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Research paper

Design, synthesis and biological evaluation of novel 5-oxo-2-thioxoimidazolidine derivatives as potent androgen receptor antagonists

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ABSTRACT

A series of novel highly active androgen receptor (AR) antagonists containing *spiro*-4-(5-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile core was designed based on the SAR studies available from the reported AR antagonists and *in silico* modeling. Within the series, compound (*R*)-**6** (ONC1−13B) and its related analogues, including its active *N*-dealkylated metabolite, were found to be the most potent molecules with the target activity (IC_{50}, androgen-sensitive human PCa LNCaP cells) in the range of 59−80 nM (inhibition of PSA production). The disclosed hits were at least two times more active than bicalutamide, nilutamide and enzalutamide within the performed assay. Several compounds were classified as partial agonists. Hit-compounds demonstrated benefit pharmacokinetic profiles in rats. Comparative SAR and 3D molecular docking studies were performed for the hit compounds elucidating the observed differences in the binding potency.

1. Introduction

Prostate cancer (PC), following after skin cancer, is the most common cancer occurred in American men, and the sixth cause of cancer-related death among the male population worldwide [1]. More than 230K new cases of prostate cancer have been estimated in the United States during 2014 by American Cancer Society and about 29,480 deaths will be, actually, registered [2]. The vast majority of PCs is initially androgen dependent, and androgen receptor (AR) is highly expressed throughout the various stages of disease playing the crucial regulatory functions in cells [3,4]. The activation of AR [5] strongly promotes prostate cancer growth and progression. Particularly, ligand binding triggers the heat-shock proteins (HSP70 and HSP90) release and subsequent receptor hyperphosphorylation leading to AR dimerization and binding to AR-associated promotor area in target genes. This signaling pathway can be efficiently blocked by competitive FDA-approved AR antagonists (antiandrogens) such as **1** (flutamide) [6], **2** (bicalutamide) [7], **3** (nilutamide) [8], **4** (enzalutamide) [9] or **5** (ARN-509) [10] (Fig. 1). Therefore, androgen deprivation/withdrawal therapy is currently regarded as the “first-line” therapeutic option for localized, early stage prostate cancer. In spite of initial high efficiency observed among a greater percentage of PCa patients, this therapeutic route leads only to a temporary reduction of PC resulting in a significant number of resistance outcomes. As a result, in clinics, classical (steroidal) AR antagonists are frequently ineffective for the treatment of advanced stages of the disease while nonsteroidal drugs are generally considered to be more potent in terms of disease prevention and selectivity thereby minimizing possible *off-target* as well as *on-target* side effects. Cells are able to

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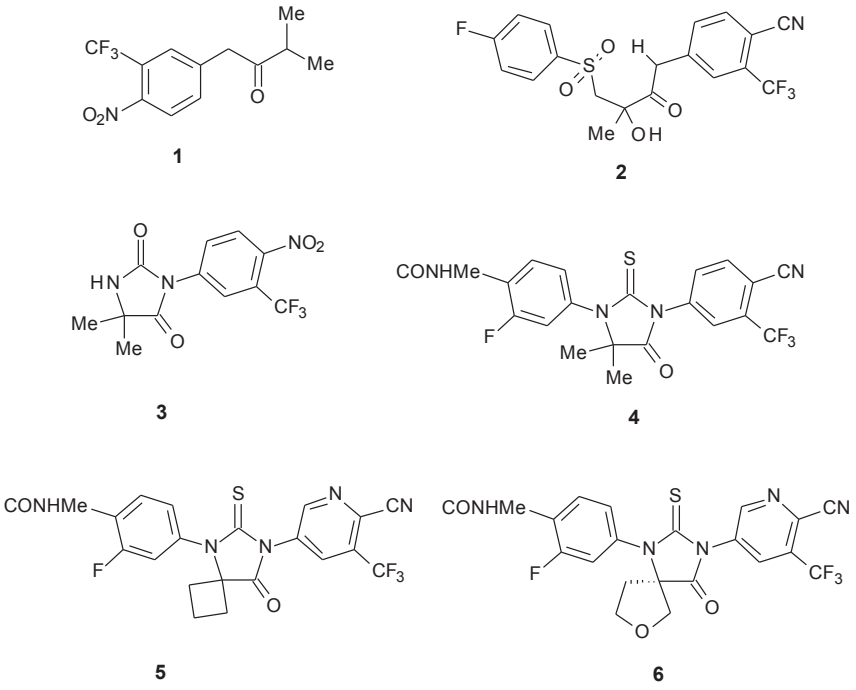

Fig. 1. Non-steroidal AR antagonists approved by FDA (**1**–**4**) and drug candidates currently evaluated in clinics (**5**,**6**).

regenerate and survive without the presence of high levels of testosterone. It is known as hormone-resistant (AIPC) forms and castration-resistant prostate cancer (CRPC) are commonly attributed to elevated AR gene expression or/and amplification [11,12], AR gene mutation [13] as well as ligand-independent AR activation, particularly through the related transcription factors and co-activators [14,15]. A great number of painstaking efforts have been made to develop novel AR antagonists with sufficient therapeutic potency against both types of PC cells with early and later stages of androgen dependence and independence, respectively [16]. In many cases the resistance is strongly associated with the pull of point mutations occurred predominantly in androgen binding site leading to the aberrant receptor up-regulation and higher sensitivity rather than down-regulation and relaxation upon antiandrogen therapy. It should be noted that AR agonists and AR antagonists share different modes of action towards the related transcriptional machinery inducing the “closed” and “open” conformations of AR-H12 helix [17–19]. Therefore, even minor modifications in the structure of a small molecule AR ligand can lead to dramatic alterations in the receptor–ligand interaction thereby providing opposite pharmacological responses. Accordingly, allosteric pockets in AR structure, including BF3 binding site [20], are currently described as promising pathway to overcome the resistance [for review see: [21–23]].

Recently, we have developed novel AR antagonist, (*R*)-**6** (Fig. 1), containing 2-thioxo-7-oxo-1,3-diaza-spiro[4.4]nonan-4-one core with *sub*-nanomolar activity [24] based on comprehensive SAR studies reported for the related analogue **4** launched in 2012 by Astellas Pharma and Medivation. Compound (*R*)-**6** showed similar to **4** and **5** mechanism of action and inhibited DHT (5α-dihydrotestosterone)-stimulated PSA expression and proliferation of prostate cancer cells, prevented binding of androgens to the AR ligand-binding domain, androgen-stimulated AR nuclear translocation and *co*-activator complex formation *in vivo* [25].

With the aim of obtaining more effective AR antagonists, we have synthesized and tested an extended series of novel (*R*)-**6** analogues (Fig. 2), including substituted 2-thioxo-7-oxa-1,3-diaza-spiro[4.4]nonan-4-ones **6**–**9**, heterocyclic analogues of 6-thioxo-5,7-diaza-spiro[3.4]octan-8-ones **10** and 2-thioxo-1,3-diaza-spiro [4.5]decan-4-ones **11**, 2-thioxo-1,3-diaza-spiro[4.5]decan-4-ones **12**–**19**, 2-thioxo-tetrahydro-pyrimidine-4-ones **20**, and thioureas **21**. We have also performed *in silico* modeling procedure for the disclosed compounds using 3D-molecular docking approach to estimate possible binding modes and diversity points.

2. Results and discussion

2.1. Chemistry

5-Methyl-2-thioxoimidazolidin-4-ones (*R*,*S*)-**6**, **11**, (*R*,*S*)-**14**, (*R*)-**14**, (*S*)-**14**, (*R*,*S*)-**15**, and (*R*,*S*)-**16** were readily obtained from 4-amino-2-fluoro-*N*-methylbenzamide (**22**) by reacting with the appropriate ketone (**23**–**28**) and trimethylsilylcyanide in the presence of ytterbium triflate (Scheme 1). The resulting product (**29**–**34**) was then treated with 4-amino-2-(trifluoromethyl)benzonitrile (**35**) and thiophosgene to generate the desired thiohydantoins mainly as **racemic mixtures**. Then, (*R*,*S*)-2-thioxo-7-oxa-1,3-diazaspiro[4.4]nonan-4-one (**6**) and (*R*,*S*)-5-methyl-5-(methoxymethyl)-2-thioxoimidazolidin-4-one (**14**) were successfully separated using chiral HPLC as optically pure compounds (*R*)-**6**, (*S*)-**6**, (*R*)-**14** and (*S*)-**14**. (*R*,*S*)-5-(Hydroxymethyl)-5-methyl-2-thioxoimidazolidin-4-one (**17**) was synthesized by BBr_3-mediated cleavage of (*R*,*S*)-5-methyl-5-(methoxymethyl)-2-thioxoimidazolidin-4-one (**14**), while (*R*,*S*)-(4-methyl-5-oxo-2-thioxoimidazolidin-4-yl)acetic acid (**18**) was obtained by the hydrolysis of ethyl ester **16** in mild alkaline conditions.

The desired (3*R*)-3-({3-fluoro-4-[(methylamino)carbonyl] phenyl}amino)tetrahydrofuran-3-carboxylic acid ((*R*)-**38**) was synthesized by the copper (I) catalysed reaction of 2-fluoro-4-iodo-*N*-methylbenzamide (**37**), which in turn was obtained from intermediate compound **22**, and (*R*)-3-aminotetrahydrofuran-3-carboxylic acid ((*R*)-**36a**) or its butyl ester (*R*)-**36b**. The reaction