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REGULAR ARTICLE

Design and synthesis of novel tetrahydrofuran cyclic urea derivatives as androgen receptor antagonists

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Abstract. In order to improve the antiproliferative activity of androgen receptor (AR) antagonists, which used clinically for the treatment of prostate cancer that is a major cause of male death in worldwide, we report the design and synthesis of a series of tetrahydrofuran cyclic urea-based non-steroidal small molecule AR antagonists and exhibit potent AR antagonistic activity. These molecules with higher stereochemical aspects have been achieved by changing the hydantoin analogue antiandrogens to 4-(2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-(trifluoromethyl)benzonitrile analogues. Here, the thio-hydantoin pharmacophore of the recently reported antagonists is replaced by tetrahydrofuran cyclic urea. The antiproliferative properties of these molecules have been evaluated against androgen-dependent (LNCaP) cell line. Among the reported molecules, 4-(2-oxohexahydro-1H-furo[3,4-d]imidazol-1-yl)-2-(trifluoromethyl)benzonitrile (**AR04**) showed significantly improved in vitro activity, IC_{50} = 3.926 μM. Molecular structure-activity relationship studies confirm that the oxetane analogue **AR04** is distinct from other synthesized AR antagonists. These results have suggested that **AR04** exhibiting their potential as a lead compound for the alternative treatment of prostate cancer.

Keywords. Prostate cancer; tetrahydrofuran cyclic urea; androgen receptor antagonist; oxetane; hydantoin.

1. Introduction

Prostate cancer (PC) is considered as one of the leading causes of all cancer deaths in most developed countries.[1] And it is one of the most common cancer among men in the USA and the second most dangerous cause of male death worldwide, after lung cancer.[2–4] Even though several treatment methods exist for PC, including castration, chemotherapy and radiation therapy, androgen deprivation is one of the main approaches to treat it at the various stages of its development, which falls under the androgen blockade therapy (ABT).[5,6] The ratio of the rate of cell proliferation to the rate of cell death determines the growth of PC cells. The rate of cell proliferation is higher than that of cell death led to continuous net growth resulting in PC. Importantly, this ratio is mainly regulated by androgens and androgen

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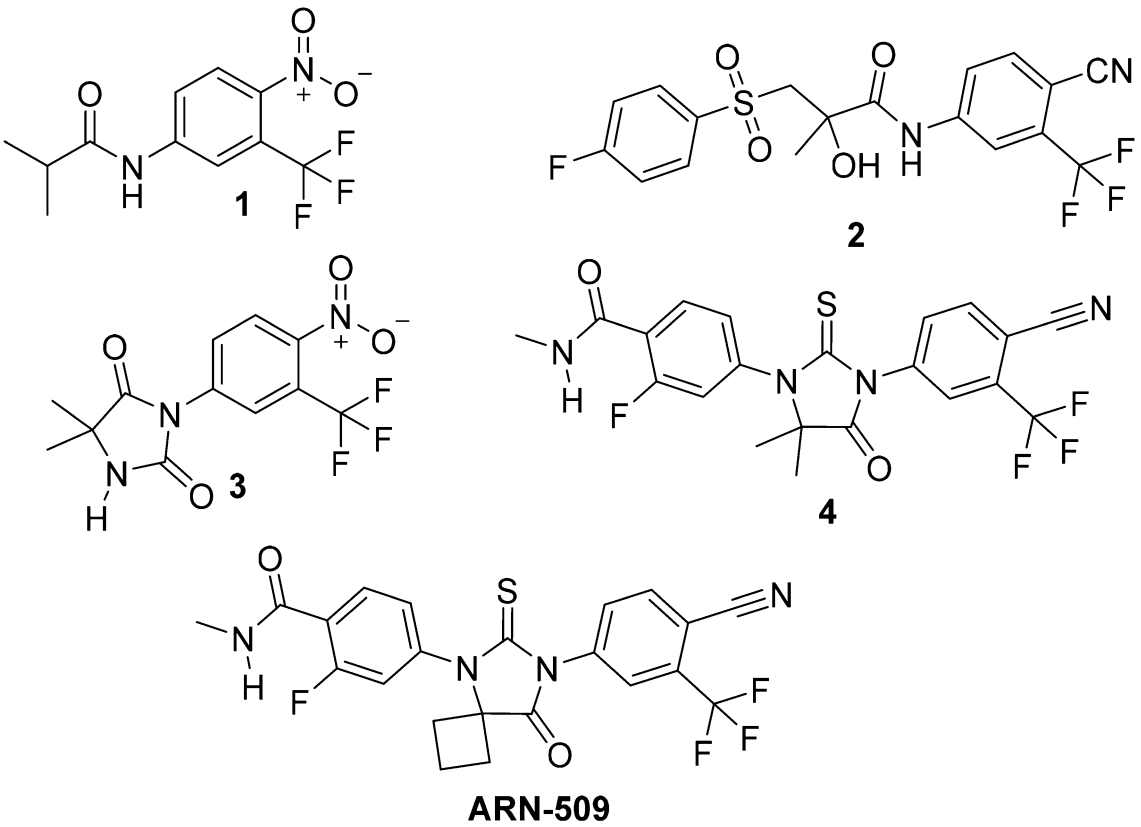


Figure 1. Chemical structures of non-steroidal AR antagonists approved by FDA.

receptors (ARs).[7,8] Since AR plays an important role in the growth of PC, AR antagonists are used for the treatment of PC clinically.

Generally, the compounds show the activity of AR antagonists commonly categorized into steroidal and non-steroidal. The commonly used FDA approved non-steroidal AR antagonists (Figure 1) for the treatment of PC are **1** (flutamide),[9] **2** (bicalutamide),[10] **3** (nilutamide),[11] **4** (enzalutamide),[12] or **5** (ARN-509).[13] Even though these drugs are highly efficient for localized, early-stage PC, after several years of treatment they became ineffective and the disease would reach the more aggressive and lethal form, also known as castration-resistant prostate cancer (CRPC).[14,15] This is because adaptive mutations on the structure of the AR, which switch the function of these drugs from antagonist to agonist led to change them as tumour-stimulating agents.[16]

In general, non-steroidal antiandrogens having the structural features that two differently substituted aromatic rings connected through linear (bicalutamide-like compounds (**2** or **3**)) or cyclic (enzalutamide-like compounds (**5** or **ARN-509**)) linkers.[17] In the former case, the amide linkage is placed in between the substituted aromatic rings and in the latter case, the amide linkage is moved to the terminal position of the aromatic ring simultaneously hydantoin unit placed between the aromatic ring resulting highly rigidified structural futures. Recently, Ivachtchenko *et al*., have developed novel thio-hydantoin based AR antagonist, **(R)-6** (Figure 2), and shows sub-nanomolar activity. They claimed that the key reason for this sub-nanomolar activity is the introduction of stereospecific spiro-moiety and fluoride at the para-position of phenyl ring.[18,19] Importantly, the new generation AR inhibitor **ODM-201** (Figure 2) is now in Phase III trial, and has shown retained activity in the F876L AR mutant,[20] whereas the amide group is placed in between the two pyrazole ring with stereospecific flexible alkyl chain. Also, one pyrazole group is linked to -Cl and –CN substituted phenyl ring. It clearly says that the thio-hydantoin unit is not necessarily important for the AR inhibitor; introduction of stereospecific centres in the compound may also be the reason for good activity. While considering the chemical structure of effective AR inhibitor, the substitution of trifluoromethyl group to one of the benzene ring is a critical factor for biological activity and the introduction of fluorine also improves anti-proliferative activity and pharmacological properties of the compounds.[21–23] Since AR agonists and AR antagonists share different modes of action towards the 'closed' and 'open' conformations of AR-H12 helix, even

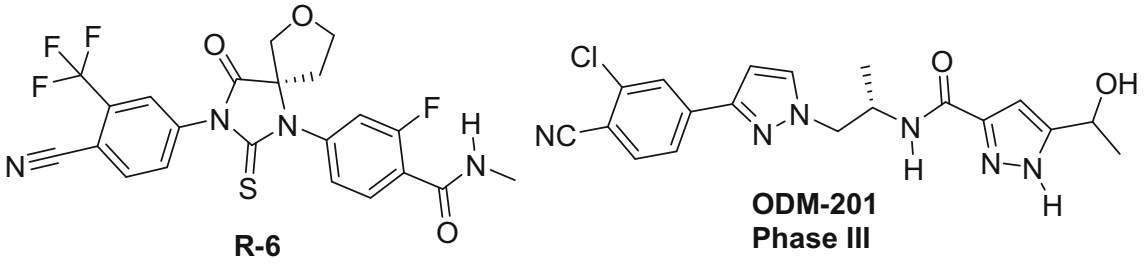


Figure 2. Chemical structures of non-steroidal AR antagonists in clinical development for the treatment of PC.

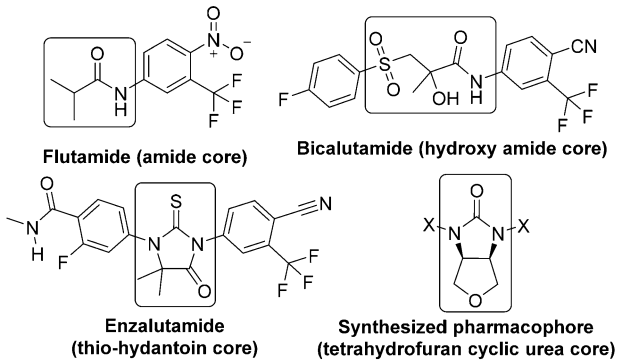


Figure 3. Chemical structures of non-steroidal AR antagonists in clinical development for the treatment of PC.

slight modifications in the chemical structure of AR ligand can lead to dramatic alterations in the receptor-ligand interaction thereby providing opposite pharmacological responses.[24–26]

With the aim to develop novel AR antagonists, we designed and synthesized series of novel tetrahydrofuran cyclic urea derivatives (Figure 3), which is distinct from Flutamide (**1**) and Enzalutamide (**5** or **ARN 509**) analogues, and their potential of anti PC activity was evaluated against the androgen-sensitive human prostate adenocarcinoma LNCaP cell line. Here, we have introduced two stereospecific carbon atoms in cyclic urea skeleton. Among the reported compounds, **ARO4** showed significantly improved *in vitro* activity, IC_{50} = 3.926 μM. We have also performed 3D-molecular docking approach to estimate possible binding modes and diverse points of the compound.

2. Experimental

2.1 *Materials*

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz Bruker Advance DPX 400/300 spectrometer in $CDCl_3$ and $(CD_3)_2SO$ using TMS as the internal standard. The chemical shifts (d) 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. Mass spectra were recorded on POLARIS Q (Thermo Scientific). Specific rotations were taken on Rudolph Autopol IV Instrument and HRMS spectra were recorded on Bruker Maxis TOF. The following commercial grade reagents and solvents were purchased from Aldrich chemicals, Bengaluru and used without further purification: *m*-Chloroperoxybenzoic acid (m-CPBA), NH_4Cl, NaN_3, Pd-C, $(BoC)_2O$, Triethyl amine (TEA), Swern oxidation, p-methoxy benzyl amine ($PMBNH_2$), Sodium cyano borohydride ($NaBH_3CN$), trifluoroacetic acid (TFA), 1,1′-carbonyl diimidazole (CDI), CuI, Trans diamine cyclohexane, K_3PO_4, LiOH, (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU), N,N-diisopropylethylamine (DIPEA), $NaNO_2$, KI, HCl, dichloromethane (DCM) (Rankem), methanol (MeOH), ethanol (EtOH), Toluene (Spectrochem), THF (Finar). The compound **12** was reached from 2,5-dihydrofuran through the reported synthetic methodologies.

2.2 *Methods*

2.2a *Model selection (protein and ligand)*: The ligands were minimized to a local energy minimum using hybrid based steepest descent till 5000 iterative steps using LBFGS algorithm[27] with default tautomeric and ionized state using EPIK.[28] The Androgen receptor (NR3C4) PDB iD :1E3G[29] was structurally optimized using protein preparation wizard Schrodinger. Hydrogen is not visible in X-ray diffraction thus hydrogen was fixed along with bond order with standard sampling using ProtAssign module.[30] Protein minimization was done using

Imperf whereby all rotatable hydrogen bond was minimized with the removal of torsional potential. The minimization is carried until RMSD cut-off of 0.30 Å for the heavy atoms. Altogether the protonation state and hydrogen bond of the structure are fixed with re-oriented clash penalty score. Grid-based ligand docking with energetics (GLIDE) was used to find favourable interactions between ligand and the receptors with flexible conformations of the ligand. Glide scoring function is given by the equation below:

$$GScore = 0.05 \times vdW + 0.15 \times Coul + Lipo + Hbond + Reward + RorB + Site + hydrophobicity$$

Glide scoring with XP descriptor with Induced Fit docking (IFD) rewards hydrophobic interactions in-between ligand and the receptors. IFD also reduces false positive of true ligand binder whereby IFD induces sidechain flexibility in the receptors.[31]

2.2b *General procedure for the synthesis of compound 7 and 8*: Synthesis begins with commercially available 2,5-dihydrofuran and reaches intermediate tert-butyl (S)-(4-oxotetrahydrofuran-3-yl) carbamate (**6**) through the reported optimized conditions. Reductive amination of **6** with p-methoxy benzyl amine ($PMBNH_2$) in the presence of ACOH and $NaBH_3CN$ in ETOH yields *trans*-tert-butyl (4-((4-methoxybenzyl)amino)tetrahydrofuran-3-yl)carbamate (**7**) and *cis*-tert-butyl (4-((4-methoxybenzyl) amino)tetrahydrofuran-3-yl)carbamate (**8**) with the yield of 42% and 38%, respectively. Both the isomers are clearly separated by preparative HPLC.[32] The ratio of (7) and (8) is 1.1:0.9.

2.2c *Trans tert-butyl (4-((4-methoxybenzyl) amino) tetrahydrofuran-3-yl) carbamate (7)*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.23 (m, 2H), 6.86-6.84 (m, 2H), 4.69 (s, 1H), 4.04-4.00 (m, 3H), 3.84-3.74 (m, 5H), 3.62-3.61 (m, 1H), 3.50-3.47 (m,1H), 3.19-3.17 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (400 MHz, DMSO-d6): δ 158.65, 155.26, 131.92, 129.35, 113.75, 79.60, 73.10, 72.17, 64.82, 60.31, 57.11, 55.18, 51.35, 28.31; HRMS (ESI-TOF): Calcd for $C_{17}H_{26}N_2O_4$ $[M + H]^+$: 323.1971; found: 323.1964.

2.2d *Cis tert-butyl (4-((4-methoxybenzyl) amino) tetrahydrofuran-3-yl) carbamate (8)*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.22 (m, 2H), 6.87-6.85 (m, 2H), 5.50 (d, J = 6.4 Hz, 1H), 4.14-4.11 (m, 1H), 4.00-3.96 (m, 1H) 3.92-3.90 (m, 1H), 3.80 (s, 3H), 3.73-3.66 (m, 3H), 3.54-3.51 (m,1H), 3.38-3.36 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 158.85, 155.87, 129.35, 113.87, 113.78, 79.48, 73.31, 71.44, 58.61, 55.24, 52.06, 51.78, 29.65, 28.43, 28.36, 28.31; HRMS (ESI-TOF): Calcd for $C_{17}H_{26}N_2O_4$ $[M + H]^+$: 323.1971; found: 323.1997.

2.2e *Cis 1-(4-methoxybenzyl) tetrahydro-1H-furo[3,4-d] imidazol-2(3H)-one (9)*: TFA (60 mL) was added to the solution of **8** (6 g, 18.61 mmol) in DCM (60 mL) at 0 °C and allowed to stir at room temperature for 12 h. After completion of the reaction, the concentration of the solvent was reduced under vacuum, diluted with a 10% aq. NaOH solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum to give a pale-yellow coloured liquid compound N-3-(4-methoxybenzyl) tetrahydrofuran-3,4-diamine (3.5 g crude). The crude product was used for the next step without any further purification. It was dissolved in THF and cooled to 0 °C. Then, TEA (6.6 mL, 47.22 mmol) and CDI (2.80 g, 17.31 mmol) were added under nitrogen atmosphere and allowed to stir at room temperature for 12 h. The mixture was poured into a brine solution and extracted by ethyl acetate, washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and purified by silica gel column chromatography (DCM–MeOH) to give **9** (3.0 g, 77%) as a white powder (M.p. 99–103 °C). ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 7.16 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.69 (s, 1H), 4.41 (d, J = 15.3 Hz, 1H), 4.09–3.95 (m, 3H), 3.81–3.78 (m, 1H), 3.73 (s, 3H), 3.70–3.66 (m, 1H), 3.41–3.37 (m, 1H), 3.44–3.42 (m, 1H), 3.22–3.17 (m, 1H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 160.31, 158.40, 129.73, 129.02, 113.86, 74.89, 70.63, 59.72, 55.00, 53.40, 44.03; HRMS (ESI-TOF): Calcd for $C_{12}H_{18}N_2O_2$ $[M + H]^+$: 249.1239; found: 249.1227.

2.2f *Cis-4-(3-(4-methoxybenzyl)-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-(trifluoromethyl) benzonitrile (10)*: A mixture of compound **9** (1.1 g, 4.43 mmol), 4-iodo-2-(trifluoromethyl)benzonitrile (1.57 g, 5.31 mmol), CuI(0.084 g, 0.443 mmol), trans-1,2-diaminocyclohexane (±) (0.050 g, 0.443 mmol) and tri-potassium phosphate (2.82 g, 13.29 mmol) in toluene (20 mL) was degassed with nitrogen for 10 min in a sealed tube and kept in a preheated oil bath at 110 °C and allowed to stir for 12 h. The reaction mixture was cooled to RT and filtered through a pad of celite. And the filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column

chromatography yields compound **10** as white solid (1.2 g, 65%). M.p. 151–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.19 (s, 1H), 7.77–7.70 (m, 2H), 7.26–7.19 (m, 2H), 7.87 (d, J = 8.7 Hz, 2H), 4.78 (d, J = 15 Hz, 1H), 4.21–4.14 (m, 2H), 4.01 (d, J = 10.8 Hz, 1H), 3.84–3.82 (m, 1H), 3.80 (s, 3H), 3.51 (dd, J_1 = 4.2, J_2 = 10.5 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 155.51, 143.37, 143.37, 135.63, 134.10, 133.67, 129.59, 127.37, 124.08, 120.44, 118.91, 115.82, 114.91, 114.78, 102.01, 72.37, 71.38, 57.93, 57.10, 55.28, 45.82; HRMS (ESI-TOF): calcd for $C_{21}H_{18}F_3N_3O_3$ $[M + H]^+$: 418.1379; found: 418.1395.

2.2g *Cis-4-(2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-(trifluoromethyl) benzonitrile (11)*: A mixture of compound **10** (1.2 g, 2.87 mmol) and TFA (20 mL) were heated to reflux for 6 h. After completion of the reaction, the mixture was cooled to room temperature and solvent was removed by vacuum. The mixture was diluted with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuum yields compound 12 (0.8 g crude) as an off white solid, which was used for the next step without any further purification. M.p. 240–244 °C; ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.57 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.92 (s, 1H), 7.67 (dd, J_1 = 2.1, J_2 = 8.7 Hz, 1H) 5.02 (q, J = 4.2 Hz, 1H), 4.33 (q, J = 4.2 Hz, 1H), 3.89–3.79 (m, 2H), 3.72–3.67 (m,1H),3.58–3.54 (m, 1H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 156.96, 144.00, 136.26, 131.75, 119.27, 116.02, 114.41, 114.34, 99.31, 74.27, 71.63, 59.81, 53.02; HRMS (ESI-TOF): Calcd for $C_{13}H_{10}F_3N_3O_2$ $[M + H]^+$: 297.2326; found: 297.2342.

2.2h *Cis ethyl 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-fluorobenzoate (12)*: A mixture of compound **11** (0.8 g, 2.69 mmol), ethyl-2-fluoro-4-iodobenzoate (0.949 g, 3.22 mmol), CuI (0.051 g, 0.269 mmol), trans-1,2-diaminocyclohexane (±) (0.030 g, 0.269 mmol) and tri-potassium phosphate (1.71 g, 8.07 mmol) in toluene (10 mL) was degassed with nitrogen for 10 min in a sealed tube and kept in a preheated oil bath at 110 °C and allowed to stir for 12 h. The reaction mixture was cooled to RT, filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography yields compound **12** (0.7 g, 56%) as pale yellow solid. M.p. 216–220 °C; ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.56 (d, J = 1.8 Hz, 1H), 8.17 (d, J = 9 Hz, 1H), 7.94–7.85 (m, 2H), 7.74 (dd, J_1 = 1.8, J_2 = 13.8 Hz, 1H), 7.58 (dd, J_1 = 1.8, J2 = 8.7 Hz, 1H), 5.25–5.14 (m 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.98–3.83 (m, 4H), 1.31 (t, J = 6.9 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 162.97, 159.83, 153.06, 143.54, 142.76, 136.39, 132.49, 131.87, 121.08, 115.92, 115.69, 113.88, 112.37, 106.50, 106.13, 101.37, 71.90, 60.76, 57.42, 57.20, 14.08; HRMS (ESI-TOF): Calcd for $C_{22}H_{17}F_4N_3O_4$ $[M + H]^+$: 464.1233; found: 464.1258.

2.2i *Cis 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-2-oxohexahydro-1H-furo[3,4-d]imidazol-1-yl)-2-fluorobenzoic acid (AR01)*: To a solution of compound **12** (0.7 g, 1.51 mmol), THF (10 mL), MeOH (10 mL) and H_2O (5 mL), lithium hydroxide monohydrate (0.316 g, 7.55 mmol) was added at room temperature and allowed to stir for another 6 h. The reaction mixture was concentrated under reduced pressure, poured into water (10 mL) and extracted with diethyl ether. The pH of aqueous layer was adjusted to 2 using cone. HCI, white precipitate is generated, which was filtered and dried to give compound **AR01** (0.550 g, 83%) as white solid. M.p. 296–300 °C; ^{1}H NMR (300 MHz, DMSO-d6, ppm): δ 13.05 (s, 1H), 8.57 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.94–7.85 (m, 2H), 7.72 (dd, J_1 = 1.8, J_2 = 13.8 Hz, 1H), 7.57 (dd, J_1 = 2.4, J_2 = 9.3 Hz, 1H), 5.25–5.14 (m, 2H), 3.98–3.83 (m, 4H). ^{13}C NMR (300 MHz, DMSO-d6, ppm): δ 164.47, 160.01, 153.12, 143.40, 142.83, 136.41, 132.81, 121.09, 115.93, 115.72, 113.80, 113.31, 109.50, 106.55, 106.17, 101.33, 71.93, 71.76, 57.45, 57.21; HRMS (ESI-TOF): Calcd for $C_{20}H_{13}F_4N_3O_4$ $[M + H]^+$: 436.0961; found: 436.09777

2.2j *Cis 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-fluorobenzamide (AR02)*: To a solution of compound **AR01** (0.100 g, 0.229 mmol) and NH_4Cl (0.036 g, 0.687 mmol) in DMF (2 mL), DIPEA (0.119 mL, 0.687 mmol) was added followed by HATU (0.109 g, 0.34 mmol) at room temperature under N_2 atmosphere and allowed to stir for another 16 h. The reaction mixture was diluted with cold water and extracted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography (DCM–MeOH) to give **AR02** (0.070 g, 70%) as white solid. M.p. 311–315 °C; ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.57 (d, J =1.5 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.86 (dd, J_1 = 2.1, J_2 = 8.7 Hz, 1H), 7.77–7.68 (m, 2H),

7.58 (s, 2H), 7.51 (dd, J_1 = 2.1, J_2 = 8.7 Hz, 1H), 5.25–5.14 (m, 2H), 3.98–3.83 (m, 4H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 164.41, 160.80, 153.17, 142.94, 141.61, 141.44, 136.40, 131.19, 120.96, 117.78, 115.89, 115.76, 114.14, 106.28, 105.90, 101.15, 71.90, 71.80, 57.47, 57.18; HRMS (ESI-TOF): Calcd for $C_{20}H_{14}F_4N_3O_4$ [M + H] $^+$: 435.0716; found: 435.0688.

2.2k *Cis 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-fluoro-N-methylbenzamide (AR03)*: This compound was also prepared by adopting the same procedure as compound **AR02** using methanamine instead of NH_4Cl. Yield (0.060 g, 58%) M.p. 274–278 °C; ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.58 (s, 1H), 8.19–8.13 (m, 2H), 7.86 (d, J = 8.7 Hz, 1H), 7.74–7.68 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 5.22–5.15 (m, 2H), 3.98–3.83 (m, 4H), 2.78 (d, J = 4.8 Hz, 3H). ^{13}C NMR (300 MHz, DMSO-d6, ppm): δ 163.32, 161.16, 157.88, 153.17, 142.94, 141.37, 141.22, 136.40, 130.87, 120.93, 118.22, 118.03, 115.76, 114.20, 106.30, 105.92, 101.14, 71.90, 71.81, 57.47, 57.18; HRMS (ESI-TOF): Calcd for $C_{21}H_{16}F_4N_4O_3$ [M + H] $^+$: 449.1477; found: 449.1466.

2.2l *Cis 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-fluoro-N-(oxetan-3-yl)benzamide (AR04)*: This compound was prepared by adopting the similar procedure as compound **AR02** using oxetan-3-amine instead of NH4Cl. Yield (0.065 g, 58%); M.p. 240–244 °C. ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.94 (d, J = 6.3 Hz, 1H), 8.58 (s, 1H), 8.17 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.76–7.65 (m, 2H), 7.53 (d, J = 8.7 Hz, 1H), 5.25–5.15 (m, 2H), 5.02–4.95 (m, 1H), 4.76 (t, J = 6.6 Hz, 2H), 4.56 (t, J = 6.6 Hz, 2H), 3.98–3.82 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 162.82, 161.5, 158.0, 153.17, 142.92, 141.58, 141.41, 136.41, 131.88, 130.84, 120.97, 117.90, 115.76, 114.19, 106.33, 105.96, 101.20, 76.83, 71.87, 71.81, 57.47, 57.18, 44.50; HRMS (ESI-TOF): Calcd for $C_{23}H_{18}F_4N_4O_4$ [M + H] $^+$: 491.1342; found: 491.1355.

2.2m *Cis 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-fluoro-N-(tetrahydro-2H-pyran-4-yl) benzamide (AR05)*: This compound was also prepared by adopting similar procedure as compound **AR02** using tetrahydro-2H-pyran-4-amine instead of NH_4Cl. Yield (0.070 g, 70%), M.p. 240–244 °C; ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.57 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.86 (dd, J_1 = 2.0, J_2 = 8.4 Hz, 1H), 7.71 (dd, J_1 = 1.6, J_2 = 13.2 Hz, 1H), 7.63 (t, J = 8.4 Hz, 1H), 7.50 (dd, J_1 = 2.0, J_2 = 8.8 Hz, 1H), 5.24–5.15 (m, 2H), 3.99–3.82 (m, 7H), 3.41–3.32 (m, 2H), 1.77 (dd, *J1* = 2.4, J_2 = 12.4 Hz, 2H), 1.59–1.49 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 162.47, 160.60, 158.14, 153.18, 142.96, 141.13, 141.03, 136.41, 131.83, 131.51, 130.72, 123.85, 121.12, 120.94, 119.04, 118.90, 115.75, 114.18, 106.32, 106.04, 101.14, 71.85, 65.93, 57.47, 57.18, 45.64, 32.22; HRMS (ESI-TOF): Calcd for $C_{25}H_{22}F_4N_4O_4$ [M + H] $^+$: 519.1655; found: 519.1610.

2.2n *Cis 4-(3-benzyl-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-(trifluoromethyl) benzonitrile (AR06)*: The solution of compound **12** (0.30 g, 1.008 mmol) in DMF (2 mL) was added to the ice cooled suspension of NaH (0.078 g, 2.016 mmol, 60% in oil, washed with hexane) in DMF (5 mL). The resulting mixture was vigorously stirred for 0.5 h under the same ice bath followed by benzyl bromide (0.258 g, 1.512 mmol) was added and allowed to stir overnight at the ambient temperature. After the reaction was completed, the mixture was poured into water (20 mL) and the extracted with ethyl acetate, washed with water and brine solution, dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography (Hexane–ethyl acetate) to give compound **AR06** (0.120 g, 30%) as off white solid. M.p. 127–131°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.15 (s, 1H), 7.77 (s, 2H), 7.38–7.28 (m, 5H), 4.86 (d, J = 11.1 Hz, 1H), 4.71 (q, J = 3.6 Hz, 1H), 4.24 (d, J = 11.4 Hz, 1H), 4.17 (q, J = 3.0 Hz, 1H), 4.03 (d, J = 7.5 Hz, 1H), 3.82 (dd, J_1 = 3.6, J_2 = 7.8 Hz, 1H), 3.51 (dd, J_1 = 2.7, J_2 = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 155.55, 143.82, 136.61, 136.33, 136.33, 131.74, 131.49, 128.62, 127.45, 123.65, 121.47, 119.41, 115.98, 114.56, 114.52, 99.62, 71.76, 70.72, 57.67, 57.46, 45.20; LCMS for C20H16F3N3O2 [M + H] $^+$: 388.12.

2.2o *Cis 4-(3-benzyl-2-oxohexahydro-1H-furo[3,4-d] imidazol-1-yl)-2-(trifluoromethyl) benzamide (**AR07**)*: A mixture of compound **AR06** (0.10 g, 0.258 mmol), TFA (10 mL) and toluene (10 mL) in a sealed tube was heated to reflux for 3 days. After completion of reaction, the reaction mixture was diluted with an aqueous solution of sodium bicarbonate, extracted with ethyl acetate, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed, and the crude product was

purified by silica gel column chromatography (70% ethyl acetate and hexane) yields compound **AR07** (0.005 g, 4.8%) as brown solid. M.p. 118–122 °C; ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.34 (d, J = 1.6 Hz, 1H), 7.85 (s, 2H), 7.58–7.50 (m, 2H), 7.48 (s, 1H), 7.38–7.27 (m, 5H), 4.99 (q, J = 4.4 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.71 (q, J = 15.6 Hz, 1H), 4.35 (d, J = 15.6 Hz, 1H), 4.22 (q, J = 4.0 Hz, 1H), 3.97 (d. J = 10.0 Hz, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.73–3.69 (m, 1H), 3.42 (dd, J_1 = 4.0, J_2 = 10.0 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d6, ppm): δ 168.73, 155.92, 140.27, 136.98, 129.68, 129.37, 128.62, 127.77, 127.39, 119.35, 114.58, 71.85, 70.93, 57.58, 57.36, 45.20; HRMS (ESI-TOF): Calcd for C20H18F3N3O3 $[M + H]^{+}$: 406.1379; found: 406.1377.

2.3 *Screening against primary prostate cancer cell lines (LNCaP) assay*

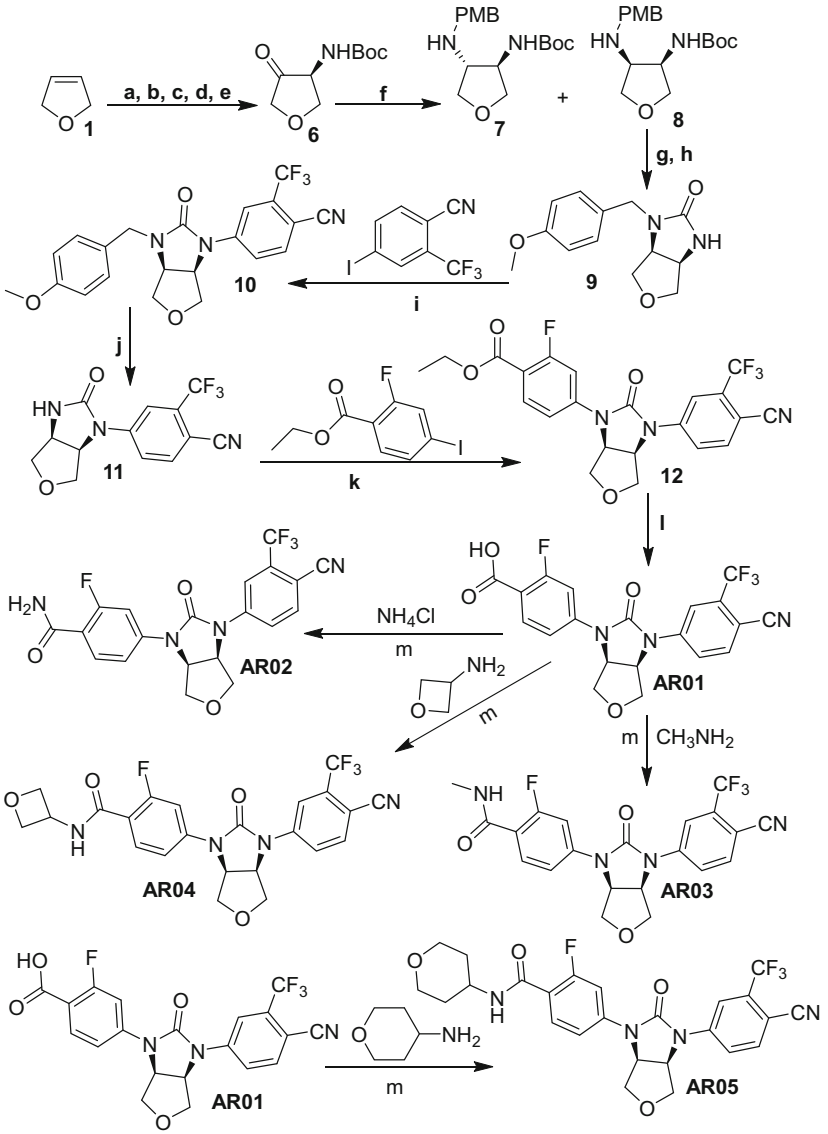
LNCaP cells (ATCC, catalogue no. CRL-1740) were propagated in RPMI-1640 (Invitrogen, catalogue no. R4130) containing 10% FBS (Fatal Bovine Serum, Gibco, catalogue no. 10270) and 1% AAS (Gibco, catalogue no. 11140-050). LNCaP cells were seeded at a density of 1000 cell per well and incubated overnight in RPM-1640 having 10% CCS(Charcol Stripped Serum, Gibco, catalogue no. 12676-029) 200X compounds were prepared in 100% DMSO Hybri max (Sigma, Catalogue no.D2650), followed by 3 fold serial dilution and intermediate stocks of 10X compound was prepared in incomplete RPMI medium. Compounds were added to respective wells, DMSO final concentration was 0.2% and incubated for 7 days, at the same time for T-0 plate 50 µL Ctglo was added and luminescence was measured. Fresh media along with compounds was replaced on day 3 and 6, on 7th day 50 µL Ctglo was added to plates and luminescence was measured, the value of T-0 was subtracted for calculation of % growth or control.

3. Results and Discussion

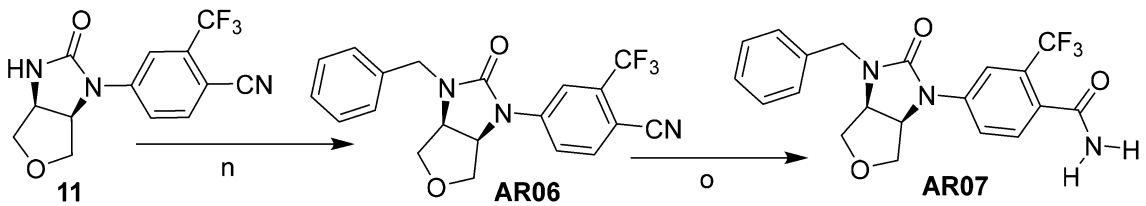
In order to develop novel AR antagonists, we focused on the structure of enzalutamide (**4**), ARN-509 and R-6. While looking at these structures, the main pharmacophore is thio-hydantoin unit linked to the trifluoro methyl and cyanophenyl groups that is the key structural feature of potent nonsteroidal AR antagonists.[17–19] With the extension of these structural features, we developed novel AR antagonists using tetrahydrofuran cyclic urea pharmacophore. To understand the effect of pharmacophore as AR antagonists, there are no changes in the remaining structural features of reported drugs. Scheme 1 shows the optimized synthetic pathway for the preparation of the newly designed compounds **AR01**, **AR02**, **AR03**, **AR04** and **AR05**. Synthesis begins with the commercially available 2,5-dihydrofuran and reaches intermediate tert-butyl-(4-oxotetrahydrofuran-3-yl) carbamate (**6**) using the reported procedures.[32]

The detailed synthetic steps from the compound **1** to **6** are shown in the supporting information (Scheme S1). Reductive amination of **6** with p-methoxy benzylamine ($PMBNH_2$) in the presence of ACOH and $NaBH_3CN$ in ETOH yields *trans*-tert-butyl-4-((4-methoxybenzyl)amino)tetrahydrofuran-3-yl)carbamate (**7**) and *cis*-tert-butyl–(4-((4-methoxybenzyl)amino)tetrahydrofuran-3-yl)carbamate (**8**) with the yield of 42% and 38%, respectively. Both the isomers are clearly separated by preparative HPLC. In order to get cyclic urea derivative of compound **7** and **8**, each compound treated with trifluoroacetic acid (TFA) followed by 1,1′-Carbonyldiimidazole (CDI) and triethyl amine (TEA) in THF; *cis* isomer **8** only gives 1-(4-methoxybenzyl)tetrahydro-1H-furo[3,4-d]imidazol-2(3H)-one (**9**) with the yield of 54%. Unfortunately, trans isomer **7** could not yield the compound **9**. This may be because the formation of highly strained five-membered oxetane ring is not possible from the *trans* isomer (**7**). The cyclic urea tetrahydrofuran derivative (**9**) reacted with 4-iodo-2-(trifluoromethyl) benzonitrile in the presence of K_3PO_4, CuI and *trans* diamine cyclohexane in toluene affords compound **10** with the yield of 55%, which treated with TFA gives compound **11** with the quantitative yield. It reacted with ethyl 2-fluoro-4-iodobenzoate in the presence of K_3PO_4, CuI and *trans* diamine cyclohexane in toluene yields compound **12**, which was treated with $LiOH.H_2O$ in MeOH, THF, H_2O to afford acid **AR01** with the yield of 83%. This acid was treated with various amines as shown in Scheme 1 yields the **AR02**, **AR03**, **AR04** and **AR05**. Finally, compound **11** was treated with Benzyl bromide in the presence of NaH in DMF affords compound **AR06** that was treated with TFA yields compound **AR07** with a quantitative yield as shown in Scheme 2.

The activity of these compounds was defined by testing their cytotoxicity effect. For this purpose, we selected the AR-positive LNCaP cell lines,[33] a cell system widely used as a model of androgen-responsive growth. LNCaP cell line inhibition data of compounds, **AR01**-**AR07** (Table 1), reveals that, except **AR04,** all the derivatives show very weak activity with the half-



Scheme 1. Synthesis of **AR01**, **AR02**, **AR03**, **AR04** and **AR05**. Reagents and conditions: (a) m-CPBA/DCM, rt; (b) $NH_4Cl/NaN_3/MeOH/H_2O$, reflux; (c) Pd/C, EtOH, Hydrogen; (d) $(Boc)_2O$, Na_2CO_3, Acetone, water, RT (e) Oxalyl chloride, THF, DMSO, TEA; (f) $PMBNH_2/MeOH/AcOH/NaBH_3CN$, rt; (g) TFA, rt; (h) CDI, TEA, THF, rt; (i) K_3PO_4, CuI, Trans diamine cyclohexane, Toluene, 110 °C; (j) TFA, reflux; (k) K_3PO_4, CuI, Trans diamine cyclohexane, Toluene, 110°C; (l) $LiOH.H_2O$, MeOH, THF, H_2O, rt; (m) HATU, DIPEA, DMF, rt.



Scheme 2. Synthesis of **AR06** and **AR07**. Reagents and conditions: (n) NaH/DMF/Benzyl bromide, rt.; (o) TFA reflux.

maximal inhibitory concentration (IC_{50}) value of around 30.002 μM. Even though all the derivatives have similar structural features, **AR04** shows remarkable activity towards the LNCaP cell line (IC_{50}: 3.926 μM.); PC cytotoxicity of **AR04** tested against the LNCaP cell line and the IC_{50} value estimated to be 3.926 μM (Figure 4). Hence, we strongly believe that the benzamide with oxetane ring plays a major role in

Table 1. AR antagonistic activity of synthesized compounds towards human prostate cancer Cell Line (LNCaP).

Compound	Type	AVG IC_{50} (μM)[a]	CLogP	$K_i \pm SD$ (nM)
AR01	Antagonist	>30.002	3.12	NA
AR02	Antagonist	>30.003	1.91	NA
AR03	Antagonist	>30.003	2.15	NA
AR04	Antagonist	3.926	2.30	389.6
AR05	Antagonist	>30.003	1.78	NA
AR06	Antagonist	>30.000	3.40	NA
AR07	Antagonist	>30.001	1.56	NA

NA not active

[a]Cell growth was promoted by 10 nM DHT and IC_{50} values for androgen-dependent cell proliferation

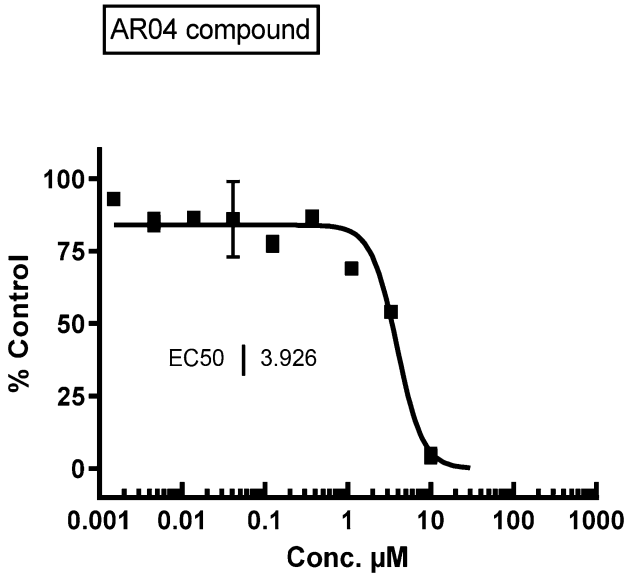


Figure 4. The percentage viability of LNCaP cells with different concentration of AR04.

the activity. In recent drug discovery systems, oxetanes have acknowledged enormous interest as an additional and/or replacement groups for gem-dimethyl and carbonyl groups with enhanced physicochemical properties. Hence, the oxetane incorporation as a pendant motif of drug molecules improves the 'druglike' properties may be due to the small and highly strained polar nature.[34]

As a result, the incorporation oxetane group in the drug molecule as an additional or replacement groups have been widely accepted in medicinal chemistry research in recent years. In this regard, the distinct activity of **AR04** claimed that the highly strained oxetane ring easily relaxes through the interactions with the surface receptor of the cell line used in this study. When compared to the AR antagonists currently employed clinically for the treatment of PC activity (bicalutamide (0.509 μM) and enzalutamide (3.641 μm)), **AR04** shows almost similar activity towards the LNCaP cell line (3.926 μM). Upon considering the chemical structure of reported highly active AR antagonist, presence of the amide group either in between the aromatic ring or at the terminal position of any one of the aromatic rings does not show any significant difference in their activity. Even though the pyran ring in **AR05** is more stable than the oxetane ring in **AR04**, the **AR04** shows very high activity than that of the **AR05** may be due to the fact that the strained ring is more important to bind with the surface receptor of the cells than the stable pyran ring. It is important to note that when comparing the structural features of enzalutamide and **AR03**, only the hydantoin ring in enzalutamide is replaced by the tetrahydrofuran cyclic urea, the **AR03** shows very poor activity. In contrast, **AR04** shows almost similar activity as enzalutamide but here, the methyl group in enzalutamide is replaced by an oxetane ring in **AR04**. It reveals that the activity is highly depending on the relationship between the linking group in between the two aromatic rings and groups linked outside of either of the aromatic ring. Also, it is concluded that the highest activity of **AR04** mainly depends on both oxetane ring and tetrahydrofuran cyclic urea units, but not only because of oxetane ring.

Molecular docking studies were performed to evaluate the proposed structural modifications. Since the compound **AR04** shows the very best activity compared to its counterparts, **AR04** was chosen as representative for the novel series of compounds and attempted to predict the reason for the activity. The docking pose of **AR04** is shown in Figure 5 and the images of the remaining compounds are shown in the Supplementary Information. The docking score is given in Table S1 (Supplementary Information).

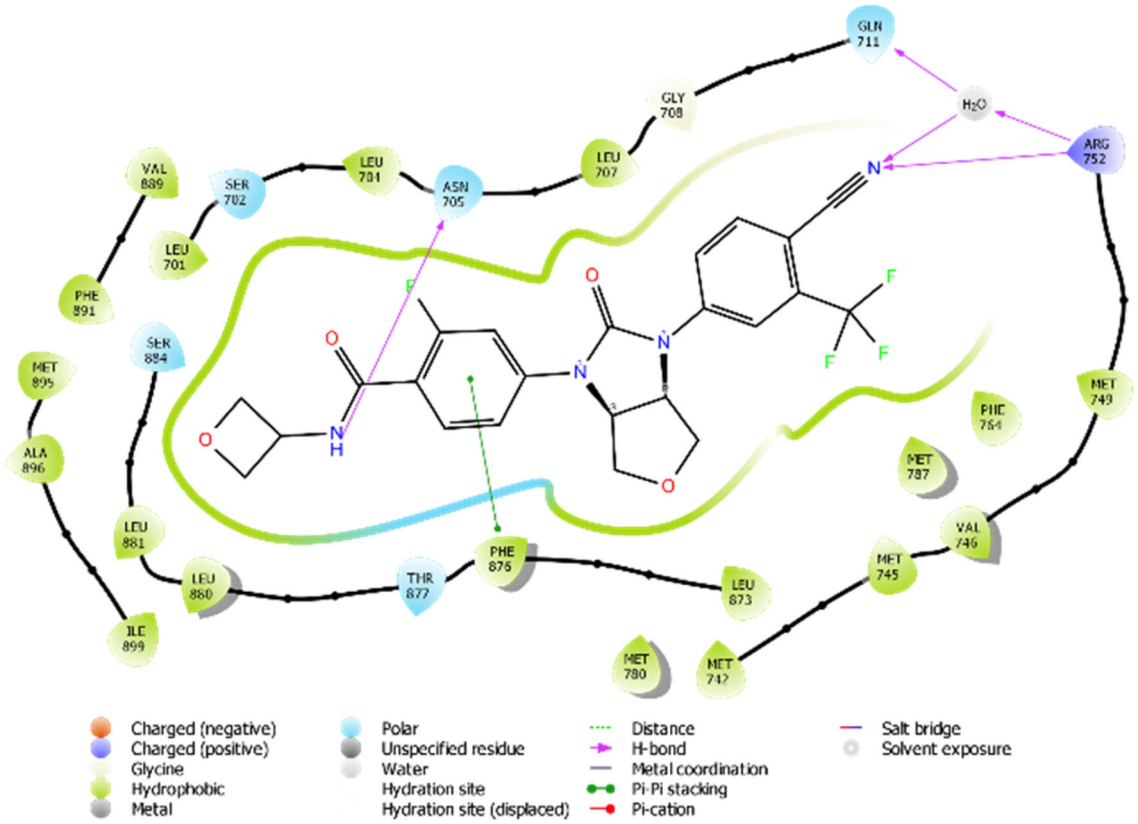


Figure 5. 2D Ligand interaction diagram of compound AR04 with anticancer target protein Androgen Receptor using Maestro (Schrödinger) program with the essential amino acid residues at the binding site are tagged in circles.

The cytochrome P450 active site consists of main residues such as Asparagine 705, Arginine 752 and Threonine 877 which binds with androgenic hormones leading to transcription factor and gene regulations. Androgen receptor (PDB iD: 1E3G) with bound drug metribolone, a synthetic high-affinity anabolic-androgenic steroid, was taken as a template model for docking analysis. Androgen receptor tends to bind with many androgenic steroids and a higher concentration of progestins tends to inhibit androgen receptor (NR3C4). Substrate mimics which can halt the regulation and has profound implication in the treatment. NR3C4 active site is in between inter-helical region of helix H2, H4 and H9. The cavity contains 5 methionine residues along with the hydrophobic cavity, 4 polar residues and one charged arginine 752. A structural antagonist with similar binding complementation might alter the regulation by differential organization altering or halting regulation. The synthesized compound tends to have a similar binding affinity with relevance to docking score shown in Table 1. The binding pose of the compounds with respect to active site residual lining is shown in Supplementary Information, Figures S1-S7. Higher affinity compounds tend to have interactions with arginine 752. Both galeterone and enzalutamide have conserved hydrogen bond with arginine 752. Importance of arginine 752 roles towards ligand binding has a role in the conformation adaptation of ligand binding.

4. Conclusions

In summary, we have designed and synthesized cyclic urea tetrahydrofuran-based compounds as a new class of non-steroidal AR antagonists. Here, we replaced the thio-hydantoin skeleton in the reported drugs into cyclic urea tetrahydrofuran. We evaluated *in vitro* activity of the synthesized compound against the androgen-sensitive LNCaP cell line. Even though all the compounds have the same structural features, the compound with oxetane ring linked amide group (**AR04**) shows very high activity than that of its counterparts confirms the role of the oxetane ring. Importantly, we believe that the activity mainly depends on both the oxetane ring and tetrahydrofuran cyclic urea units, but not only because of the oxetane ring. It indirectly represents that introduction of the strained oxetane ring along with pharmacophore is a

very useful strategy while designing new drugs for the treatment of prostate cancer.

Supplementary Information (SI)

Detailed synthetic route up to compound 6 is shown in Scheme S1. The docking poses of AR01, AR02, AR03, AR05, AR06, AR07 and compound 5 are shown in Figures S1, S2, S3, S4, S5, S6 and S7, respectively. ^{1}H, ^{13}C NMR and HRM spectra of all the precursors and target compounds are shown in the supporting information.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Siegel R, Ma J, Zhao Z and Jemal A 2014 Cancer Statistics *CA-Cancer J. Clin.* **64** 9
2. Rathkopf D and Scher H I 2013 Androgen receptor antagonists in castration-resistant prostate cancer *Cancer J.* **19** 43
3. Siegel R L, Miller K D and Jemal A 2016 Cancer statistics *CA Cancer J. Clin.* **66** 7
4. Ferlay J, Shin H R, Bray F, Forman D, Mathers C and Parkin D M 2010 Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008 *Int. J. Cancer* **127** 2893
5. Perlmutter M A and Lepor H 2007 Androgen Deprivation Therapy in the Treatment of Advanced Prostate Cancer *Rev. Urol.* **9** S3
6. Haendler B and Cleve A 2012 Recent developments in antiandrogens and selective androgen receptor modulators *Mol. Cell Endocrinol.* **352** 79
7. Denmeade S R, Lin X S, Isaacs J T 1996 Role of programmed (apoptotic) cell death during the progression and therapy for prostate cancer *Prostate* **28** 251
8. Tan M H, Li J, Xu H E, Melcher K and Yong E L 2015 Androgen receptor: structure, role in prostate cancer and drug discovery *Acta Pharmacol. Sinica* **36** 3
9. Peets E A, Henson M F and Neri R 1974 On the Mechanism of the Anti-androgenic Action of Flutamide (α-α-α-Trifluoro-2-methyl-4'-nitro-m-propionotoluidide) in the Rat *Endocrinology* **94** 532
10. Furr B J, Valcaccia B, Curry B, Woodburn J R, Chesterson G and Tucker H 1987 A novel nonsteroidal, peripherally selective antiandrogen *J. Endocrinol.* **113** R7
11. Decensi A, Guarneri D, Paoletti M C, Lalanne J M, Merlo F and Boccardo F 1991 Phase II Study of the Pure Non-steroidal Antiandrogen Nilutamide in Prostatic Cancer *Eur. J. Cancer* **27** 1100
12. Tran C, Ouk S, Clegg N J, Chen Y, Watson P A, Arora V, Wongvipat J, Smith-Jones P M, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen C D, Higano C S, Beer T M, Hung D, Scher H I, Jung M E and Sawyers C L 2009 Development of a second-generation antiandrogen for treatment of advanced prostate cancer *Science* **324** 787
13. Rathkopf D E, Morris M J, Fox J J, Danila D C, Slovin S F, Hager J H, Rix P J, Maneval E C, Chen I, Geonen M, Fleisher M, Larson S M, Sawyers C L and Scher H I 2013 Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer *J. Clin. Oncol.* **31** 3525
14. Taplin M -E 2008 Androgen receptor: role and novel therapeutic prospects in prostate cancer *Expert Rev. Anticancer Ther.* **8** 1495
15. Ross R K, Pike M C, Coetzee G A. Reinchardt J K V, Yu M C, Feigelson H, Stanczyk F Z, Kolonel L N and Henderson B E 1998 Androgen Metabolism and Prostate Cancer: Establishing a Model of Genetic Susceptibility *Cancer Res.* **58** 4497
16. Scher H I and Kelly W K 1993 Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer *J. Clin. Oncol.* **11** 1566
17. Ferroni C, Pepe A, Kim Y S, Lee S, Guerrini A, Parenti M D, Tesei A, Zamagni A, Cortesi M, Zaffaroni N, De Cesare M, Beretta G L, Trepel J B, Malhotra S V and Varchi G 2017 1,4-Substituted Triazoles as Nonsteroidal Anti-Androgens for Prostate Cancer Treatment *J. Med. Chem.* **60** 3082
18. Ivachtchenko A V and Mitkin O D 2012 Cyclic N, N'-diarylthioureas and N, N'-diarylureas-androgen receptor antagonists, anticancer agent, method for preparation and use thereof *Appl. CA* 20112806051
19. Ivachtchenko A V, Ivanenkov Y A, Mitkin O D, Vorobiev A A, Kuznetsova I V, Shevkun N A, Koryakova A G, Karapetian R N, Trifelenkov A S, Kravchenko D V, Veselov M S and Chufarova N V 2015 Design, synthesis and biological evaluation of novel 5-oxo-2-thioxoimidazolidine derivatives as potent androgen receptor antagonists *Eur. J. Med. Chem.* **99** 51
20. Fizazi K, Albiges L, Loirot Y and Massard C 2015 ODM-201: a new-generation androgen receptor inhibitor in castration-resistant prostate cancer *Expert Rev. Anticancer Ther.* **15** 1007
21. O'Hagan D and Harper D B 1999 Fluorine-containing natural products *J. Fluor. Chem.* **100** 127
22. Smart B E 2001 Fluorine substituent effects (on bioactivity) *J. Fluor. Chem.* **109** 3
23. Wang J, Sanchez-Rosello M, Aceňa J L, Pozo C D, Sorochinsky A E, Fustero S, Soloshonok V A and Liu H 2014 Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011) *Chem. Rev.* **114** 2432
24. Ban F, Leblanc E, Li H, Munuganti R S, Frewin K, Rennie P S and Cherkasov A 2014 Discovery of 1H-Indole-2-carboxamides as Novel Inhibitors of the

Androgen Receptor Binding Function 3 (BF3) *J. Med. Chem.* **57** 6867
25. Andersen R J, Mawji N R, Wang J, Wang G, Haile S, Myung J R, Watt K, Tam T, Yang Y, Banuelos C A, Williams D E, McEwan I J, Wang Y and Sadar M D 2010 Regression of castrate-recurrent prostate cancer by a small-molecule inhibitor of the amino-terminus domain of the androgen receptor *Cancer Cell* **17** 535
26. Caboni L, Kinsella G K, Blanco F, Fayne D, Jagoe W N, Carr M, Williams D C, Meegan M J and Lloyd D G 2012 "True" Antiandrogens—Selective Non-Ligand-Binding Pocket Disruptors of Androgen Receptor–Coactivator Interactions: Novel Tools for Prostate Cancer *J. Med. Chem.* **55** 1635
27. Ponder J W and Richards F M 1987 An efficient newton-like method for molecular mechanics energy minimization of large molecules *J. Comput. Chem.* **8** 1016
28. Shelley J C, Cholleti A, Frye L L, Greenwood J R, Timlin M R and Uchimaya M 2007 Epik: a software program for pKa prediction and protonation state generation for drug-like molecules *J. Comput. Aided Mol. Des.* **21** 681
29. Matias P M, Donner P, Coelho R, Thomaz M, Peixoto C, Macedo S, Otto N, Joschko S, Scholz P, Wegg A, Bäsler S, Schäfer M, Egner U and Carrondo M A 2000 Structural Evidence for Ligand Specificity in the Binding Domain of the Human Androgen Receptor: Implications for pathogenic gene mutations *J. Biol. Chem.* **275** 26164
30. Sastry G M, Adzhigirey M, Day T, Annabhimoju R and Sherman W J 2013 Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments *J. Comput. Aided Mol. Des.* **27** 221
31. Sherman W, Beard H S and Farid R 2006 Use of an induced fit receptor structure in virtual screening *Chem. Biol. Drug Des.* **67** 83
32. Jadhav P K, Saeed A, Green J E, Krishnan V, Matthews D P and Stephenson G A 2013 *Selective Androgen Receptor Modulators* WO *2013/055577*Al.
33. Migliaccio A, Castoria G, Giovannelli P and Auricchio F 2010 Cross talk between epidermal growth factor (EGF) receptor and extra nuclear steroid receptors in cell lines *Mol. Cell. Endocrinol.* **327** 19
34. Bull J A, Croft R A, Davis O A, Doran R and Morgan K F 2016 Oxetanes: Recent advances in synthesis, reactivity, and medicinal chemistry *Chem. Rev.* **116** 12150