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Synthesis, biological evaluation and SAR of naftopidil-based arylpiperazine derivatives

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ABSTRACT

For the development of potential anti-prostate cancer agents, **24** kinds of novel naftopidil-based arylpiperazine derivatives have been synthesized and characterized by spectroscopic methods. Their antitumor activities were evaluated against several classical prostate cancer cell lines including PC-3, LNCaP, and DU145. Among all the compounds, **9**, **13**, **17**, **21** and **27** showed strong cytotoxic activities against DU145 cells (IC_{50} < 1 μM). Further testing confirmed that compound **17** inhibited the growth of DU145 cells by inducing cell cycle arrest at G0/G1 phase. Besides, antagonistic activities of compounds (**9**, **13**, **17**, **21** and **27**) towards a_1-ARs (α_{1A}, α_{1B}, and α_{1D}) were further evaluated using dual-luciferase reporter assays, and the compounds **13** and **17** exhibited better a_1-ARs subtype selectivity. The structure–activity relationship (SAR) of these developed arylpiperazine derivatives was rationally discussed. Taken together, these results suggested that further development of such compounds may be of great interest.

Prostate cancer (PCa) is the most frequently diagnosed non-cutaneous solid cancer in men in the U.S. and it is the second most lethal cancer.[1] The development and progression of prostate cancer is directly related to the nuclear steroidal androgen receptor (AR),[2–5] which regulates the binding of androgens like testosterone (T) and its active metabolite dihydrotestosterone (DHT). Testosterone is the principal androgen in the blood, while DHT is the most potent androgen in the cells.[6] In order to induce their biological effects, androgens have to bind to the AR: the hormone-receptor complex binds DNA and modulates gene expression.[7] Upon androgen stimulation, the proliferation of prostate cells is increased and a malignant tumor can develop.[7]

Current therapies (radical prostatectomy, chemotherapy, local radiotherapy, or hormonotherapy) are successful in treating localized disease (androgen-dependent prostate cancer).[8] However, for non-organ-confined disease, especially metastatic prostate cancer (androgen-independent prostate cancer), upon the onset of it no significantly effective therapies exist,[9–12] and androgen ablation therapy has been the major therapeutic modality for advanced prostate cancer.[13] Consequently, novel anti-cancer drugs are needed to stop the progression of prostate cancer at later stages.

Naftopidil (Fig. 1) is an α_1-adrenoceptor blocker, which belongs to the phenyl piperazine derivatives, and used for treating lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).[14] The studies demonstrated that naftopidil inhibited cell proliferation, and caused cell cycle arrest in LNCaP and PC-3 cells.[15] Moreover, naftopidil decreases PCa tumor growth by altering tumor–stroma interactions, and the antiproliferative effect of it is not related to androgen sensitivity of the cells or the a_1-AR subtype expression in PCa cells.[16] In addition, other studies have displayed that arylpiperazine derivatives have anti-proliferative properties.[17–19] Inspired by these, we sought to apply such strategy to developing targeted arylpiperazine derivatives for the treatment of prostate cancer. Recently, we have reported a series of arylpiperazine derivatives as anticancer drugs for site-directed chemotherapy of prostate cancer. Indeed, these new hybrids

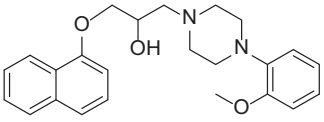

Fig. 1. Structures of naftopidil.

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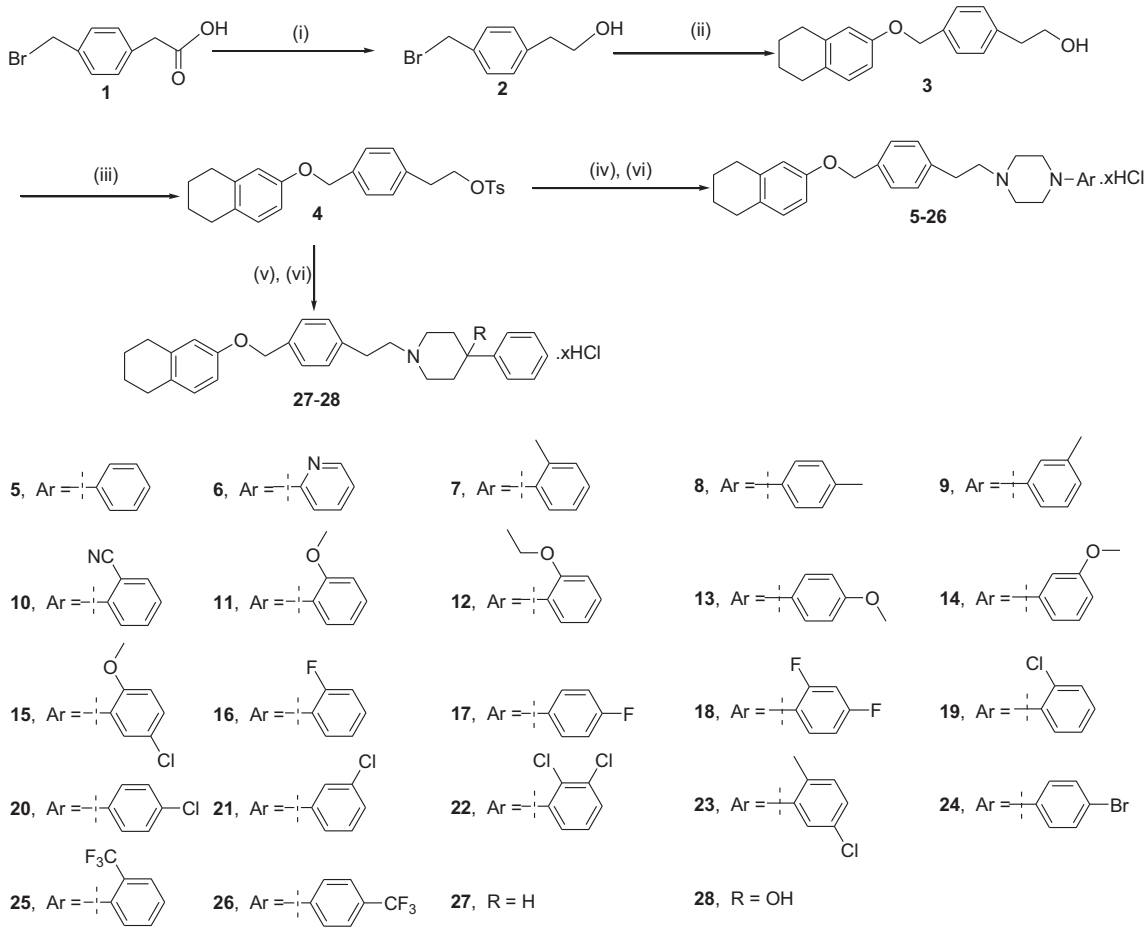

Scheme 1. Reagents and conditions are as follows: (i) $BH_3{\cdot}S(CH_3)_2$, anhydrous THF, 11 h; (ii) 5,6,7,8-tetrahydronaphthalen-2-ol, K_2CO_3, CH_3CN, 85 °C, 16 h; (iii) TsCl, Et_3N and 4-dimethylaminopyridine (catalytic amount), Cl_2CH_2, 0 °C, 16 h; (iv) arylpiperazines, K_2CO_3, CH_3CN, 85 °C, 16 h; (v) phenylpiperidines, K_2CO_3, CH_3CN, 85 °C, 16 h; (vi) HCl, AcOEt, rt, 0.5 h.

showed moderate to significant cytotoxic activity in prostate cancer cell lines.[20–22] As part of our group's continuing efforts to study the arylpiperazine derivatives and the core framework of naftopidil, herein we report the synthesis of a series of new naftopidil-based arylpiperazine derivatives (Scheme 1), and the anticancer activities of the products were evaluated against three prostate cancer cell lines (PC-3, LNCaP and DU145). Furthermore, antagonistic activities of representative compounds towards a_1-adrenergic receptors (a_1-ARs) were further evaluated by dual-luciferase reporter assays. A simple SAR study was also explored to facilitate the further development of the arylpiperazine derivatives. As expected, some synthesized compounds exhibited significant cytotoxic activities against the LNCaP and DU145 cells, and showed better a_1-ARs subtype selectivity.

Scheme 1 illustrates the synthesis of arylpiperazine derivatives **5–28** *via* a four-step reaction using 2-(4-(bromomethyl)phenyl) acetic acid **1** as starting material. The first step involved a reduction reaction between **1** and borane–methyl sulfide complex (2 M in tetrahydrofuran) to synthesize **2**, and the obtained crudes were directly used in the next step without further purification. After the nucleophilic substitution reaction was carried out between compound **2** and 5,6,7,8-tetrahydronaphthalen-2-ol using CH_3CN as solvent in the presence of potassium carbonate at 85 °C for 16 h, and compound **3** was obtained (70% yield from **1**). Subsequently, compound **4** (95% yield) was obtained by reacting **3** with 4-toluene-sulfonyl chloride using CH_2Cl_2 as solvent in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine at 0 °C for 16 h. Finally, compound **4** were treated with various arylpiperazines or phenylpiperidines (1.2 eq) in the presence of K_2CO_3 (6 eq) to obtain derivatives **5–28** in moderate to good yields. (60–82%). All synthesized products (HCl salts) have been confirmed based on their expected *m/z* of $[M+1]^+$, ^1H NMR, ^{13}C NMR spectra and elemental analyses (C, H, and N).

All the target compounds were screened for *in vitro* cytotoxicity against a panel of three human prostate cancer cell lines including PC-3, LNCaP, and DU145 in comparison to their effects in normal non-cancer human prostate epithelial WPMY-1 cell line using the CCK-8 assay.[23–25] Naftopidil and finasteride[26] were taken as reference compounds and the results are reported in terms of IC_{50} values. The results are summarized in Table 1.

As shown in Table 1, the tested compounds exhibited strong activities against LNCaP and DU145 cells, and displayed excellent selective activity for LNCaP and DU145 cells over PC-3 cells. For example, all the compounds exhibited moderate to weak cytotoxic activities against PC-3 cells except **14**. For LNCaP cells, thirteen compounds possessed higher activities than naftopidil and finasteride (IC_{50} < 10 μM), and the majority of compounds displayed low cytotoxic character toward normal human prostate epithelial cell (WPMY-1) with >50 μM of IC_{50}. In addition, seven compounds are more potent than naftopidil and finasteride against DU145 cells. Among these compounds, compounds **9**, **13**, **17**, **21** and **27** exhibited the most potent activity against DU145 cells with IC_{50} values of 0.83, 0.93, 0.90, 0.86 and 0.95 μM, which were 41-, 37-, 38-, 40- and 36-fold more active than naftopidil (Fig. 2), respectively, and exhibited low cytotoxic character toward normal human prostate epithelial cell (WPMY-1) with >50 μM of IC_{50}.