European Journal of Medicinal Chemistry 46 (2011) 3291–3301

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Aldol derivatives of Thioxoimidazolidinones as potential anti-prostate cancer agents

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ARTICLE INFO

Article history:
Received 10 December 2010
Received in revised form
18 April 2011
Accepted 19 April 2011
Available online 29 April 2011

Keywords:
Thioxoimidazolidinone
Aldol
Prostate
Androgen

ABSTRACT

The paper discusses the synthesis and stereochemical aspects of the *anti* aldol products, 3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidines. The stereochemistry observed in the aldol reactions with benzaldehydes was explained by transition state model of the endocyclic (*E*)-enolate formed from the rigid 4-oxo-2-thioxoimidazolidine skeleton. Proton NMR and ROESY spectral analyses were carried out to identify the *syn* and *anti* conformations of the aldol diastereomers. Configurations of the enantiomers of the representative *anti* aldol product 3-(4-chlorophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine was determined by single crystal XRD studies. The compounds were screened *in vitro* against prostate cancer cell lines, PC-3 and LNCaP and the most potent derivatives were identified.

1. Introduction

Prostate cancer [1] has emerged as the second leading cause of cancer deaths in males [2–6]. Though the development of prostate cancer is mainly related to androgens and androgen receptor, the exact cause is still unknown. Currently androgen antagonists are being used in the treatment of prostate cancer, which involves two classes of compounds, steroidal and non-steroidal (Fig. 1) [7,8]. Although non-steroidal compounds are more preferred due to lesser cross-reactivity with other receptors [9], they have several limitations such as resistance to therapy arising from mutation, development of relapse as a result of the outgrowth of androgen independent tumour cells, metastasis and hepatotoxicity. The drawbacks of currently available prostate cancer drugs emphasise the urgent need to develop novel therapeutic agents to control metastatic prostate cancer.

2-Thioxoimidazolidinones which are highly useful synthetic intermediates, have found a myriad of applications in the area of therapeutics [10–14]. The 3,5-disubstituted-2-thioxoimidazolidinones and their nucleosides exhibit high potency against the Herpes Simplex Virus (HSV) [13], Human Immunodeficiency Virus (HIV) [14] and leukaemia [14]. The skeleton also forms an integral part of COX inhibitors [15] and fatty acid amide hydrolase inhibitor templates [16,17].

Recently thioxoimidazolidinones were reported as anti-prostate cancer agents, selectively inhibiting the androgen receptor (Fig. 2) [18]. Our interests and research works on biologically active heterocyclic scaffolds [19–23] resulted in identifying a new class of antagonists based on 4-oxo-2-thioxoimidazolidine; their synthesis, stereochemical aspects and preliminary biological results are discussed herein. The target molecules were designed on the basis of structure based approach, considering the structures of the marketed non-steroidal anti-prostate cancer agents. The chiral hydroxy group of (*R*)-bicalutamide plays a crucial role in hydrogen bonding

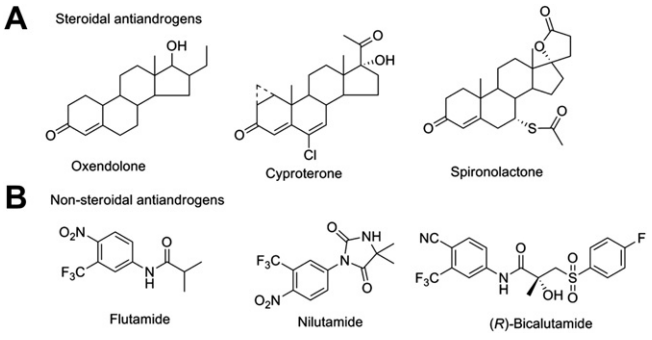

Fig. 1. Steroidal (A) and non-steroidal (B) anti-prostate cancer agents.

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doi:10.1016/j.ejmech.2011.04.050

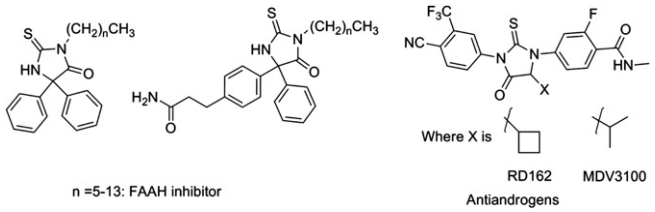


Fig. 2. Biologically important scaffolds based on imidazolidinone.

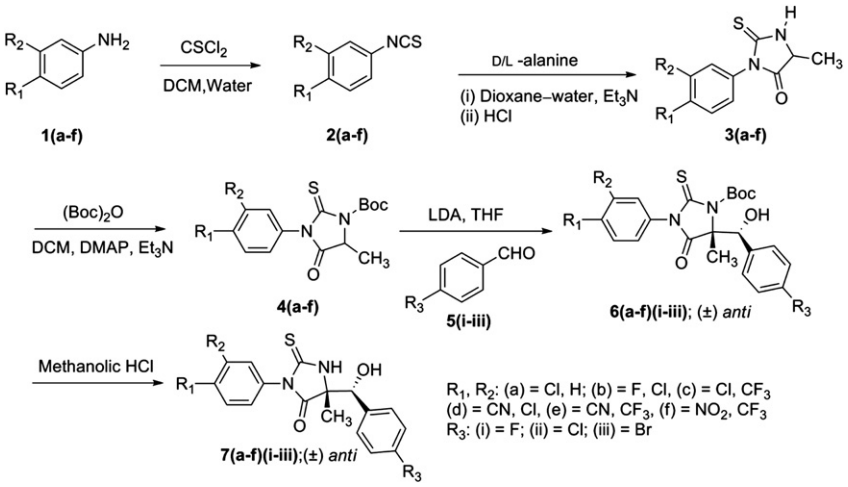
interactions with Leu-704 and Asn-705 of the androgen receptor as revealed by the X-ray crystal structure of the mutant W741L AR bound to (*R*)-bicalutamide [24,25]. Also the (*R*)-bicalutamide adopts a bent conformation with the hydroxy group making direct contacts with the residues of helix 12 of the androgen receptor. These aspects along with detailed examination of other possible hydrogen bonding and van der Waals interactions invoked in us the idea of having an analogous conformationally restricted molecule incorporating the salient features of bicalutamide, nilutamide and flutamide. A convenient approach to this was to lock the amide nitrogen by suitably substituted functional groups at the position alpha to the amide carbonyl and this led to the conceptualisation of 3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidines as anti-prostate cancer agents.

2. Results and discussion

Aryl isothiocyanates **2(a–f)** prepared from the anilines **1(a–f)** [26], were cyclized using D/L-alanine in the presence of triethylamine in a mixture of dioxane–water as the medium followed by addition of conc. HCl to afford 3-(substituted phenyl)-5-methyl-4-oxo-2-thioxoimidazolidines **3(a–f)** [27]. The free NH group of the 4-oxo-2-thioxoimidazolidines were protected using di-*tert*-butyl dicarbonate with *N*,*N*-dimethylaminopyridine (DMAP) and triethylamine in DCM to afford **4(a–f)**. Aldol reactions were performed with 4-halobenzaldehydes **5(i–iii)** using LDA, and the resultant adducts **6(a–f)(i–iii)** were deprotected using methanolic HCl to yield 3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl)]-5-methyl-4-oxo-2-thioxoimidazolidines **7(a–f)(i–iii)** (Scheme 1).

As a model reaction, 3-(4-chlorophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine **4(a)** was reacted with benzaldehyde **5(iv)** using LDA (Scheme 2). The resultant *anti* and *syn* aldol adducts **6(a)(iv)** and **6'(a)(iv)** were obtained in the ratio 70:30. Examination of the ^{1}H NMR spectra of the isolated diastereomers revealed that in the case of diastereomer **6(a)(iv)** the C5 methyl protons were shielded, resonating at 1.45 ppm in comparison to the other isomer **6'(a)(iv)** where the methyl protons resonated at 1.76 ppm (Table 1). ROESY spectrum of the isomer **6(a)(iv)** showed a very intense interaction between the phenyl and methyl groups (Refer the supplementary data Fig. S1 and Fig. S2) and therefore it may be assumed that this diastereomer for which the methyl protons are shielded, the methyl adopts a *syn* relationship with the phenyl group and an *anti* relationship with the hydroxy group while for diastereomer **6'(a)(iv)** with methyl protons deshielded, the phenyl and hydroxy groups are oriented *anti* and *syn*, respectively to the methyl group. Thus it can be concluded that aldol reaction of the 4-oxo-2-thioxoimidazolidine **4(a)** with benzaldehyde **5(iv)** afforded the *anti* isomer as the major product, which is widely observed to be the case with enolates of cyclic and acylic systems with *E* geometry [28–34]. With 4-halobenzaldehydes **5(i–iii)** we observed diastereospecificity as only one diastereomer was formed, irrespective of the lithium base (*n*-BuLi, LDA or LHMDS) employed with no appreciable variations either in yield or selectivity. Comparison of the ^{1}H NMR spectra of *syn* and *anti* diastereomers obtained from benzaldehyde with the diastereomers **6(a–f)(i–iii)** formed from 4-halobenzaldehydes, provided sufficient grounds to believe that the product formed exclusively was the *anti* isomer in all the cases. To demonstrate this, the ^{1}H NMR methyl shifts of the diastereomer **6(a)(iv)** and **6'(a)(iv)** are compared with **6(a)(ii)** in Table 1. Observation of the diastereospecificity is intriguing and may be attributed to stereoelectronic factors, while the precise reasons need to be investigated by computational methods.

The *anti* diasteroselectivity can be explained from the transition states illustrated in Fig. 3. The phenyl and methyl groups are in a diequatorial conformation in the transition state **TS-I** and this is possible only if they are *trans* to each other. Energetically this would be the most stable conformation and the diaxial *trans* conformer would be much less favored. The transition state **TS-II** with the methyl group oriented axial and the phenyl group disposed equatorial represents a *cis* isomer and is less stable when compared to the diequatorial *trans* conformer. The most stable diequatorial conformation would thus lead to an *anti* diastereoselectivity in product formation. An assignment of the stereochemistry would indicate that the transition state **TS-I** would lead to (*S*,*R*) configurations at C5 and C6 for the *anti* aldol and (*R*,*S*) for its enantiomer whereas the *syn* aldol arising from the transition state **TS-II** will have the configurations (*R*,*R*), and (*S*,*S*) for its enantiomer.



Scheme 1. Synthesis of 3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl)]-5-methyl-4-oxo-2-thioxoimidazolidines.