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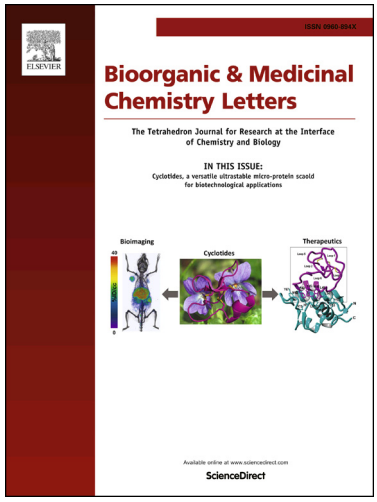

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PII: S0960-894X(18)30273-7
DOI: https://doi.org/10.1016/j.bmcl.2018.03.070
Reference: BMCL 25724

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 14 January 2018
Revised Date: 16 March 2018
Accepted Date: 24 March 2018

Please cite this article as: Chen, H., Wang, C-L., Sun, T., Zhou, Z., Niu, J-X., Tian, X-M., Yuan, M., Synthesis, Biological Evaluation and SAR of Naftopidil-based Arylpiperazine Derivatives, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.03.070

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.

Keywords: Synthesis; Derivatives; Prostate cancer; CCK-8; Structure-activity relationship

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

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hormone-receptor complex binds DNA and modulates gene expression.[7] Upon androgen stimulation, the proliferation of prostate cells is increased and a malignant tumour 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 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.

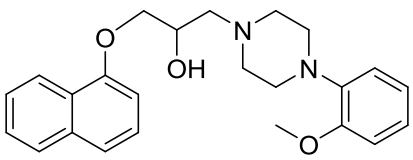
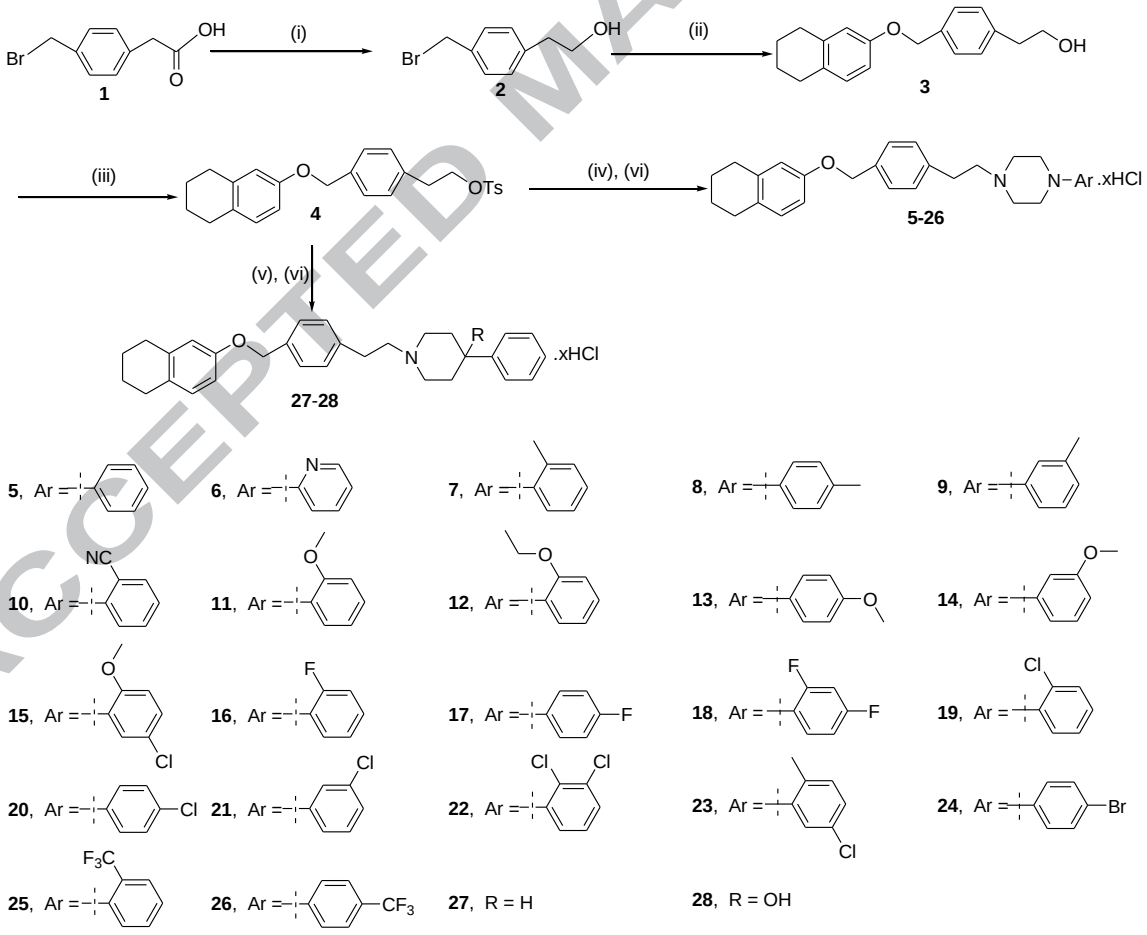


Fig. 1. Structures of naftopidil

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 ^oC 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 $[M+1]^+$, ^{1}H-NMR, ^{13}C-NMR spectra and elemental analyses (C, H, and N).



Scheme 1. Reagents and conditions are as follows: (i) $BH_3.S(CH_3)_2$, anhydrous THF, 11 h; (ii) 5,6,7,8-tetrahydronaphthalen-2-ol, K_2CO_3, CH_3CN, 85 ^oC, 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

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.

Table 1 In vitro cytotoxicity of compounds **5**–**28**

Compd.	IC_{50} (μM)[a]			
	PC-3[b]	LNCaP[b]	DU145[b]	WPMY-1[b]
5	>50	6.53 ± 0.26	>50	>50
6	29.22 ± 0.18	2.92 ± 0.19	11.15 ± 0.46	49.21
7	25.49 ± 0.18	32.85 ± 0.42	>50	>50
8	>50	>50	25.10 ± 0.51	>50
9	56.83 ± 0.12	>50	0.83 ± 0.13	>50
10	31.97 ± 0.21	1.99 ± 0.15	29.69 ± 0.27	>50
11	>50	3.62 ± 0.10	2.24 ± 0.08	28.07 ± 0.39
12	>50	27.98 ± 0.08	>50	>50
13	76.47± 0.57	46.16 ± 0.15	0.93 ± 0.19	>50
14	2.84 ± 0.10	8.02 ± 0.10	28.09 ± 0.80	29.14 ± 0.60
15	>50	>50	25.05 ± 0.81	47.03 ± 1.20
16	27.27 ± 0.16	7.57 ± 0.16	>50	>50
17	57.32 ± 0.61	48.18 ± 1.27	0.90 ± 0.20	>50
18	>50	4.40 ± 0.15	>50	>50
19	31.29 ± 0.15	4.68 ± 0.06	>50	>50
20	>50	>50	>50	>50
21	46.72 ± 0.20	17.33 ± 0.64	0.86 ± 0.20	>50
22	>50	3.06 ± 0.23	23.11 ± 0.67	>50
23	>50	7.81 ± 0.06	>50	>50
24	>50	>50	21.07 ± 0.49	>50
25	>50	6.09 ± 0.15	>50	>50
26	>50	>50	>50	>50
27	10.49 ± 0.08	3.94 ± 0.21	0.95 ± 0.10	>50
28	>50	3.03 ± 0.14	3.38 ± 0.11	31.74 ± 0.49
naftopidil	42.10 ± 0.79	22.36 ± 0.61	34.58 ± 0.31	>50
finasteride	17.83	14.53	13.53	–

[a] IC_{50} values are taken as means ± standard deviation from three experiments.

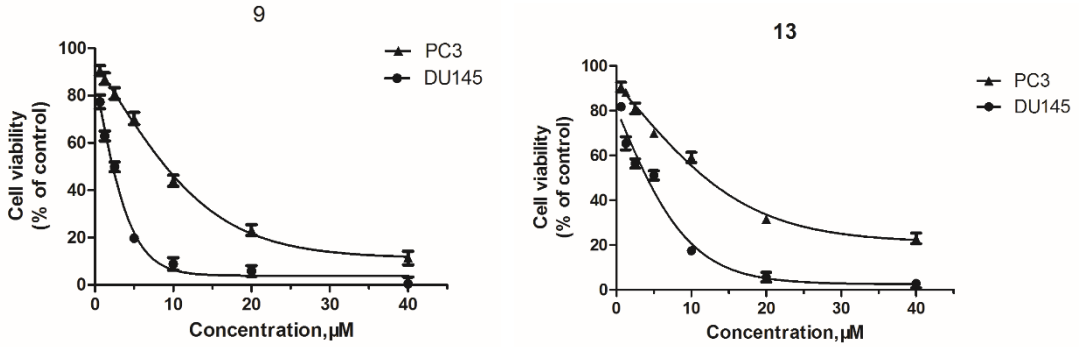
[b] PC-3, androgen-insensitive human prostate cancer cell line; LNCaP, androgen-sensitive human prostate cancer cell line; DU145, androgen-insensitive human prostate cancer cell line; WPMY-1, normal non-cancer human prostate epithelial cell line.

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}.

Taking compound **5** as a lead, the SAR investigation was mainly focused on the variation of phenyl group at the 4-position of piperazine ring with other aryl group and the substitute's type and position on the phenyl group as a required group for antitumor activity. Firstly, in replacing the phenyl group at the 4-position of piperazine ring with pyridinyl group, the resultant compound **6** displayed improved cytotoxic activity against the tested cancer cells. However, compound **6** exhibited cytotoxic activities against WPMY-1 cells. The position of the substituent on the phenyl interestingly affected the cytotoxic activities. Amongst the compounds containing a methyl substituent, the order of the cytotoxic activities of compounds **7** (2-CH_3), **8** (4-CH_3), and **9** (3-CH_3) against DU145 cells could be placed as following: **9** > **8** > **7**. Also, compounds **19**, **20** and **21** had the similar results. In addition, compounds **7**, **8** and **9** exhibited moderate to weak cytotoxic activities against PC-3, LNCaP, and DU145 cells except **14** against DU145 cells, and exhibited low cytotoxic character toward normal human prostate epithelial cell (WPMY-1) with >50 μM of IC_{50}. However, the compounds with electron-donating groups on the phenyl group showed another rule, for instance, the cytotoxic activities of compounds **11** (2-OCH_3), **13** (4-OCH_3), and **14** (3-OCH_3) against DU145 cells could be placed as following: **13** (IC_{50} = 0.93 μM) > **11** (IC_{50} = 2.24 μM) > **14** (IC_{50} = 28.09 μM). But for LNCaP cells, the order of activity was obviously different, such as compounds **11** (IC_{50} = 3.62 μM) and **14** (IC_{50} = 8.02 μM) exhibited a more effective cytotoxic activity than compound **13** (IC_{50} = 46.16 μM). Moreover, compound **14** (IC_{50} = 2.84 μM) exhibited strong activities against PC-3 cells. The similar results were also found in compounds **16** (2-F, IC_{50} = 7.57 μM) *vs.* **17** (4-F), **19** (2-Cl, IC_{50} = 4.68 μM) *vs.* **20** (4-Cl), as well as

25 (2-CF_3, IC_{50} = 6.09 μM) *vs.* **26** (4-CF_3) for LNCaP cells. However, those compounds exhibited moderate to weak cytotoxic activities against PC-3 cells. In addition, compounds with difluoro-substituents on the phenyl showed higher effectiveness than those with monofluoro-substituent. For example, the cytotoxic activity of compound **18** (2,4-F_2, IC_{50} = 4.40 μM) exhibited a more effective cytotoxic activity than compounds **16** and **17** against LNCaP cells. Moreover, compound **18** also exhibited excellent selective activity for LNCaP cells over other tested cancer cells, and displayed low cytotoxic character toward normal human prostate epithelial cell (WPMY-1) with >50 μM of IC_{50}. Compound **23** (2-CH_3, 5-Cl, IC_{50} = 7.81 μM) exhibited higher cytotoxic activity than compounds **7** (2-CH_3) and **21** (3-Cl) against LNCaP cells, exhibited excellent selective activity for LNCaP cells over PC-3 and DU145 cells. Piperidine compounds **27** and **28** exhibited strong cytotoxic activities against LNCaP and DU145 cells. Especially, compound **27** (IC_{50} = 0.95 μM) exhibited potent cytotoxic activity against DU145 cells. Moreover, compound **27** exhibited low cytotoxic character toward normal human prostate epithelial cell (WPMY-1) with >50 μM of IC_{50}.

PC-3 and DU145 cells are androgen insensitive cell lines, however, PC-3 cells are insensitive to derivatives. The literatures have reported that DU145 (p53 mutant) carries a missense mutation on both alleles of the p53 gene, while PC-3 (p53 null) has only one p53 allele with frame-shift mutation.[27] In DU145 cells, KAI1, p53 and c-Jun were significantly activated by drugs. However, in PC-3 cells, only KAI1 and c-Jun genes were activated and the expression of the p53 gene was undetectable.[28] p53 is one of the most commonly mutated genes in human cancer and loss of wild-type function through mutation or deletion can have profound effects on how cells respond to cell stress.[29] So, it is possible that the expression of p53 gene is a crucial determinant of derivatives sensitivity in prostate cancer DU145 cells.



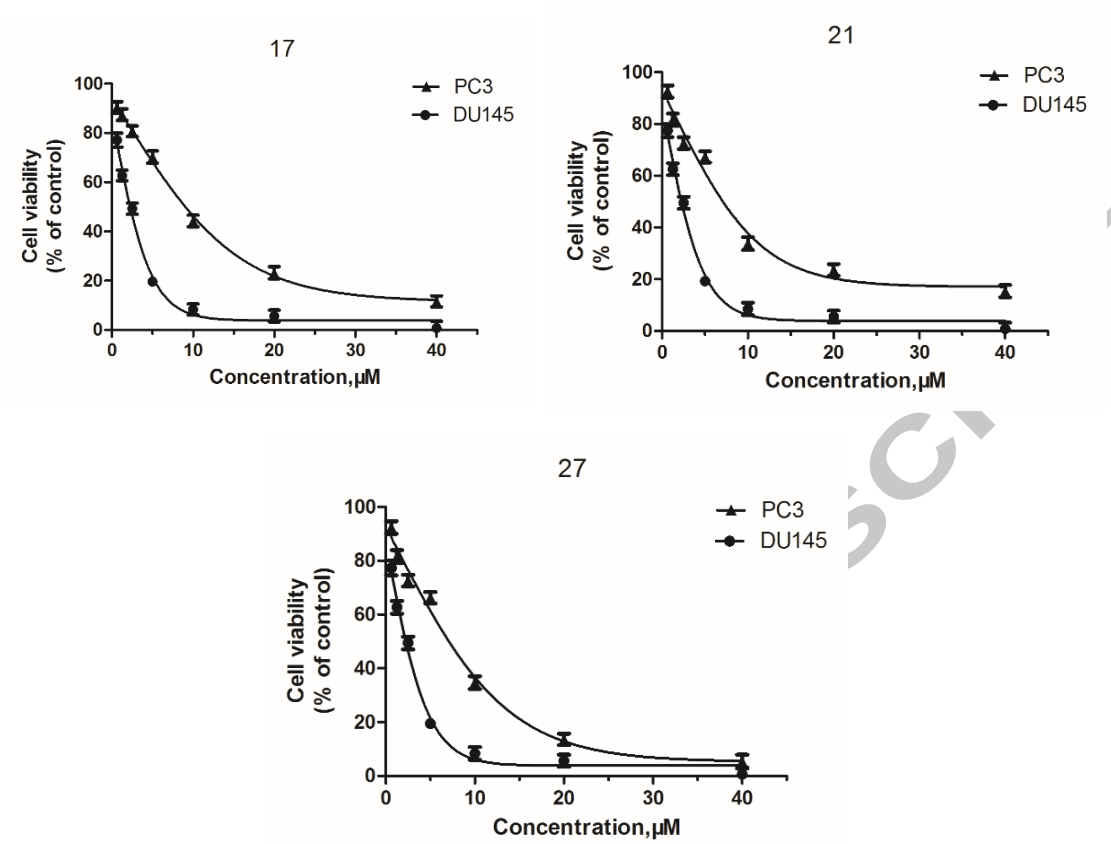


Fig. 2. Arylpiperazine derivatives **9**, **13**, **17**, **21** and **27** inhibited cell viability (percent relative to control) in prostate cell lines PC-3 and DU145. The all cells were exposed to escalating concentrations of arylpiperazine derivatives respectively for 24 h, and the cell viability was detected by CCK-8 assay.

To examine the mechanism by which **13** and **17** inhibits cell proliferation, we evaluated the effect of **13** and **17** on cell cycle progression. DU145 cells were not only treated with DMSO (0.1%) alone as controls but were also treated with **13** (8 μM) and **17** (6 μM) for 24 h and then stained with propidium iodide (PI). The effects of **13** and **17** on the cell cycle distribution of DU145 were evaluated by flow cytometry. Representative flow histograms are shown in Fig. 3. Compound **17** with electron-withdrawing group have significantly increased the number of DU145 cells in the G0/G1 phase compared with vehicle treated controls. However, compound **13** with electron-donating groups have no significant differences compared with CTL. We hypothesized that **13** has other mechanism in inhibiting cancer cell proliferation.

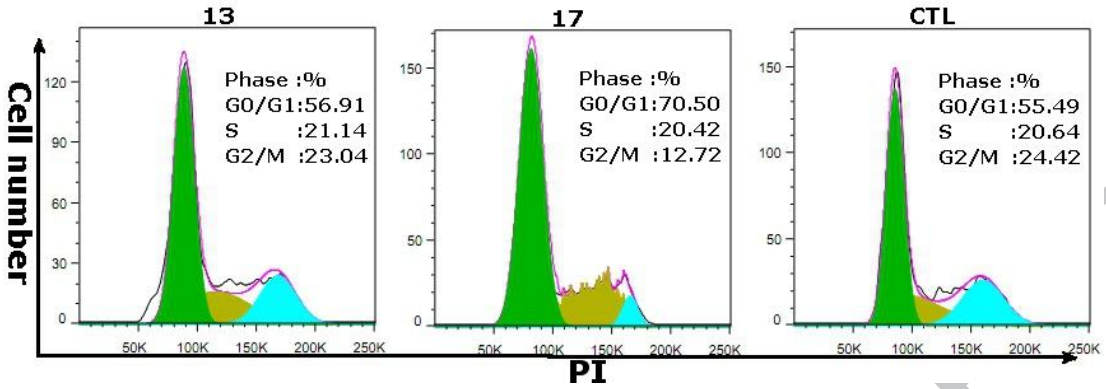


Fig. 3. Cell cycle analysis of DU145 cells treated with **13** (8 μM) and **17** (6 μM) for 24 h through flow cytometry.

To further investigate whether or not the antiproliferative effect of **13** and **17** on DU145 cells, apoptosis is conducted with flow cytometry stained with Annexin-V/PI. DU145 cells were treated with **13** (8 μM), **17** (6 μM) and CTL (0.1% DMSO) for 24 h. The results are showed in Fig. 4. No significant differences were seen between **13**, **17** and CTL. The results suggested that the compounds **13** and **17** had no effect on DU145 cell survival. Therefore, the mechanism of **13** and **17** in inhabiting cancer cells growth are not involved with the apoptosis.

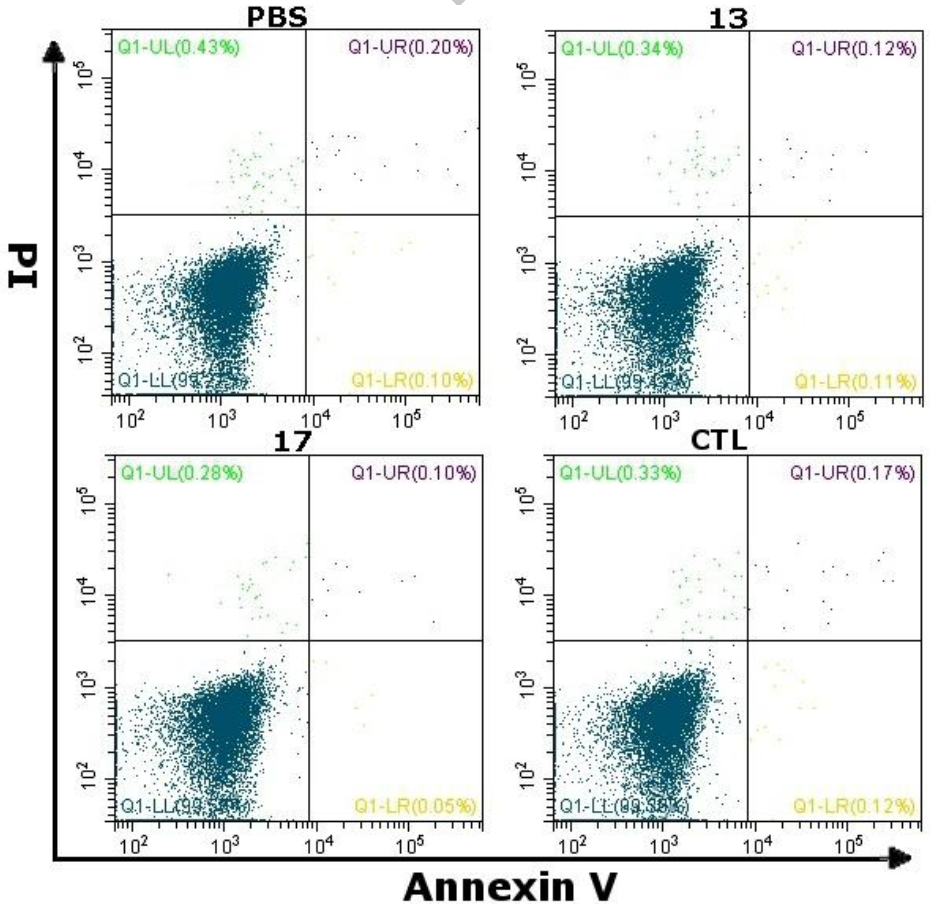


Fig. 4. Externalization of phosphatidylserine in DU145 treated with **13** (8 μM) and **17**

(6 μM) for 24 h was detected through Annexin V/PI double staining assay. The cell population in the lower right quadrant represents early apoptotic cells, whereas the population in the upper right quadrant represents late apoptotic cells or dead cells.

Prostate cancer and benign prostatic hyperplasia are common diseases in elderly males, and the studies have shown that androgen receptor-mediated androgen affects the incidence of the benign prostatic hyperplasia and prostate cancer. Moreover, previous studies have shown arylpiperazine derivatives may act as potential α_{1a} and/or α_{1a}- + α_{1d}-selective ligands for the treatment of benign prostatic hyperplasia (BPH).[30] So, we also further evaluated antagonistic activities of **9, 13, 17, 21 and 27** towards a_1-ARs (Table 2) using dual-luciferase reporter assays[30,31] to identify a_1-AR subselective antagonist candidates to treat BPH from arylpiperazine derivatives with potent anticancer activities. As previously reported in the literature,[30] in the a_1-ARs's pockets, the key amino residues around the binding pocket of the three subtypes (α_{1a}, α_{1b}, and α_{1d}) were differentiated. The conformations of Ile193 in a_{1a} and Val193 in a_{1b} were entirely different, and the different conformations of the same amino residues at the same region of the three subtypes can induce change in the active pocket conformation. The above results indicated that there was different conformation in the same binding ligand, and the different conformations of the same amino residues in the three subtypes can also induce change. In a_{1a}, Ile193 was closer to the binding pocket, exhibited hydrogen bonding interaction with the ligand. So, as shown in Table 2, compared to arylpiperazine derivatives with the isoindoline-1,3-dione moiety (**11** (4-OCH_3) and **14** (4-F)),[30] compound **13** (4-OCH_3) with the tetrahydronaphthalenyl moiety exhibited better a_{1A} subtype selectivity over a_{1b} (a_{1b}/a_{1a} ratio = 16.1), and it is possible to promote intermolecular hydrogen bonding with Ile193 amino residue in a_{1a}-AR model. However, compound **17** (4-F) with electron-withdrawing group is possible to interact with other amino residues or by charge–charge intramolecular interactions to match the pocket of a_{1d}-AR, and exhibited better a_{1d} subtype selectivity (a_{1b}/a_{1d} ratio = 10.9). The results provide valuable information for further finding more new potential drugs in clinic in treating BPH.

Table 2 Antagonistic activities (IC_{50}) on α_1-ARs (α_{1a}, α_{1b}, and α_{1d}) of compounds **9, 13, 17, 21** and **27**

	IC_{50} (nM)[a]			Selectivity ratio	
Compd.	α_{1a}	α_{1b}	α_{1d}	α_{1b}/α_{1a}	α_{1b}/α_{1d}
9	502.12	583.21	826.47	1.2	0.7
13	57.58	972.31	736.47	16.7	1.3
17	1073.85	1124.56	102.85	1.0	10.9
21	1212.48	998.17	287.18	0.8	3.5

27	567.63	672.65	452.84	1.2	1.5
naftopidil	555	634	55.2	1.1	11.48

[a] IC_{50} values are taken as means from three experiments.

This paper has reported the synthesis of a novel class of arylpiperazine derivatives containing 5,6,7,8-tetrahydronaphthalenyl moiety and their antitumor activities against several classical prostate cancer cell lines including PC-3, LNCaP, and DU145, as well as antagonistic activities of the test compounds towards a_1-ARs. The results showed that some compounds are more potent than positive drugs naftopidil and finasteride against LNCaP and DU145 cells. Especially, compounds **9**, **13**, **17**, **21** and **27** demonstrated a relatively strong cytotoxicities against DU145 cells (IC_{50} <1 μM), and compound **17** inhibited the growth of DU145 cells by inducing cell cycle arrest at G0/G1 phase. Moreover, compounds **13** (a_{1B}/a_{1A} ratio = 16.7) and **17** (a_{1B}/a_{1D} ratio = 10.9) exhibited better a_1-ARs subtype selectivity. The SARs were discussed based on the obtained experimental data. Taken together, these results suggested that such type of compounds could serve as the promising candidates for the treatment of prostate cancer and benign prostatic hyperplasia. Further research involving other novel class of arylpiperazine derivatives is in progress.

Acknowledgment

The work was supported by the Natural Science Foundation of China (No. 81401462), Henan Province Science and Technology Attack Plan Foundation (No. 162102310477), the Key Scientific Research Project of Higher Education of Henan Province (Nos. 16A350008, 17A150039 and 17B350001) and National Scientific Research Foundation of Luoyang Normal University (No. 2015-PYJJ-005). We also thank Dr. W. Yi for helpful instruction.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at…

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Graphical Abstract