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Original article

Aldol derivatives of Thioxoimidazolidinones as potential anti-prostate cancer agents

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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

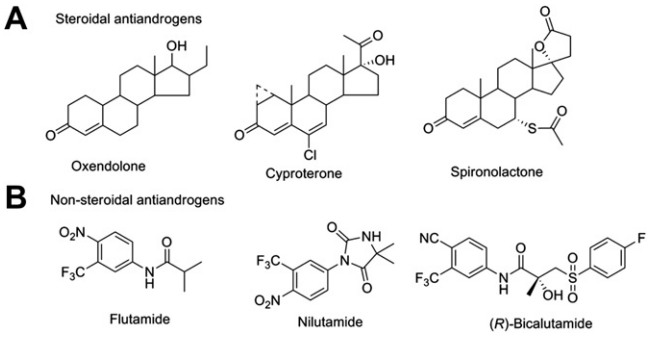

Fig. 1. Steroidal (A) and non-steroidal (B) anti-prostate cancer agents.

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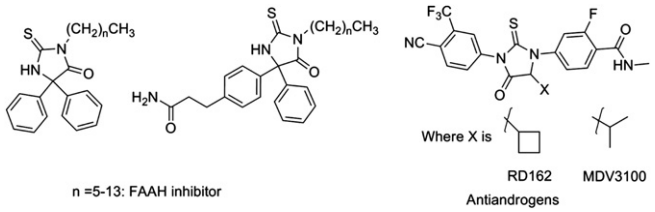


Fig. 2. Biologically important scaffolds based on imidazolidinone.

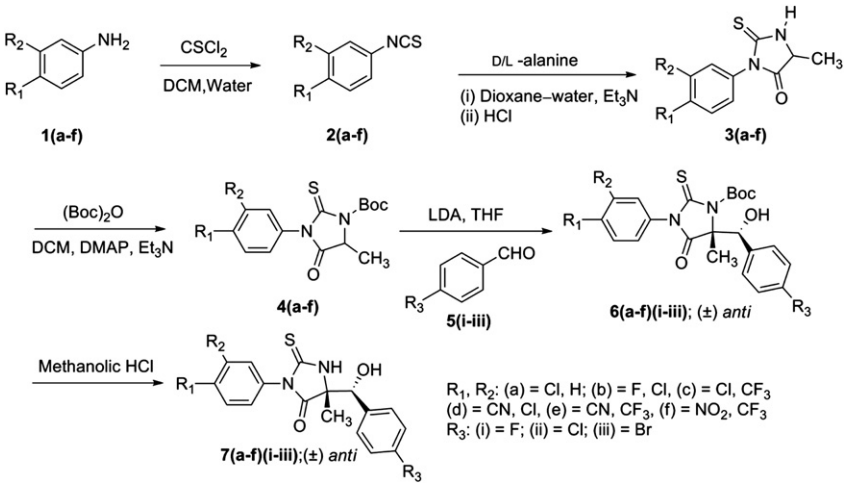
interactions with Leu-704 and Asn-705 of the androgen receptor as revealed by the X-ray crystal structure of the mutant W741L AR bound to (*R*)-bicalutamide [24,25]. Also the (*R*)-bicalutamide adopts a bent conformation with the hydroxy group making direct contacts with the residues of helix 12 of the 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

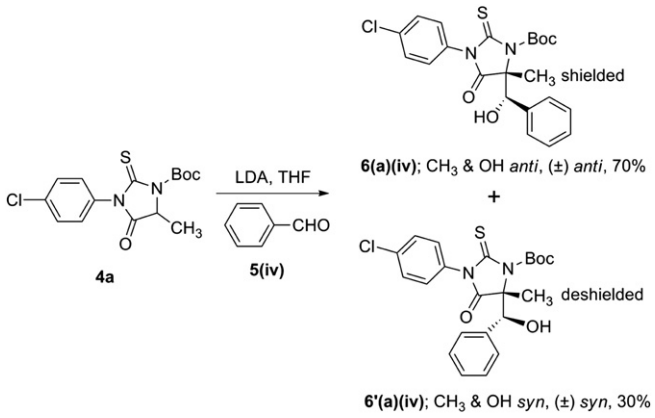
Aryl isothiocyanates **2(a–f)** prepared from the anilines **1(a–f)** [26], were cyclized using D/L-alanine in the presence of triethylamine in a mixture of dioxane–water as the medium followed by addition of conc. HCl to afford 3-(substituted phenyl)-5-methyl-4-oxo-2-thioxoimidazolidines **3(a–f)** [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.



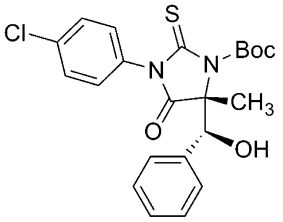
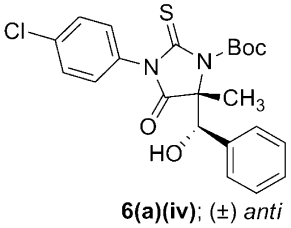
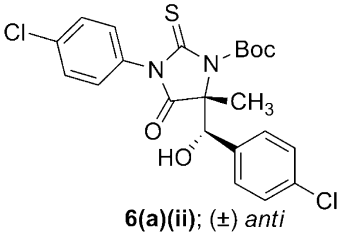
Scheme 1. Synthesis of 3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl)]-5-methyl-4-oxo-2-thioxoimidazolidines.



Scheme 2. *Anti* and *syn* isomers of 3-(4-chlorophenyl)-5-(phenyl hydroxy methyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid *tert*-butyl ester.

Efforts were then directed to confirm the stereochemistry of the *anti* aldol products. To separate the enantiomers of the *anti* aldol, chiral derivatisation of **6(a)(ii)** was tried with (*R*)-α-methoxyphenylacetic acid (*R*-MPA) [35–37], retaining the *tert*-butyloxycarbonyl group, owing to the apprehension that after deprotection the free nitrogen of the thioxoimidazolidinone may interfere with the subsequent reaction. But the reaction failed under the conditions attempted (Scheme 3). Subsequently the deprotected compound **7(a)(ii)** was subjected to reaction with (*R*)-MPA using *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC.HCl) and DMAP in DCM. Quite interestingly the hydroxy group underwent derivatization without any interference from nitrogen of the thioxoimidazolidinone (Scheme 3).

Table 1
Chemical shift (ppm) comparison of aldol diastereomers.

Entry	Product	Methyl	*t*-Butyl
1	 **6'(a)(iv)**; (±) *syn*	1.76	1.43
2	 **6(a)(iv)**; (±) *anti*	1.45	1.39
3	 **6(a)(ii)**; (±) *anti*	1.44	1.39

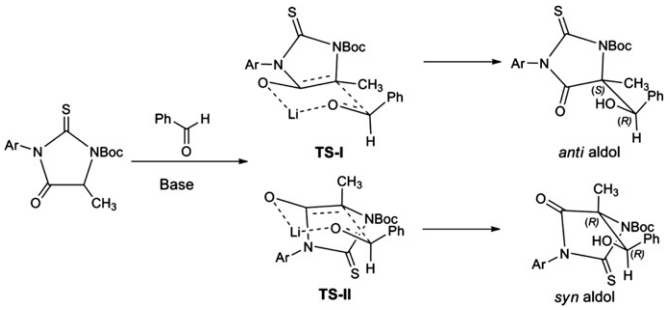
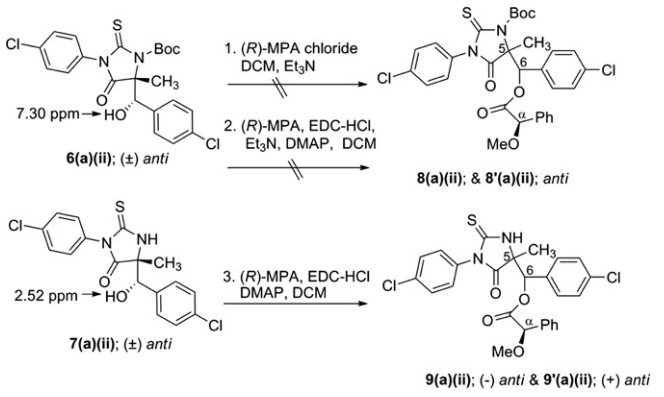


Fig. 3. Transition state models for the formation of *anti* and *syn* aldol diastereomers.

The conformation of **6(a)(ii)** is greatly facilitated through intramolecular hydrogen bonding which is evident from the proton signal at 7.30 ppm and hence strongly internally bonded hydroxy group might have failed to undergo derivatization while the hydroxy signal at 2.50 ppm for **7(a)(ii)** indicated the absence of intramolecular hydrogen bonding. Thus a third chiral centre of known and fixed configuration was incorporated, thereby converting the two enantiomers of **7(a)(ii)** into diastereomers **9(a)(ii)** and **9'(a)(ii)** which were conveniently separated using preparative thin layer chromatography and characterized by ^{1}H NMR (Table 2).

The configurations were confirmed by single crystal X-ray analysis. Though diastereomers **9(a)(ii)** and **9'(a)(ii)** were subjected to crystallization, suitable crystals were formed only for diastereomer **9(a)(ii)** which was analyzed and a perspective view of this diastereomer with the atom numbering is given in Fig. 4. The crystal structure shows that the stereochemistry at C5 and C6 are (*S*,*R*) for diastereomer **9(a)(ii)** of the *anti* aldol MPA ester. Consequently diastereomer **9'(a)(ii)** of the *anti* aldol MPA ester should have the opposite configuration (*R*,*S*) at the chiral centres; it being the other *anti* aldol enantiomer.

The *anti* aldol adducts of 5-methyl-3-(substituted phenyl)-4-oxo-2-thioxoimidazolidines **7(a–f)(i–iii)** were then subjected to biological evaluation on prostate cancer cell lines. The cytotoxicity of the thioxoimidazolidinones were studied *in vitro* on PC-3 and LNCaP prostate cancer cell lines with doxorubicin and flutamide respectively as the positive controls. Each cell line was treated with solutions of 0.001 nM–100 μM of the test compound. All the *anti* aldol diastereomers were found to decrease the cell viability as determined by colorimetric MTT assay, with IC_{50} values ranging from micromolar to nanomolar concentrations (Table 3). Interestingly none of the compounds exhibited agonistic effect on LNCaP cells. For the highly active compounds plots of %viability against



Scheme 3. Chiral derivatization of secondary alcohol with (*R*)-MPA.

Table 2
Chemical shift (ppm) comparison of (*R*)-MPA esters of **7(a)(ii)**.

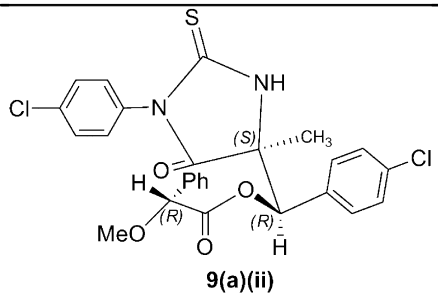
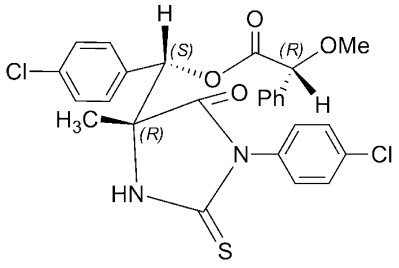
Entry	Product	H of (*R*)-MPA	NH of thioxo-imi dazolidinone
1	 **9(a)(ii)**	4.782	7.088
2	 **9'(a)(ii)**	4.756	7.043

Table 3
Cytotoxic activity of compounds on PC-3 and LNCaP prostate cancer cell lines by MTT assay.[a,b]

Entry	Compound	R_1	R_2	R_3	IC_{50} (μM) on PC-3 cells	IC_{50} (μM) on LNCaP cells
1	Doxorubicin[c]	–	–	–	1.03	nd[d]
2	Flutamide[c]	–	–	–	nd[d]	0.90
3	**7(a)(i)**	Cl	H	F	1.23	0.86
4	**7(a)(ii)**	Cl	H	Cl	>100	>100
5	**7(a)(iii)**	Cl	H	Br	>100	>100
6	**7(b)(i)**	F	Cl	F	>100	>100
7	**7(b)(ii)**	F	Cl	Cl	>100	98.2
8	**7(b)(iii)**	F	Cl	Br	>100	~100
9	**7(c)(i)**	Cl	CF_3	F	>100	~100
10	**7(c)(ii)**	Cl	CF_3	Cl	1.24	0.960
11	**7(c)(iii)**	Cl	CF_3	Br	0.923	0.500
12	**7(d)(i)**	CN	Cl	F	>100	93.200
13	**7(d)(ii)**	CN	Cl	Cl	>100	>100
14	**7(d)(iii)**	CN	Cl	Br	>100	~100
15	**7(e)(i)**	CN	CF_3	F	>100	~100
16	**7(e)(ii)**	CN	CF_3	Cl	0.988	0.507
17	**7(e)(iii)**	CN	CF_3	Br	1.15	0.880
18	**7(f)(i)**	NO_2	CF_3	F	89	33
19	**7(f)(ii)**	NO_2	CF_3	Cl	1.19	0.939
20	**7(f)(iii)**	NO_2	CF_3	Br	>100	73.4

[a] The data represents the mean of three experiments.
[b] The (±) *anti* aldol isomers were screened.
[c] Used as a positive control.
[d] nd = not determined.

doses for PC-3 and LNCaP cell lines are provided (Figs. 5 and 6). Toxicity studies on LNCaP cells may suggest an androgen dependent mechanistic pathway. The corresponding thioxooxazolidinone derivatives synthesized by an analogous procedure [21] exhibited poorer activity on PC-3 and LNCaP cell lines with IC_{50} values in the range of 100 μM or more (Refer the Supplementary data, Table S1), which illustrated the significance of the thioxoimidazolidinone scaffold. Compounds **7(a)(i), 7(c)(ii), 7(c)(iii), 7(e)(ii), 7(e)(iii)** and **7(f)(ii)** showed activity equal to or better than the standards doxorubicin and flutamide on both PC-3 and LNCaP cell lines. Compound **7(c)(iii)**, with an aryl A ring bearing the electron withdrawing groups Cl and CF_3 at the *para* and *meta* positions, exhibited the highest toxicity with IC_{50} values of 0.92 μM on PC-3 cells and 0.50 μM on LNCaP cells. Most of the reported antiprostatic compounds contain the functional groups CN and CF_3 or NO_2 and CF_3 at the *para* and *meta* positions in the aromatic A ring of the parent skeleton [8,38,39]. But a similar substitution on this pharmacophore did not remarkably improve the outcome (compare **7(e,f)(i–iii)** with **7(c)(ii,iii)**, Table 3). It was also observed that the substituent on the aromatic B ring played a prominent role with the activity decreasing in the order Br ≥ Cl >>>> F. The general cytotoxicity of these compounds was examined on the non-cancerous cells MCF-10A, and found to be non-toxic at 1.0 μM concentration. Also a low level of toxicity on breast cancer cells MCF-7 gave convincing evidence for the selectivity of these compounds towards prostate cancer cells (Refer the supplementary data, Fig. S13). The biological evaluation of the newly synthesized 4-oxo-2-thioxoimidazolidine derivatives further helped in identifying a highly potent pharmacophore based on 5-methyl-3-

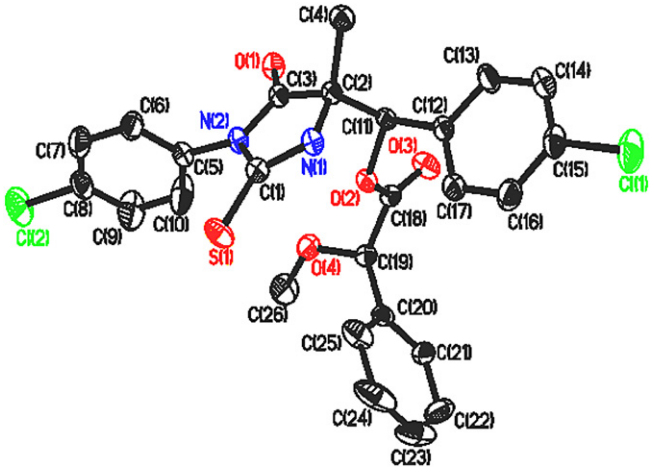


Fig. 4. ORTEP diagram of the diastereomer **9(a)(ii)**, hydrogen atoms were omitted for clarity.

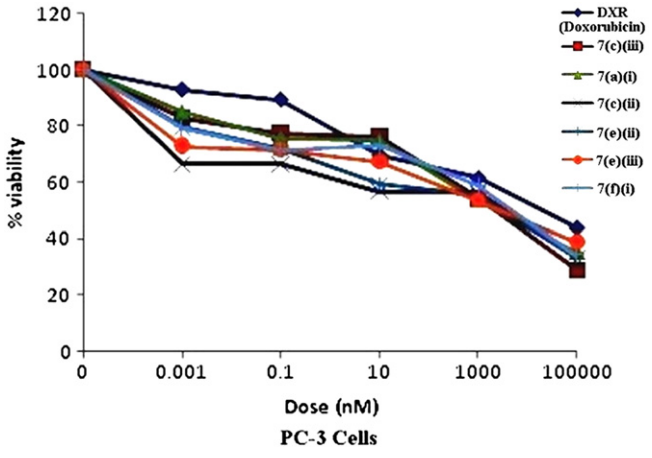


Fig. 5. Dose-response curves of most potent compounds on PC-3 cells.

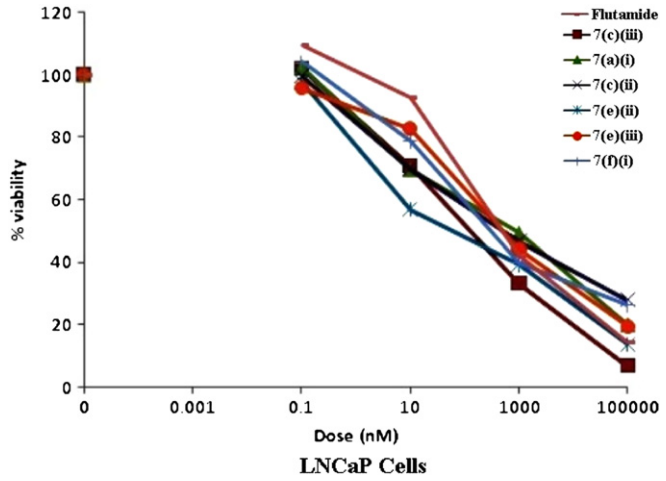


Fig. 6. Dose-response curves of most potent compounds on LNCaP cells.

(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-4-oxo-2-thioimidazolidine skeleton. Further, the asymmetric synthesis of the active *anti* aldol enantiomer of the representative compound has to be carried out and its pharmacological properties need to be investigated in depth.

3. Conclusions

The aldol reactions of 5-methyl-3-(substituted phenyl)-4-oxo-2-thioxoimidazolidines afforded the *anti* isomer stereospecifically. Biological evaluations of the *anti* isomers on PC-3 and LNCaP prostate cancer cells demonstrated inhibition of cell growth. The highly potent compound **7(c)(iii)** demonstrated cytotoxicity better than doxorubicin and flutamide on PC-3 and LNCaP cells respectively. Further development of this scaffold may help to discover a potential therapeutic for the control and prevention of prostate cancer.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz/300 MHz and 100 MHz/75 MHz, respectively on Bruker Advance DPX 400/300 spectrometers in $CDCl_3/CD_3OD/(CD_3)_2SO$ using TMS as the internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. The IR spectra were recorded on a Nicolet Impact Spectrometer as KBr pellets for solid samples. Mass spectra were recorded on POLARIS Q (Thermo Scientific) GC-MSMS, Maldi-TOF/TOF. Specific rotations were taken on Rudolph Autopol IV Instrument and HRMS spectra were recorded on Bruker Maxis TOF. The reactions were monitored by TLC (Merck). Evaporation of solvents was performed under reduced pressure using a rotary evaporator. Melting points are uncorrected. Commercial grade reagents and solvents were used without further purification; *n*-butyllithium, lithium diisopropylamide (LDA), lithium hexamethyldisilazane (LHMDS), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC.HCl), (*R*)-(-)-α-methoxyphenylacetic acid (*R*-MPA), 4-chloro-3-trifluoromethylaniline, 4-amino-2-chlorobenzonitrile (Aldrich), 4-fluoro-3-chloroaniline, triethylamine, thiophosgene, 1,4-dioxane, di-*tert*-butyl dicarbonate, *N*,*N*-dimethylaminopyridine (DMAP), THF (Spectrochem); dichloromethane (DCM) 4-chloroaniline (Merck) and sodium hydrogen carbonate (CDH).

4.2. General procedure for the synthesis of aryl isothiocyanates **2**

In a typical experiment, a solution of sodium hydrogen carbonate (62.72 mmol) in 20 mL of water was stirred for 10 min and to it was added dichloromethane (20 mL) followed by substituted aniline (15.68 mmol). The reaction mixture was cooled to 0 °C, thiophosgene (23.52 mmol) was introduced dropwise over a period of 30 min and continuously stirred at room temperature for 1 h. The reaction mixture was washed with brine solution; the organic layer was dried over anhydrous sodium sulphate and concentrated to get a crude gummy compound which was recrystalized in hexane under cold condition. The precipitate was filtered and dried to get the desired compound. The products were characterized by analytical and spectral methods.

4.2.1. 4-chlorophenyl isothiocyanate **2(a)**

Yield 81%; white solid; mp 134–136 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.18 (m, 2H), 7.31–7.36 (m, 2H); MS: *m*/*z* (GC-MSMS) 169.03 $(M)^{+}$.

4.2.2. 3-chloro-4-fluorophenyl isothiocyanate **2(b)**

Yield 75%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.16 (m, 2H), 7.29–7.37 (m, 1H); MS: *m*/*z* (GC-MSMS) 187.01 $(M)^{+}$.

4.2.3. 4-chloro-3-trifluoromethylphenyl isothiocyanate **2(c)**

Yield 70%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.34 (m, 1H), 7.42–7.54 (m, 2H); MS: *m*/*z* (GC-MSMS) 237.07 $(M)^{+}$.

4.2.4. 3-chloro-4-cyanophenyl isothiocyanate **2(d)**

Yield 73%; light yellow solid; mp 85–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.22 (m, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H); MS: *m*/*z* (GC-MSMS) 193.96$(M)^{+}$.

4.2.5. 4-cyano-3-trifluoromethylphenyl isothiocyanate **2(e)**

Yield 65%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.49 (m, 1H), 7.59 (d, $J = 8.2$ Hz, 1H), 7.83 (d, $J = 8.2$ Hz, 1H); MS: *m*/*z* (GC-MSMS) 228.01$(M)^{+}$.

4.2.6. 4-nitro-3-trifluoromethylphenyl isothiocyanate **2(f)**

Yield 68%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.53 (m, 1H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.97 (d, $J = 8.6$ Hz, 1H); MS: *m*/*z* (GC-MSMS) 248.11$(M)^{+}$.

4.3. General procedure for the synthesis of 3-(substituted phenyl)-5-methyl-4-oxo-2-thioxoimidazolidines **3**

In a typical experiment, triethylamine (1.2 mmol) was added to a solution of aryl isothiocyanate (0.59 mmol) in dioxane–water (2 mL:6 mL) mixture at 0 °C. An aqueous solution of D/L-alanine (0.7 mmol) was added to it and the solution was stirred for 30 min, followed by the addition of conc. HCl until the pH became ~2. The reaction mixture was stirred for another 2 h and the precipitate formed was filtered and dried to yield the desired compound. The products were characterized by analytical and spectral methods.

4.3.1. 3-(4-chlorophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine **3(a)**

Yield 85%; white solid; mp 203–206 °C; ν_{max} 1755, 3168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, $J = 7.0$ Hz, 3H), 4.32–4.38 (m, 1H), 7.28 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.82 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.58, 56.04, 130.00, 130.10, 131.52, 135.83, 174.32, 183.69; MS: *m*/*z* (Maldi TOF/TOF) 241.32 $(M + H)^{+}$.

4.3.2. 3-(3-chloro-4-fluorophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine ***3(b)***

Yield 87%; white solid; mp 221–224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (d, J = 6.8 Hz, 3H), 4.34–4.40 (m, 1H), 7.28–7.30 (m, 2H), 7.43–7.44 (m, 1H), 7.73 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.05, 55.47, 117.11, 121.84, 128.35, 128.43, 130.78, 157.03, 173.61, 182.88; MS: m/z (Maldi TOF/TOF) 259.32 $(M + H)^+$.

4.3.3. 3-(4-chloro-3-trifluoromethylphenyl)-5-methyl-4-oxo-2-thioxoimidazolidine ***3(c)***

Yield 84%; white solid; mp 185–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (d, J = 7.2 Hz, 3H), 4.36–4.41 (m, 1H), 7.49–7.51 (m, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.83 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.01, 55.55, 120.85, 123.57, 127.58, 129.12, 131.17, 132.19, 133.20, 173.41, 182.40; MS: m/z (Maldi TOF/TOF) 309.37 $(M + H)^+$.

4.3.4. 3-(4-chloro-3-cyanophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine ***3(d)***

Yield 86%; brick red solid; mp 238–240 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 1.57 (d, J = 7.0 Hz, 3H), 4.35–4.40 (m, 1H), 7.49–7.52 (m, 1H), 7.66–7.67 (m, 1H), 7.83–7.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 20.20, 59.58, 116.98, 119.25, 131.41, 133.92, 137.99, 140.81, 141.72, 178.19, 185.26; MS: m/z (Maldi TOF/TOF) 266.32 $(M + H)^+$.

4.3.5. 4-(4-methyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl) benzonitrile ***3(e)***

Yield 70%; white solid; mp 185–188 °C; FTIR (KBr) ν: cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, J = 7.0 Hz, 3H), 4.39–4.46 (m, 1H), 7.16 (brs, 1H, NH), 7.79 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 7.97 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 17.08, 55.58, 110.28, 114.76, 127.27, 131.87, 133.03, 133.47, 135.31, 136.55, 172.89, 181.42; MS: m/z (Maldi TOF/TOF) 300.38$(M)^+$.

4.3.6. 5-methyl-3-(4-nitro-3-(trifluoromethyl)phenyl)-4-oxo-2-thioxoimidazolidine ***3(f)***

Yield 85%; yellow solid; 205–208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (d, J = 7.0 Hz, 3H), 4.42–4.47 (m, 1H), 7.28 (brs, 1H, NH), 7.81–7.84 (m, 1H), 7.94 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.12, 55.52, 125.81, 127.95, 128.01, 131.48, 132.63, 136.14, 172.81, 181.44; MS: m/z (Maldi TOF/TOF) 320.43$(M)^+$.

4.4. General procedure for the synthesis of 3-(substituted phenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***4***

In a typical experiment, to a dichloromethane solution of 3-(substituted phenyl)-5-methyl-4-oxo-2-thioxoimidazolidine (27.08 mmol), triethylamine (32.49 mmol) was added at 0 °C. This was followed by the addition of di-*tert*-butyl dicarbonate (32.49 mmol) and *N*,*N*-dimethylaminopyridine (0.27 mmol). The liberation of CO_2 along with a change in appearance of the reaction mixture to yellow was observed. The reaction mixture was stirred for 30 min, and then washed with 1 N aq. HCl, aq. $NaHCO_3$ solution and the organic layer was dried and concentrated to get the desired compound. The products were characterized by analytical and spectral methods.

4.4.1. 3-(4-chlorophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***4(a)***

Yield 84%; white solid; mp 149–151 °C; ν_{max} 1755 and 3168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 9H), 1.72 (d, J = 4.2 Hz, 3H), 4.68–4.72 (m, 1H), 7.18–7.20 (m, 2H), 7.46–7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.95, 28.13, 58.75, 86.01, 130.17, 130.45, 131.63, 136.10, 149.12, 172.45, 179.31; MS: m/z (Maldi TOF/TOF) 363.42 $(M + Na)^+$.

4.4.2. 3-(3-chloro-4-fluorophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***4(b)***

Yield 93%; white solid; mp 143–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 1.73 (d, J = 6.8 Hz, 3H), 4.67–4.72 (m, 1H), 7.13–7.17 (m, 1H), 7.29 (s, 1H), 7.32–7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.40, 28.02, 58.21, 85.61, 117.09, 121.82, 128.81, 128.94, 131.15, 148.49, 157.17, 171.79, 178.50; MS: m/z (Maldi TOF/TOF) 381.53 $(M + Na)^+$.

4.4.3. 3-(4-chloro-3-trifluoromethylphenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***4(c)***

Yield 94%; white solid; mp 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 9H), 1.75 (d, J = 6.8 Hz, 3H), 4.70–4.75 (m, 1H), 7.40–7.42 (m, 1H), 7.61–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.38, 28.02, 58.29, 85.77, 120.79, 128.06, 129.69, 131.23, 132.40, 133.05, 133.58, 148.47, 171.61, 178.07; MS: m/z (Maldi TOF/TOF) 431.51 $(M + Na)^+$.

4.4.4. 3-(4-chloro-3-cyanophenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***4(d)***

Yield 90%; white solid; mp 129–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 1.74 (d, J = 6.8 Hz, 3H), 4.71–4.73 (m, 1H), 7.33–7.36 (m, 1H), 7.50–7.51 (m, 1H), 7.80 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.45, 27.66, 58.90, 86.50, 114.79, 115.70, 128.32, 131.04, 134.88, 137.70, 138.06, 148.93, 171.75, 177.91; MS: m/z (Maldi TOF/TOF) 388.39 $(M + Na)^+$.

4.4.5. tert-butyl-3-(4-cyano-3-(trifluoromethyl)phenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylate ***4(e)***

Yield 81%; white solid; mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 1.76 (d, J = 8.0 Hz, 3H), 4.73–4.79 (m, 1H), 7.66–7.68 (m, 1H), 7.79 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.35, 28.01, 58.39, 86.08, 110.83, 114.58, 120.37, 127.51, 132.58, 135.48, 136.59, 148.36, 171.17, 177.18; MS: m/z (Maldi TOF/TOF) 422.54 $(M + Na)^+$.

4.4.6. tert-butyl-3-(3-nitro-4-trifluoromethylphenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylate ***4(f)***

Yield 85%; white solid; mp 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 1.74 (d, J = 8.0 Hz, 3H), 4.75–4.80 (m, 1H), 7.70–7.72 (m, 1H), 7.82 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.36, 28.01, 58.48, 86.12, 126.02, 128.71, 128.37, 133.42, 136.16, 148.37, 171.21, 177.20.

4.5. General procedure for the synthesis of 3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6***

In a typical experiment, 3-(substituted phenyl)-5-methyl-4-oxo-2-thioxoimidazolidin-1-carboxylic acid *tert*-butyl ester (4.1 mmol), dissolved in anhydrous THF (50 mL) and cooled to −78 °C, was treated with LDA (2.0 mL, 1.8 M solution) under nitrogen atmosphere and stirred for 30 min. 4-Halobenzaldehyde (4.9 mmol) was added to the reaction mixture, stirred for another 30 min, then quenched with saturated aq. NH_4Cl and extracted into ethyl acetate. The organic layer was dried and concentrated to provide a gummy compound. The crude product was purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate–hexane mixture as the eluent to provide the desired compound. The products were characterized by analytical and spectral methods.

4.5.1. 3-(4-chlorophenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(a)(i)***

Rf 0.44, EtOAc–hexane, 3:7; yield 40%; white solid; mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.44 (s, 3H), 5.72 (s, 1H), 7.14–7.18 (m, 2H), 7.25–7.27 (m, 2H), 7.41–7.44 (m, 3H), 7.47–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.72, 27.63, 66.91, 78.95, 83.69, 116.12, 129.07, 129.15, 129.48, 129.68, 129.72, 131.30, 135.47, 151.47, 173.88, 183.15; HRMS (ESI-TOF) calcd for $C_{22}H_{22}ClFN_2O_4S$ ($[M + Na]^+$): 487.0871; found: 487.0878.

4.5.2. 3-(4-chlorophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(a)(ii)***

Rf 0.41, EtOAc–hexane, 3:7; yield 47%; white solid; mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.44 (s, 3H), 5.70 (s, 1H), 7.25–7.27 (m, 2H), 7.30 (brs, 1H, OH), 7.36–7.39 (m, 2H), 7.44–7.46 (m, 4H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.73, 27.64, 66.70, 78.94, 83.76, 128.57, 129.37, 129.48, 129.72, 131.30, 132.39, 135.47, 135.70, 151.44, 173.76, 183.14; HRMS (ESI-TOF) calcd for $C_{22}H_{22}Cl_2N_2O_4S$ ($[M + Na]^+$): 503.0575; found: 503.0581.

4.5.3. 3-(4-chlorophenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(a)(iii)***

Rf 0.41, EtOAc–hexane, 3:7; yield 46%; white solid; mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.46 (s, 3H), 5.70 (s, 1H), 7.28–7.30 (m, 2H), 7.33–7.35 (m, 2H), 7.48–7.52 (m, 2H), 7.61–7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.72, 27.66, 66.73, 79.00, 83.85, 123.84, 128.84, 129.54, 129.73, 131.20, 132.36, 132.88, 135.50, 151.45, 173.81, 183.16; HRMS (ESI-TOF) calcd for $C_{22}H_{22}BrClN_2O_4S$ ($[M + Na]^+$): 547.0070; found: 547.0067.

4.5.4. 3-(3-chloro-4-fluorophenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(b)(i)***

Rf 0.46, EtOAc–hexane, 3:7; yield 47%; white solid; mp 188–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.45 (s, 3H), 5.74 (s, 1H), 7.16–7.20 (m, 2H), 7.23–7.26 (m, 1H), 7.27–7.31 (m, 1H), 7.39–7.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.59, 27.63, 67.01, 78.98, 83.91, 116.17, 116.94, 121.79, 128.62, 128.70, 129.06, 129.19, 129.56, 130.91, 151.45, 157.23, 173.84, 182.89; HRMS (ESI-TOF) calcd for $C_{22}H_{21}ClF_2N_2O_4S$ ($[M + Na]^+$): 505.0777; found: 505.0771.

4.5.5. 3-(3-chloro-4-fluorophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(b)(ii)***

Rf 0.46, EtOAc–hexane, 3:7; yield 39%; white solid; mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.46 (s, 3H), 5.73 (s, 1H), 7.24–7.31 (m, 2H), 7.39–7.41 (m, 3H), 7.46–7.48 (m, 2H), 7.71 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.57, 27.65, 66.93, 79.00, 84.04, 116.98, 121.82, 128.56, 128.72, 129.11, 129.44, 130.88, 132.20, 135.70, 151.44, 157.24, 173.79, 182.90; HRMS (ESI-TOF) calcd for $C_{22}H_{21}Cl_2FN_2O_4S$ ($[M + Na]^+$): 521.0481; found: 521.0485.

4.5.6. 3-(3-chloro-4-fluorophenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(b)(iii)***

Rf 0.46, EtOAc–hexane, 3:7; yield 44%; white solid; mp 79–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.45 (s, 3H), 5.73 (s, 1H), 7.24–7.26 (m, 2H), 7.33–7.35 (m, 2H), 7.38–7.40 (m, 1H), 7.60–7.62 (m, 2H), 7.98 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.56, 27.67, 66.92, 79.08, 84.08, 117.01, 121.81, 123.86, 128.66, 128.84, 129.02, 130.85, 132.38, 132.72, 151.45, 157.23, 173.81, 182.90; HRMS (ESI-TOF) calcd for $C_{22}H_{21}BrClFN_2O_4S$ ($[M + Na]^+$): 564.9976; found: 564.9983.

4.5.7. 3-(4-chloro-3-trifluoromethylphenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(c)(i)***

Rf 0.47, EtOAc–hexane, 3:7; yield 39%; white solid; mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.46 (s, 3H), 5.71 (s, 1H), 7.09 (brs, 1H, OH), 7.15–7.19 (m, 2H), 7.40–7.44 (m, 2H), 7.46–7.49 (m, 1H), 7.64–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.81, 27.55, 66.93, 78.87, 83.89, 116.22, 116.44, 127.80, 127.85, 129.00, 129.08, 129.54, 131.42, 132.28, 132.87, 151.42, 173.55, 182.30; HRMS (ESI-TOF) calcd for $C_{23}H_{21}ClF_4N_2O_4S$ ($[M + Na]^+$): 555.0745; found: 555.0752.

4.5.8. 3-(4-chloro-3-trifluoromethylphenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(c)(ii)***

Rf 0.47, EtOAc–hexane, 3:7; yield 43%; white solid; mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.47 (s, 3H), 5.72 (s, 1H), 7.38–7.40 (m, 2H), 7.45–7.50 (m, 3H), 7.64–7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.71, 27.56, 66.93, 78.93, 84.03, 120.84, 123.56, 127.73, 127.78, 128.52, 129.31, 129.63, 131.35, 132.22, 133.47, 135.74, 151.41, 173.53, 182.35; HRMS (ESI-TOF) calcd for $C_{23}H_{21}Cl_2F_3N_2O_4S$ ($[M + Na]^+$): 571.0449; found: 571.0456.

4.5.9. 3-(4-chloro-3-trifluoromethylphenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(c)(iii)***

Rf 0.47, EtOAc–hexane, 3:7; yield 38%; white solid; mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.47 (s, 3H), 5.70 (s, 1H), 7.32–7.34 (m, 2H), 7.48–7.50 (m, 1H), 7.60–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.72, 27.57, 66.83, 78.98, 84.03, 120.84, 123.56, 127.73, 128.79, 129.30, 131.35, 131.86, 132.30, 132.75, 132.88, 133.46, 151.41, 173.50, 182.33; HRMS (ESI-TOF) calcd for $C_{23}H_{21}BrClF_3N_2O_4S$ ($[M + Na]^+$): 614.9944; found: 614.9938.

4.5.10. 3-(3-chloro-4-cyanophenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(d)(i)***

Rf 0.34, EtOAc–hexane, 3:7; yield 40%; white solid; mp 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.47 (s, 3H), 5.75 (s, 1H), 7.15–7.20 (m, 2H), 7.41–7.45 (m, 3H), 7.54–7.55 (m, 1H), 7.71 (brs, 1H, OH), 7.82 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.58, 27.60, 67.29, 78.99, 84.07, 114.11, 115.21, 116.20, 129.07, 129.16, 129.37, 129.40, 130.07, 134.25, 137.38, 137.46, 151.35, 173.33, 181.66; HRMS (ESI-TOF) calcd for $C_{23}H_{21}ClFN_3O_4S$ ($[M + Na]^+$): 521.0823; found: 512.0823.

4.5.11. 3-(3-chloro-4-cyanophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(d)(ii)***

Rf 0.34, EtOAc–hexane, 3:7; yield 44%; white solid; mp 197–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.48 (s, 3H), 5.75 (s, 1H), 7.38–7.47 (m, 5H), 7.54–7.55 (m, 1H), 7.81–7.83 (m, 1H), 8.00 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.56, 27.60, 67.24, 79.01, 84.22, 114.11, 115.20, 127.53, 128.56, 128.92, 129.59, 130.02, 132.05, 134.29, 135.75, 137.29, 151.34, 173.27, 181.69; HRMS (ESI-TOF) calcd for $C_{23}H_{21}Cl_2N_3O_4S$ ($[M + Na]^+$): 528.0526; found: 528.0524.

4.5.12. 3-(3-chloro-4-cyanophenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(d)(iii)***

Rf 0.34, EtOAc–hexane, 3:7; yield 37%; white solid; mp 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.47 (s, 3H),

5.69 (s, 1H), 7.30–7.32 (m, 2H), 7.41–7.43 (m, 2H), 7.53–7.54 (m, 1H), 7.60–7.62 (m, 2H), 7.80–7.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.63, 27.65, 66.98, 79.04, 84.18, 114.14, 115.21, 124.03, 127.52, 128.78, 130.06, 132.43, 132.56, 134.27, 137.33, 137.50, 151.30, 173.19, 181.61; HRMS (ESI-TOF) calcd for $C_{23}H_{21}BrClN_3O_4S$ ($[M + Na]^+$): 572.0023; found: 572.0011.

4.5.13. 5-[(4-fluorophenyl) hydroxy methyl]-3-(4-cyano-3-trifluoromethylphenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(e)(i)***

Rf 0.34, EtOAc–hexane, 3:7; yield 46%; white solid; mp 197–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.53 (s, 3H), 5.71 (s, 1H), 6.91 (brs, 1H, OH), 7.15–7.20 (m, 2H), 7.39–7.43 (m, 2H), 7.73–7.75 (m, 1H), 7.81 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.52, 27.24, 64.98, 76.82, 85.46, 127.39, 128.04, 128.17, 128.60, 128.92, 128.97, 129.15, 129.27, 129.30, 133.99, 135.27, 137.81, 172.56, 179.15; HRMS (ESI-TOF) calcd for $C_{24}H_{21}F_4N_3O_4S$ ($[M + Na]^+$): 546.1087; found: 546.1081.

4.5.14. 5-[(4-chlorophenyl) hydroxy methyl]-3-(4-cyano-3-trifluoromethylphenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(e)(ii)***

Rf 0.34, EtOAc–hexane, 3:7; yield 39%; white solid; mp 181–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.48 (s, 3H), 5.72 (s, 1H), 7.37–7.39 (m, 2H), 7.42–7.48 (m, 3H), 7.55–7.56 (m, 1H) 7.82 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.62, 27.55, 67.07, 78.98, 84.16, 114.14, 115.21, 127.52, 128.53, 129.47, 130.06, 132.04, 134.26, 135.85, 137.34, 137.49, 151.31, 173.22, 181.62; HRMS (ESI-TOF) calcd for $C_{24}H_{21}ClF_3N_3O_4S$ ($[M + Na]^+$): 562.0791; found: 562.0778.

4.5.15. 5-[(4-bromophenyl) hydroxy methyl]-3-(4-cyano-3-trifluoromethylphenyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(e)(iii)***

Rf 0.32, EtOAc–hexane, 3:7; yield 45%; white solid; mp 198–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.49 (s, 3H), 5.70 (s, 1H), 7.30–7.32 (m, 2H), 7.53–7.62 (m, 3H), 7.74 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.60, 27.64, 67.01, 79.05, 84.15, 113.97, 115.20, 124.06, 127.52, 129.01, 130.06, 132.39, 132.59, 134.25, 136.63, 137.32, 137.47, 151.32, 173.22, 181.60; HRMS (ESI-TOF) calcd for $C_{24}H_{21}BrF_3N_3O_4S$ ($[M + Na]^+$): 606.0286; found: 606.0283.

4.5.16. 5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-3-(4-nitro-3-trifluoromethylphenyl)-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(f)(i)***

Rf 0.32, EtOAc–hexane, 3:7; yield 54%; white solid; mp 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.50 (s, 3H), 5.73 (s, 1H), 7.09 (brs, 1H, OH), 7.17–7.21 (m, 2H), 7.42–7.45 (m, 2H) 7.77–7.80 (m, 1H), 7.84–7.85 (m, 1H), 8.04 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.82, 27.55, 67.07, 78.93, 84.07, 116.29, 116.50, 125.90, 128.20, 128.25, 128.97, 129.05, 129.39, 129.43, 133.03, 136.38, 151.31, 173.17, 181.30; HRMS (ESI-TOF) calcd for $C_{23}H_{21}F_4N_3O_6S$ ($[M + Na]^+$): 566.0985; found: 566.0985.

4.5.17. 5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-3-(4-nitro-3-trifluoromethylphenyl)-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(f)(ii)***

Rf 0.32, EtOAc–hexane, 3:7; yield 47%; white solid; mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.51 (s, 3H), 5.71 (s, 1H), 7.19 (brs, 1H, OH), 7.39 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H) 7.77–7.80 (m, 1H), 7.84–7.85 (m, 1H), 8.05 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.78, 27.55, 66.99, 78.93, 84.20, 125.95, 128.18, 128.24, 128.46, 128.68, 128.97, 129.53, 132.04, 133.06, 135.93, 136.32, 151.29, 173.12, 181.29; HRMS (ESI-TOF) calcd for $C_{23}H_{21}ClF_3N_3O_6S$ ($[M + Na]^+$): 582.0689; found: 582.0695.

4.5.18. 5-[(4-bromophenyl) hydroxy methyl]-5-methyl-3-(4-nitro-3-trifluoromethylphenyl)-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester ***6(f)(iii)***

Rf 0.32, EtOAc–hexane, 3:7; yield 44%; white solid; mp 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.50 (s, 3H), 5.71 (s, 1H), 7.21 (brs, 1H, OH), 7.32 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H) 7.77–7.84 (m, 2H), 8.05 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.77, 27.60, 66.90, 78.99, 84.20, 124.10, 125.94, 128.23, 128.73, 128.93, 131.93, 132.46, 132.57, 133.06, 136.33, 151.28, 173.11, 181.29; HRMS (ESI-TOF) calcd for $C_{23}H_{21}BrF_3N_3O_6S$ ($[M + Na]^+$): 626.0184; found: 626.0157.

4.5.19. 3-(4-chlorophenyl)-5-(phenyl hydroxy methyl)-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester. ***6(a)(iv)***

Anti isomer: *Rf* 0.29, EtOAc–hexane, 1:3; white solid; mp 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.44 (s, 3H), 5.73 (s, 1H), 7.25–7.27 (m, 2H), 7.28 (brs, 1H, OH), 7.41–7.42 (m, 1H), 7.43–7.44 (m, 3H), 7.45–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.83, 27.65, 66.90, 79.56, 83.42, 127.20, 129.08, 129.44, 129.54, 129.80, 131.42, 133.81, 135.39, 151.54, 174.03, 183.04; HRMS (ESI-TOF) calcd for $C_{22}H_{23}ClN_2O_4S$ ($[M + Na]^+$): 469.0965; found: 469.0963. **6'(a)(iv)**; *syn* isomer: *Rf* 0.37, EtOAc–hexane, 1:3; white solid; mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.76 (s, 3H), 5.75 (s, 1H), 6.51–6.53 (m, 2H), 7.25–7.29 (m, 2H), 7.36–7.39 (m, 5H), 7.77 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.19, 27.62, 68.24, 80.16, 83.81, 127.38, 128.61, 129.22, 129.42, 129.84, 131.44, 133.78, 135.18, 151.92, 172.88, 182.29; HRMS (ESI-TOF) calcd for $C_{22}H_{23}ClN_2O_4S$ ($[M + Na]^+$): 469.0965; found: 469.0970.

4.6. General procedure for the synthesis of 3-(substituted phenyl)-5-[(4-substituted phenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine **7**

In a typical experiment, to a solution of 3-(substituted phenyl)-5-[(4-substituted phenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylic acid *tert*-butyl ester (0.32 mmol) in dichloromethane was added methanolic HCl (2.5 mL, 1 M solution) and stirred for 12 h. The reaction mixture was concentrated to provide a crude solid compound which was purified by column chromatography on silica gel (60–120 mesh) using a mixture of ethyl acetate and hexane as the eluent to get the desired product. The products were characterized by analytical and spectral methods.

4.6.1. 3-(4-chlorophenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(a)(i)***

Rf 0.60, EtOAc–hexane, 2:3; yield 90%; white solid; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 2.47 (brs, 1H, OH), 5.01 (s, 1H), 6.95 (brs, 1H, NH), 7.13–7.17 (m, 2H), 7.25–7.34 (m, 2H), 7.40–7.48 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 18.23, 68.36, 75.76, 114.42, 128.51, 129.25, 129.94, 130.12, 132.22, 134.19, 134.84, 176.32, 182.91; HRMS (ESI-TOF) calcd for $C_{17}H_{14}ClFN_2O_2S$ ($[M + Na]^+$): 387.0347; found: 387.0348.

4.6.2. 3-(4-chlorophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(a)(ii)***

Rf 0.60, EtOAc–hexane, 2:3; yield 85%; white solid; mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.52 (brs, 1H, OH), 5.02 (s, 1H), 6.96 (brs, 1H, NH), 7.25–7.30 (m, 2H), 7.37–7.39 (m, 2H), 7.43–7.49 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 18.18, 68.25, 75.93, 127.92, 128.50, 129.01, 129.93, 132.21, 133.87, 134.18, 137.63, 176.21, 182.92; HRMS (ESI-TOF) calcd for $C_{17}H_{14}Cl_2N_2O_2S$ ($[M + Na]^+$): 403.0051; found: 403.0047.

4.6.3. 3-(4-chlorophenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(a)(iii)***

Rf 0.60, EtOAc–hexane, 2:3; yield 95%; white solid; mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 2.57 (brs, 1H, OH), 5.01 (s, 1H), 6.98 (brs, 1H, NH), 7.25–7.26 (m, 1H), 7.32–7.36 (m, 3H), 7.47–7.51 (m, 2H), 7.59–7.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 18.19, 68.22, 75.98, 121.93, 128.52, 129.32, 129.94, 130.95, 132.19, 134.19, 138.09, 176.18, 182.91; HRMS (ESI-TOF) calcd for $C_{17}H_{14}BrClN_2O_2S$ ($[M + Na]^+$): 446.9546; found: 446.9541.

4.6.4. 3-(3-chloro-4-fluorophenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(b)(i)***

Rf 0.64, EtOAc–hexane, 2:3; yield 78%; white solid; mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.48 (brs, 1H, OH), 5.04 (s, 1H), 6.95 (brs, 1H, NH), 7.15–7.19 (m, 2H), 7.21–7.25 (m, 2H), 7.40–7.45 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 18.14, 68.46, 75.99, 114.45, 116.16, 120.44, 129.00, 129.25, 129.34, 130.19, 130.23, 130.81, 134.76, 176.16, 182.64; HRMS (ESI-TOF) calcd for $C_{17}H_{13}ClF_2N_2O_2S$ ($[M + Na]^+$): 405.0252; found: 405.0247.

4.6.5. 3-(3-chloro-4-fluorophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(b)(ii)***

Rf 0.64, EtOAc–hexane, 2:3; yield 85%; white solid; mp 175–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.56 (brs, 1H, OH), 5.02 (s, 1H), 7.04 (brs, 1H, NH), 7.20–7.25 (m, 2H), 7.37–7.41 (m, 3H), 7.44–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.83, 67.88, 76.16, 116.88, 117.10, 121.63, 128.45, 128.51, 129.26, 130.83, 135.50, 135.57, 157.08, 174.93, 183.07; HRMS (ESI-TOF) calcd for $C_{17}H_{13}Cl_2FN_2O_2S$ ($[M + Na]^+$): 420.9957; found: 420.9949.

4.6.6. 3-(3-chloro-4-fluorophenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(b)(iii)***

Rf 0.64, EtOAc–hexane, 2:3; yield 88%; white solid; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 2.65 (brs, 1H, OH), 4.99 (s, 1H), 7.13–7.27 (m, 2H), 7.29–7.33 (m, 2H), 7.38–7.39 (m, 1H), 7.58–7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.84, 67.95, 76.23, 116.91, 121.63, 123.59, 128.46, 129.06, 130.83, 132.19, 136.07, 157.08, 159.59, 175.03, 182.95; HRMS (ESI-TOF) calcd for $C_{17}H_{13}BrClFN_2O_2S$ ($[M + Na]^+$): 464.9452; found: 464.9448.

4.6.7. 3-(4-chloro-3-trifluoromethylphenyl)-5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(c)(i)***

Rf 0.71, EtOAc–hexane, 2:3; yield 70%; white solid; mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 2.54 (brs, 1H, OH), 5.02 (s, 1H), 7.07 (brs, 1H, NH), 7.14–7.19 (m, 2H), 7.41–7.51 (m, 3H), 7.63–7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.84, 68.05, 76.19, 116.03, 116.24, 127.70, 127.76, 128.83, 128.91, 131.44, 132.18, 132.72, 132.88, 133.19, 174.80, 182.60; HRMS (ESI-TOF) calcd for $C_{18}H_{13}ClF_4N_2O_2S$ ($[M + Na]^+$): 455.0220; found: 455.0221.

4.6.8. 3-(4-chloro-3-trifluoromethylphenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(c)(ii)***

Rf 0.75, EtOAc–hexane, 2:3; yield 79%; white solid; mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 2.63 (brs, 1H, OH), 5.02 (s, 1H), 7.15 (brs, 1H, NH), 7.37–7.39 (m, 2H), 7.43–7.49 (m, 3H), 7.63–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.80, 68.03, 76.17, 120.87, 123.59, 127.73, 128.46, 129.13, 129.45, 131.39, 132.20, 132.72, 133.23, 133.50, 174.77, 182.57; HRMS (ESI-TOF) calcd for $C_{18}H_{13}Cl_2F_3N_2O_2S$ ($[M + Na]^+$): 470.9925; found: 470.9925.

4.6.9. 3-(4-chloro-3-trifluoromethylphenyl)-5-[(4-bromophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine ***7(c)(iii)***

Rf 0.75, EtOAc–hexane, 2:3; yield 74%; white solid; mp 162–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H), 2.58 (brs, 1H, OH), 5.02 (s, 1H), 7.03 (brs, 1H, NH), 7.32–7.34 (m, 2H), 7.47–7.51 (m, 1H), 7.59–7.60 (m, 1H), 7.61–7.67 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 22.01, 72.38, 79.99, 125.08, 125.99, 131.62, 131.94, 132.26, 133.23, 134.93, 135.68, 136.45, 137.38, 141.85, 179.72, 186.09; HRMS (ESI-TOF) calcd for $C_{18}H_{13}BrClF_3N_2O_2S$ ($[M + Na]^+$): 514.9420; found: 514.9415.

4.6.10. 2-chloro-4-[4-{(4-fluorophenyl) hydroxy methyl}-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl]benzonitrile ***7(d)(i)***

Rf 0.58, EtOAc–hexane, 2:3; yield 65%; white solid; mp 178–181 °C; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 1.34 (s, 3H), 6.19 (s, 1H), 7.15–7.22 (m, 2H), 7.35–7.44 (m, 3H), 7.58 (s, 1H), 8.09–8.14 (m, 1H), 10.52 (brs, 1H, NH); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 18.99, 69.19, 75.52, 112.37, 114.92, 115.95, 128.82, 130.09, 130.17, 130.45, 135.26, 135.63, 135.67, 138.93, 175.39, 180.98; HRMS (ESI-TOF) calcd for $C_{18}H_{13}ClFN_3O_2S$ ($[M + Na]^+$): 412.0299; found: 412.0295.

4.6.11. 2-chloro-4-[4-{(4-chlorophenyl) hydroxy methyl}-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl]benzonitrile ***7(d)(ii)***

Rf 0.61, EtOAc–hexane, 2:3; yield 73%; white solid; mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 2.52 (brs, 1H, OH), 5.04 (s, 1H), 6.96 (brs, 1H, NH), 7.32–7.40 (m, 2H), 7.44–7.48 (m, 3H), 7.59–7.60 (m, 1H), 7.79–7.82 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 19.39, 69.97, 77.43, 114.02, 116.36, 129.21, 129.39, 130.42, 131.06, 131.34, 135.32, 137.36, 138.85, 139.90, 176.83, 183.01; HRMS (ESI-TOF) calcd for $C_{18}H_{13}Cl_2N_3O_2S$ ($[M + Na]^+$): 428.0004; found: 427.9992.

4.6.12. 2-chloro-4-[4-{(4-bromophenyl) hydroxy methyl}-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl]benzonitrile ***7(d)(iii)***

Rf 0.61, EtOAc–hexane, 2:3; yield 67%; white solid; mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 2.52 (brs, 1H, OH), 5.02 (s, 1H), 6.98 (brs, 1H, NH), 7.32–7.34 (m, 2H), 7.43–7.46 (m, 1H), 7.52–7.54 (m, 1H), 7.59–7.63 (m, 2H), 7.79–7.81 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 19.40, 69.92, 77.48, 114.11, 116.37, 123.52, 129.79, 130.73, 132.36, 132.41, 135.41, 137.38, 139.42, 139.88, 176.81, 183.00; HRMS (ESI-TOF) calcd for $C_{18}H_{13}BrClN_3O_2S$ ($[M + Na]^+$): 471.9498; found: 471.9493.

4.6.13. 4-{4-[(4-fluorophenyl) hydroxy methyl]-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl}-2-trifluoromethyl benzonitrile ***7(e)(i)***

Rf 0.60, EtOAc–hexane, 2:3; yield 58%; white solid; mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.60 (brs, 1H, OH), 5.06 (s, 1H), 6.95 (brs, 1H, NH), 7.06–7.22 (m, 3H), 7.38–7.57 (m, 1H), 7.76–7.98 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.81, 68.25, 76.26, 115.54, 116.07, 116.29, 126.91, 128.89, 128.97, 132.06, 132.78, 135.21, 135.33, 136.33, 136.84, 174.42, 181.62; HRMS (ESI-TOF) calcd for $C_{19}H_{13}F_4N_3O_2S$ ($[M + Na]^+$): 446.0562; found: 446.0562.

4.6.14. 4-{4-[(4-chlorophenyl) hydroxy methyl]-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl}-2-trifluoromethyl benzonitrile ***7(e)(ii)***

Rf 0.60, EtOAc–hexane, 2:3; yield 55%; white solid; mp 179–181 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.40 (s, 3H), 4.89 (s, 1H), 7.36–7.41 (m, 5H), 7.51–7.52 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 23.03, 72.53, 79.91, 117.15, 119.30, 131.38, 132.45, 132.68, 133.96, 137.95, 138.51, 140.54, 140.93, 141.72, 179.26, 185.57; HRMS (ESI-TOF) calcd for $C_{19}H_{13}ClF_3N_3O_2S$ ($[M + Na]^+$): 462.0267; found: 462.0266.

4.6.15. 4-{4-[(4-bromophenyl) hydroxy methyl]-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl}-2-trifluoromethyl benzonitrile ***7(e)(iii)***

Rf 0.60, EtOAc–hexane, 2:3; yield 62%; white solid; mp 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.64 (brs, 1H, OH), 5.03 (s, 1H), 7.20 (brs, 1H, NH), 7.32–7.43 (m, 2H), 7.60–7.62 (m, 2H), 7.75–7.78 (m, 1H), 7.83–7.86 (m, 1H), 7.91–7.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.79, 68.09, 76.32, 110.29, 114.78, 123.80, 126.83, 128.85, 131.80, 132.04, 132.30, 133.86, 135.23, 135.87,

136.78, 174.30, 181.59; HRMS (ESI-TOF) calcd for $C_{19}H_{13}BrF_3N_3O_2S$ ($[M + H]^+$): 483.9942; found: 483.9941.

4.6.16. 5-[(4-fluorophenyl) hydroxy methyl]-5-methyl-3-(4-nitro-3-trifluoromethylphenyl)-4-oxo-2-thioxoimidazolidine **7(f)(i)**

Rf 0.61, EtOAc–hexane, 2:3; yield 50%; white solid; mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.43 (brs, 1H, OH), 5.07 (s, 1H), 6.99 (brs, 1H, NH), 7.17–7.21 (m, 2H), 7.43–7.46 (m, 2H), 7.80–7.82 (m, 1H), 7.90–7.93 (m, 1H), 8.02–8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.83, 68.13, 76.27, 116.17, 116.38, 125.85, 128.14, 128.84, 128.92, 132.69, 132.83, 136.42, 174.34, 181.65; HRMS (ESI-TOF) calcd for $C_{18}H_{13}F_4N_3O_2S$ ($[M + Na]^+$): 466.0461; found: 466.0447.

4.6.17. 5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-3-(4-nitro-3-trifluoromethylphenyl)-4-oxo-2-thioxoimidazolidine **7(f)(ii)**

Rf 0.60, EtOAc–hexane, 2:3; yield 60%; white solid; mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 2.60 (brs, 1H, OH), 5.05 (s, 1H), 7.11 (brs, 1H, NH), 7.39–7.47 (m, 4H), 7.79–7.81 (m, 1H), 7.87–7.89 (m, 1H), 8.03 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.95, 68.93, 76.05, 125.53, 127.74, 127.87, 127.92, 127.99, 129.00, 133.53, 134.03, 137.17, 137.37, 147.06, 175.41, 181.47; HRMS (ESI-TOF) calcd for $C_{18}H_{13}ClF_3N_3O_2S$ ($[M + H]^+$): 460.0345; found: 460.0340.

4.6.18. 5-[(4-bromophenyl) hydroxy methyl]-5-methyl-3-(4-nitro-3-trifluoromethylphenyl)-4-oxo-2-thioxoimidazolidine **7(f)(iii)**

Rf 0.60, EtOAc–hexane, 2:3; yield 57%; white solid; mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.62 (brs, 1H, OH), 5.03 (s, 1H), 7.14 (brs, 1H, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.58–7.63 (m, 2H), 7.79–7.81 (m, 1H), 7.88–7.89 (m, 1H), 8.03 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.75, 68.08, 76.31, 125.74, 125.85, 128.05, 128.11, 128.73, 128.78, 131.84, 132.31, 132.83, 135.84, 136.38, 174.31, 181.64; HRMS (ESI-TOF) calcd for $C_{18}H_{13}BrF_3N_3O_2S$ ($[M + Na]^+$): 525.9660; found: 525.9641.

4.7. Synthesis of (R)-MPA ester **9**

To a solution of 3-(4-chlorophenyl)-5-[(4-chlorophenyl) hydroxy methyl]-5-methyl-4-oxo-2-thioxoimidazolidine (0.06 g, 0.16 mmol) in DCM (5 mL), (*R*)-MPA (0.026 g, 0.16 mmol), DMAP (0.3 g, 0.17 mmol) and EDC.HCl (0.2 g, 0.17 mmol) were added. The reaction mixture was stirred at room temperature for 1 h, then washed with dilute HCl and the organic layer dried over anhydrous sodium sulphate was concentrated to afford the (*R*)-MPA ester of **7(a)(ii)** (white solid, 0.083 g, 70%, mixture of diastereomers). The diastereomers obtained were separated by preparative thin layer chromatography using a mixture of ethyl acetate and hexane (3:7) as the eluent. The products were characterized by analytical and spectral methods.

4.7.1. (R)-[(R)-(4-chlorophenyl){(S)-1-(4-chlorophenyl)-4-methyl-5-oxo-2-thioxoimidazolidin-4-yl}methyl]-2-methoxy-2-phenylacetate **9(a)(ii)**

Rf 0.61, EtOAc–hexane, 2:3; $[\alpha]_D^{20}$ − 88° (c 1.00, $CHCl_3$); white solid; mp 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.341 (s, 3H, CH_3), 3.304 (s, 3H, OCH_3), 4.782 (s, 1H, MPA), 5.808 (s, 1H, sec. alcohol), 6.98–7.00 (m, 2H), 7.088 (brs, 1H, NH), 7.11–7.15 (m, 2H), 7.24–7.26 (m, 2H), 7.36–7.45 (m, 7H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 19.98, 58.13, 67.53, 77.86, 83.27, 128.49, 129.44, 129.86, 130.03, 130.16, 130.39, 131.64, 133.10, 134.38, 134.66, 134.82, 136.81, 169.86, 175.07, 183.24; HRMS (ESI-TOF) calcd for $C_{26}H_{22}Cl_2N_2O_4S$ ($[M + Na]^+$): 551.0575; found: 551.0578.

4.7.2. (R)-[(S)-(4-Chlorophenyl){(R)-1-(4-chlorophenyl)-4-methyl-5-oxo-2-thioxoimidazolidin-4-yl}methyl]-2-methoxy-2-phenylacetate **9'(a)(ii)**

Rf 0.52, EtOAc–hexane, 2:3; $[\alpha]_D^{20}$ + 45° (c 1.00, $CHCl_3$); white solid; mp 89–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.391 (s, 3H, CH_3), 3.373 (s, 3H, OCH_3), 4.756 (s, 1H, MPA), 5.833 (s, 1H, sec. alcohol), 6.76–6.79 (m, 2H), 7.043 (brs, 1H, NH), 7.15–7.22 (m, 2H), 7.18–7.21 (m, 2H), 7.32–7.34 (m, 2H) 7.35–7.43 (m, 3H), 7.47–7.51 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.95, 60.33, 70.31, 81.26, 85.81, 131.26, 131.99, 132.39, 132.60, 132.64, 132.67, 133.76, 135.73, 136.30, 138.35, 138.58, 139.60, 172.71, 178.47, 186.66; HRMS (ESI-TOF) calcd for $C_{26}H_{22}Cl_2N_2O_4S$ ($[M + Na]^+$): 551.0575; found: 551.0580.

4.8. X-ray crystallographic data

Both diastereomers **9(a)(ii)** and **9'(a)(ii)** were subjected to crystallization, crystals were formed only from diastereomer **9(a)(ii)** (DCM: Hexane = 1:2, v/v) and a single crystal with dimension 0.35 × 0.23 × 0.20 mm was mounted and used for data collection. The intensity data were collected; and the lattice parameters and standard deviations were obtained. The data were corrected for Lorentz and polarization factors. The structure was solved by Direct Methods using SHELX-97 [40] package and also refined using the same. Crystallographic data for the compound **9(a)(ii)** has been deposited with the Cambridge Crystallographic Data Centre, **CCDC No. 733607.** Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.9. In-vitro cytotoxicity evaluation

4.9.1. Cell lines and cell culture

Human prostate carcinoma cells, PC-3 and LNCaP, were obtained from National Centre for Cell Science (NCCS), India. The cells were cultured in DMEM and RPMI1640 respectively, containing 10% FBS and 1% penicillin-streptomycin. DMEM, RPMI1640, FBS, flutamide and doxorubicin were obtained from Sigma. MTT was obtained from Hi-Media. Cell cultures were maintained in flasks under standard conditions: incubation at 37 °C and 5% CO_2. All the subcultures were used prior to passage 15. Cells were routinely passaged using 0.25% trypsin/0.1% EDTA. For treatment, cells were cultured in the presence of increasing concentrations (10^{-12} M, 10^{-10} M, 10^{-8} M, 10^{-6} M and 10^{-4} M) of compounds for 24 h.

4.9.2. In-vitro cytotoxicity measurements

All *in-vitro* experiments for cell proliferation/inhibition were performed in triplicates. PC-3 cells were originally derived from advanced androgen independent bone metastasized prostate cancer [41]. For the PC-3 cell growth inhibition assay, cells were cultured in DMEM supplement and trypsinized, further diluted to 2.0×10^4 cell/mL with DMEM supplemented with 10% fetal bovine serum. This cell suspension was transferred to 96-well microtiter plates, and incubated in the presence or absence of increasing concentration of positive control (doxorubicin) or the test compounds (10^{-12} M, 10^{-10} M, 10^{-8} M, 10^{-6} M and 10^{-4} M) at 37 °C and 5% CO_2 [42]. After 24 h incubation, cells were treated with MTT solution for 4h in a cell culture incubator at 37 °C and 5% CO_2. Cell proliferation was determined by the MTT method [43,44]. MTT which is a tetrazolium salt is converted into insoluble formazan by mitochondrial dehydrogenases in live cells. Formazan is dissolved in DMSO (Merck) and absorbance was measured at dual wavelength of 550 nm and 630 nm on an ELISA plate spectrophotometer (Biotrek Instruments). Similar experiments were performed in LNCaP cells also. Since LNCaP cells have demonstrated androgen dependent cell growth [41]; promotion and inhibition of cell

growth was considered as agonistic and antagonistic respectively. These cells are known to possess an aberrant AR with a mutation of 877Thr to Ala. LNCaP cells were cultured as described above in RPMI1640 media and were transferred into a 96-well plate with a 2.0×10^4 cell/mL well density supplemented with testosterone (final concentration in each well was kept 10 nM) [45]. After 24 h, the cells were treated with testosterone in the presence or absence of each concentration of positive control (Flutamide) or test compounds (10^{-10} M, 10^{-8} M, 10^{-6} M and 10^{-4} M) for another 24 h. The total number of viable cells relative to viable cells in untreated control was plotted. For LNCaP cells, the number of cells on wells with testosterone alone was defined as 100% viability.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.04.050.

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