 (m, 1H), 7.65 (d, 1H, *J* = 6.5 Hz), 7.59–7.51 (m, 3H), 7.39 (d, 2H, *J* = 8.0 Hz), 7.32–7.21 (m, 4H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 4.53 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.9 Hz), 3.63 (d, 2H, *J* = 10.9 Hz), 3.51–3.01 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.3, 150.2, 138.9, 136.3, 135.3, 133.9, 130.6, 129.9, 129.4, 129.0, 128.3, 127.4, 126.9, 126.0, 125.9, 125.7, 120.8, 116.8, 56.8, 51.3, 46.2, 43.0, 29.6; Anal. Calcd. for $C_{30}H_{31}N_3O.2HCl$: C, 68.96; H, 6.37; N, 8.04. Found: C, 68.59; H, 6.42; N, 7.89.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-2-naphthamide dihydrochloride (**14**): White solid; Yield: 37%; Mp 188–189 °C (HCl salt); MS (ESI, *m*/*z*): 450.2 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 9.24 (t, 1H, *J* = 6.0 Hz), 8.52 (s, 1H), 8.13–7.88 (m, 4H), 7.72–7.50 (m, 2H), 7.35 (d, 2H, *J* = 8.0 Hz), 7.30–7.09 (m, 4H), 7.01 (d, 2H, *J* = 8.0 Hz), 6.86 (t, 1H, *J* = 7.2 Hz), 4.52 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.9 Hz), 3.62 (d, 2H, *J* = 10.9 Hz), 3.48–2.93 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.9, 149.2, 138.0, 135.2, 133.8, 131.9, 131.4, 128.8, 128.5, 128.3, 127.6, 127.4, 127.3, 127.2, 126.4, 123.9, 119.7, 115.7, 55.8, 50.3, 45.1, 42.2, 28.6; Anal. Calcd. for $C_{30}H_{31}N_3O.2HCl$: C, 68.96; H, 6.37; N, 8.04. Found: C, 68.62; H, 6.43; N, 7.93.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-4-fluoro-1-naphthamide dihydrochloride (**15**): White solid; Yield: 50%; Mp 202–203 °C (HCl salt); MS (ESI, *m*/*z*): 468.1 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 9.11 (t, 1H, *J* = 6.0 Hz), 8.39–8.20 (m, 1H), 8.11 (dd, 1H, *J* = 6.4, 3.2 Hz), 7.76–7.58 (m, 3H), 7.48–7.15 (m, 7H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 4.52 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.9 Hz), 3.63 (d, 2H, *J* = 10.9 Hz), 3.46–3.00 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.9, 160.0, 157.5, 149.7, 138.2, 135.7, 131.7, 131.1, 129.2, 128.8, 128.0, 127.7, 127.1, 126.1, 126.0, 125.7, 123.1, 122.9, 120.1, 116.1, 109.0, 108.8, 56.2, 50.7, 45.5, 42.5, 29.0; Anal. Calcd. for $C_{30}H_{30}N_4O.2HCl$: C, 66.66; H, 5.97; N, 7.77. Found: C, 66.40; H, 6.23; N, 7.53.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-1*H*-indole-2-carboxamide dihydrochloride (**16**): White solid; Yield: 57%; Mp 163–164 °C (HCl salt); MS (ESI, *m*/*z*): 439.1 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.63 (s, 1H), 11.47 (s, 1H), 9.11 (t, 1H, *J* = 6.0 Hz), 7.60 (d, 1H, *J* = 8.0 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 7.30–6.97 (m, 9H), 6.87 (t, 1H, *J* = 7.2 Hz), 4.49 (d, 2H, *J* = 6.0 Hz), 3.81 (d, 2H, *J* = 10.8 Hz), 3.61 (d, 2H, *J* = 10.8 Hz), 3.36–3.02 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.2, 149.6, 138.4, 136.6, 135.7, 131.8, 129.2, 128.7, 127.7, 127.2, 123.4, 121.6, 120.2, 119.8, 116.2, 112.4, 102.9, 56.2, 50.7, 45.6, 42.0, 29.0; Anal. Calcd. for $C_{28}H_{30}N_4O.2HCl$: C, 65.75; H, 6.31; N, 10.95. Found: C, 65.59; H, 6.45; N, 10.69.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-5-fluoro-1*H*-indole-2-carboxamid dihydrochloride (**17**): White solid; Yield: 47%; Mp 193–194 °C (HCl salt); MS (ESI, *m*/*z*): 457.1 [M+1]$^+$; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.75 (s, 1H), 11.17 (s, 1H), 9.16 (t, 1H, *J* = 6.0 Hz), 7.50–7.21 (m, 9H), 7.07–6.94 (m, 3H), 6.86 (t, 1H, *J* = 7.2 Hz), 4.48 (d, 2H, *J* = 6.0 Hz), 3.81 (d, 2H, *J* = 10.8 Hz), 3.61 (d, 2H, *J* = 10.8 Hz), 3.34–3.04 (m, 8H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.9, 158.2, 156.3, 149.7, 138.3, 135.7, 133.4, 133.3, 129.3, 128.8, 127.7, 127.3, 127.2, 120.2, 116.1, 113.7, 113.6, 112.3, 112.0, 105.9, 105.7, 102.9, 56.3, 50.7, 45.6, 42.0, 29.1; Anal. Calcd. for $C_{28}H_{29}FN_4O.2HCl$: C, 63.52; H, 5.90; N, 10.58. Found: C, 63.87; H, 5.99; N, 10.47.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzofuran-2-carboxamide (**18**): White solid; Yield: 56%; Mp 166–167 °C; MS (ESI, *m*/*z*): 440.1 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (t, 1H, *J* = 6.0 Hz), 7.77 (d, 1H, *J* = 7.8 Hz), 7.65 (d, 1H, *J* = 8.3 Hz), 7.56 (s, 1H), 7.46 (t, 1H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.5 Hz), 7.26–7.17 (m, 6H), 6.91 (d, 2H, *J* = 8.0 Hz), 6.76 (t, 1H, *J* = 7.2 Hz), 4.45 (d, 2H, *J* = 6.0 Hz), 3.12 (br s, 4H), 2.88–2.51 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.6, 154.8, 151.6, 149.7, 139.5, 137.3, 129.4, 129.1, 127.9, 127.7, 127.3, 124.2, 123.3, 119.2, 115.8, 112.3, 110.1, 110.0, 60.2, 53.2, 48.7, 42.5, 32.9; Anal. Calcd. for $C_{28}H_{29}N_3O_2$: C, 76.51; H, 6.65; N, 9.56. Found: C, 76.48; H, 6.74; N, 9.47.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzo[b]thiophene-2-carboxamide dihydrochloride (**19**): White solid; Yield: 34%; Mp 176–177 °C (HCl salt); MS (ESI, *m*/*z*): 456.2 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.51 (s, 1H), 9.42 (t, 1H, *J* = 6.0 Hz), 8.20 (s, 1H), 8.08–7.88 (m, 2H), 7.51–7.38 (m, 2H), 7.34 (d, 2H, *J* = 8.0 Hz), 7.30–7.20 (m, 4H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 4.47 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.8 Hz), 3.62 (d, 2H, *J* = 10.8 Hz), 3.41–3.05 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.0, 150.0, 140.7, 140.4, 139.7, 138.4, 136.3, 129.7, 129.2, 128.3, 126.7, 125.7, 125.5, 125.4, 123.3, 120.6, 116.6, 56.6, 51.1, 46.0, 43.0, 40.7, 40.5, 40.3, 29.4; Anal. Calcd. for $C_{28}H_{29}N_3OS.2HCl$: C, 63.63; H, 5.91; N, 7.95. Found: C, 63.40; H, 6.06; N, 7.65.

N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzo[b]thiophene-3-carboxamide dihydrochloride (**20**): White solid; Yield: 27%; Mp 179–180 °C (HCl salt); MS (ESI, *m*/*z*): 456.1 [M+1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 9.08 (t, 1H, *J* = 6.0 Hz), 8.53–8.38 (m, 2H), 8.04 (d, 1H, *J* = 7.7 Hz), 7.49–7.20 (m, 8H), 7.01 (d, 2H, *J* = 8.0 Hz), 6.86 (t, 1H, *J* = 7.2 Hz), 4.48 (d, 2H, *J* = 6.0 Hz), 3.82 (d, 2H, *J* = 10.8 Hz), 3.62 (d, 2H, *J* = 10.8 Hz), 3.44–3.04 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.6, 149.0, 138.9, 137.8, 136.8, 135.0, 130.3, 128.6, 128.1, 127.1, 124.3, 124.3, 124.0, 122.2, 119.5, 115.5, 55.6, 50.1, 44.9, 41.5, 39.7, 39.5, 39.3, 28.4; Anal. Calcd. for $C_{28}H_{29}N_3OS.2HCl$: C, 63.63; H, 5.91; N, 7.95. Found: C, 63.27; H, 6.00; N, 7.87.

*2.7. General procedure for the preparation of arylpiperazine derivative hydrochloride salts **21–23***

To a solution of **6** (100 mg, 3.39 mmol) in toluene (20 mL) was added the corresponding acid anhydride (1.5 equiv.). The reaction

mixture was stirred at reflux for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through a Buchner funnel. After filtration the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1/7, v/v) as eluent to afford the corresponding products (**21**–**23**). To a solution of above corresponding products in ethyl acetate was added dropwise 4 mol/L HCl solution in ethyl acetate (50 mL), while maintaining stirring for 0.5 h. Then the resulting solid was collected by filtration to give corresponding hydrochloride salts as a white solid.

2-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-5-fluoroisoindoline-1,3-dione dihydrochloride (**21**): White solid; Yield: 38%; Mp 201–202 °C (HCl salt); MS (ESI, *m/z*): 444.1 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.30 (s, 1H), 7.96 (dd, 1H, *J* = 8.2, 4.5 Hz), 7.78 (dd, 1H, *J* = 7.4, 2.2 Hz), 7.73–7.63 (m, 1H), 7.29 (d, 3H, *J* = 8.3 Hz), 7.25 (d, 3H, *J* = 8.3 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 6.86 (t, 1H, *J* = 7.2 Hz), 4.75 (s, 2H), 3.81 (d, 2H, *J* = 9.8 Hz), 3.61 (d, 2H, *J* = 9.8 Hz), 3.42–2.96 (m, 8H); Anal. Calcd. for $C_{27}H_{26}FN_3O.2HCl$: C, 62.79; H, 5.46; N, 8.14. Found: C, 63.03; H, 5.59; N, 7.91.

2-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-5-chloroisoindoline-1,3-dione dihydrochloride (**22**): White solid; Yield: 45%; Mp 204–205 °C (HCl salt); MS (ESI, *m/z*): 460.1 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H), 7.90 (dd, 1H, *J* = 8.0, 4.6 Hz), 7.80–7.65 (m, 2H), 7.30 (d, 3H, *J* = 8.0 Hz), 7.26 (d, 3H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.1 Hz), 6.78 (t, 1H, *J* = 7.2 Hz), 4.76 (s, 2H), 3.82 (d, 2H, *J* = 9.8 Hz), 3.63 (d, 2H, *J* = 9.8 Hz), 3.46–2.94 (m, 8H); Anal. Calcd. for $C_{27}H_{26}ClN_3O_2.2HCl$: C, 60.85; H, 5.30; N, 7.89. Found: C, 60.74; H, 5.38; N, 7.91.

2-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-5,6-dichloroisoindoline-1,3-dione (**23**): White solid; Yield: 40%; Mp 103–104 °C; MS (ESI, *m/z*): 494.1 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 2H), 7.42–7.09 (m, 6H), 6.91 (d, 2H, *J* = 8.0 Hz), 6.76 (t, 1H, *J* = 7.2 Hz), 4.73 (s, 2H), 3.29 (br s, 4H), 3.11 (br s, 4H), 2.74 (t, 2H, *J* = 7.2 Hz), 2.56 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.6, 150.7, 139.5, 137.1, 133.5, 131.3, 128.6, 127.1, 125.1, 118.4, 115.0, 59.2, 52.3, 47.8, 40.7, 32.0; Anal. Calcd. for $C_{27}H_{25}Cl_2N_3O_2$: C, 65.59; H, 5.10; N, 8.50; Found: C, 65.45; H, 5.12; N, 8.46.

2.8. Biological activity

2.8.1. Cell culture

PC-3 and WPMY-1 cells were cultured in Dulbecco's modification Eagle's medium (DMEM, Invitrogen, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS, Hyclone, Logan, UT, USA), 100 U/mL penicillin and 0.1 mg/mL streptomycin (Invitrogen). DU145 cells were cultured in RPMI1640 media supplemented with 10% fetal bovine serum (FBS, Hyclone), 100 U/mL penicillin and 0.1 mg/mL streptomycin (Invitrogen). LNCaP cells were cultured in F12 media supplemented with 10% fetal bovine serum (FBS, Hyclone), 100 U/mL penicillin and 0.1 mg/mL streptomycin (Invitrogen). The cells were incubated at 37 °C in a humidified atmosphere with 5% CO_2.

2.8.2. Assessment of antitumor activity by CCK-8 assay

Cell proliferation was measured with the Cell Counting Kit-8 (CCK-8) assay kit (Dojindo Corp., Kumamoto, Japan). Cells were harvested during logarithmic growth phase and seeded in 96-well plates at a density of 1×10^5 cells/mL, and cultured at 37 °C in a humidified incubator (5% CO_2) for 24 h, followed by exposure to various concentrations of compounds tested for 24 h. Subsequently 10 μL of CCK-8 (Dojindo) was added to each well, the cells were then incubated for an additional 1 h at 37 °C to convert WST-8 into formazan. Cell growth inhibition was determined by measuring the absorbance (Abs) at λ = 450 nm using a microplate reader. Three independent experiments were performed. Cell growth inhibition was calculated according to the following equation:

$$\text{Growth inhibition} = \left(1 - \frac{\text{OD of treated cells}}{\text{OD of control cells}}\right) \times 100\%$$

The half maximal inhibitory concentrations (IC_{50}) were obtained from liner regression analysis of the concentration–response curves plotted for each tested compound.

3. Results and discussion

3.1. Chemistry

As depicted in Scheme 1, a series of novel arylpiperazine derivatives were synthesized starting from the commercially available 2-(4-(bromomethyl)phenyl)acetic acid **1**. First, compound **1** was reduced to alcohol **2** in the presence of a borane–methyl sulfide complex (2 mol/L in tetrahydrofuran) at 0 °C for 1 h, and then at room temperature for 10 h. The intermediate **2** was directly used without further purification. The nucleophilic substitution reaction of compound **2** with phthalimide potassium salt in the presence of potassium carbonate (K_2CO_3) gave compound **3** (70% yield from compound **1**) after 16 h at reflux. Compound **3** was treated with 4-toluene-sulfonyl chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine at 0 °C for 16 h to generate compound **4** (95% yield). The reaction of compound **4** with N-Phenylpiperazine in the presence of K_2CO_3 at reflux for 16 h gave arylpiperazine derivative **5**, and then the deprotection of the phthaloyl group gave amine compound **6**. The intermediate **6** was directly used without further purification. Finally, the condensation of compound **6** and various acids (in the presence of DIPEA and HATU) or acid anhydrides gave arylpiperazine derivatives **7**–**23** (27%–59% yield; Scheme 1). The structures of the compounds (as their HCl salts) were confirmed using ^{1}H NMR, ^{13}C NMR, MS and elemental analyses (C, H, and N).

3.2. Evaluation of the bioactivity

The synthesized target compounds **7**–**23** were evaluated for their *in vitro* cytotoxic activities against the three human prostate cancer cell lines (PC-3, LNCaP, and DU145), and compared with their effects on human prostate epithelial cell line WPMY-1 by CCK-8 assay [19–23]. The results are summarized in Table 1. As shown in Table 1, some compounds exhibited strong cytotoxic activities against the tested cancer cell lines, and even exhibited much better activity than naftopidil. For example, the compounds **8**–**10**, **13** and **16**–**20** exhibited strong cytotoxic activities against the tested cancer cell lines ($IC_{50} < 10$ μmol/L), and these compounds exhibited weak cytotoxic effects on human epithelial prostate normal cells WPMY-1. In addition, compounds **10** and **20** showed potent activity against tested cancer cells.

The SAR analysis revealed the following: (1) Compared to compound **7**, compound **13** (IC_{50} = 2.31 and 6.73 μmol/L, respectively) exhibited potent cytotoxic activities against LNCaP and DU145 cells. These results suggest that the introduction of a large hydrophobic group was beneficial for anti-cancer activity. Moreover, compound **13** exhibited weak cytotoxic effects on human epithelial prostate normal cells WPMY-1. (2) Compound **8** exhibited strong cytotoxic activities against PC-3 cells compared with compound **9**, however, these activities decreased significantly in DU145 cells. (3) Compound **10** exhibited a more effective cytotoxic activity than compounds **11** and **12** against tested cancer cells. These results suggest that the introduction of a large group was beneficial for anti-cancer activity. In addition, compound **10**

Table 1
In vitro cytotoxicity of compounds **7**–**23**.

Compd.	IC_{50} (μmol/L)[a]			
	PC-3[b]	LNCaP[b]	DU145[b]	WPMY-1[b]
5	>50	>50	2.23 ± 0.29	>50
7	33.42 ± 0.67	>50	13.26 ± 0.48	>50
8	1.05 ± 0.27	>50	>50	43.06 ± 0.39
9	>50	13.44 ± 0.54	4.06 ± 0.07	>50
10	1.18 ± 0.08	6.23 ± 0.24	1.23 ± 0.09	>50
11	47.69 ± 1.67	33.21 ± 0.68	44.62 ± 1.02	>50
12	32.60 ± 0.14	25.26 ± 0.60	26.06 ± 1.13	>50
13	>50	2.31 ± 0.05	6.73 ± 0.30	>50
14	>50	>50	>50	>50
15	>50	33.30 ± 0.49	>50	>50
16	5.50 ± 0.34	>50	5.50 ± 0.32	>50
17	>50	29.57 ± 0.43	2.42 ± 0.30	>50
18	27.60 ± 0.04	17.79 ± 0.20	5.17 ± 0.17	>50
19	>50	14.30 ± 0.56	8.21 ± 0.60	40.12 ± 1.40
20	5.30 ± 0.14	3.29 ± 0.09	1.23 ± 0.08	>50
21	>50	>50	>50	>50
22	>50	32.16 ± 1.62	22.17 ± 1.25	>50
23	>50	>50	47.70 ± 1.14	>50
Naftopidil	42.10 ± 0.79	22.36 ± 0.61	34.58 ± 0.31	>50

[a] IC_{50} values are taken as means ± standard deviation from three experiments.
[b] PC-3, LNCaP and DU145, human prostate cancer cell line; WPMY-1, the human prostate epithelial cell line.

exhibited weak cytotoxic effects on human epithelial prostate normal cells WPMY-1. (4) Compound **14** lost potency (IC_{50} > 50 μmol/L) against LNCaP and DU145 cells compared with compound **13**. These results suggest that the introduction of β-naphtholyl group was detrimental for anti-cancer activity. (5) Moreover, compounds containing α-indolyl group showed better activity for PC-3 cells than did the α-naphtholyl group for PC-3 cells, as exemplified by compound **16** (IC_{50} = 5.50 μmol/L) which showed strong activity, while compound **13** lost potency (IC_{50} > 50 μmol/L). (6) Compounds **16**, **18** and **19** containing heteroatom at the aryl group displayed potent cytotoxic activity against DU145 cells (IC_{50} = 5.50, 5.17 and 8.21 μmol/L, respectively). Moreover, these compounds exhibited weak cytotoxic effects on human epithelial prostate normal cells WPMY-1. In addition, compounds **18** and **19** showed excellent selective activity for DU145 cells over the other tested cancer cells. (7) Compared to compound **19**, compound **20** (IC_{50} = 5.30, 3.29 and 1.23 μmol/L, respectively) exhibited strong cytotoxic activities against PC-3, LNCaP and DU145 cells. These results suggest that the introduction of a 3-benzo[b]thiophenyl group was beneficial for anti-cancer activity. (8) To compare the cytotoxic activities of arylpiperazine amide derivatives **7**–**23** against PC-3, LNCaP and DU145 cells, arylpiperazine imide derivatives **21**–**23** (Scheme 1) were synthesized. As shown in Table 1, compounds **21**–**23** exhibited weak to moderate cytotoxic activities against the tested cancer cell lines, however, the intermediate **5** (IC_{50} = 2.23 μmol/L) exhibited strong cytotoxic activities against DU145 cells.

4. Conclusion

This paper has reported the synthesis and biological evaluation against three human prostate cancer cells and human prostate epithelial cells of a novel class of arylpiperazine derivatives. Some compounds exhibited strong cytotoxic activities against tested cancer cell lines. Compounds **8**, **10** and **20** demonstrated a relatively strong cytotoxicity against PC-3 and DU145 cells (IC_{50} < 2 μmol/L). These positive results could serve as a valuable guideline for further research on arylpiperazine derivatives as novel anti-prostate cancer agents. Further research involving other classes of arylpiperazine derivatives is in progress.

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