Supplementary Information

A combined study of quantum chemical calculation and molecular docking of some hydantoin and thiohydantoin related compounds

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Experimental Section

General methods

In these experiments, all the chemicals and reagents werepurchased from Sigma Aldrich and were used as pure. Following the literature procedure of Armarego and Chai, purificationand drying of reagents and solvents were carried out. On Merck aluminium sheets pre-coated with Kiesselgel, 60 GF254 of 0.25-mm thickness, thin layer chromatographic analysis was performed. All the melting points in an open glass capillary were calculated using the Stuart melting point apparatus (Model: SMP 10) and are uncorrected. Infrared spectra were acquired using KBr discs (4000–400 cm^{-1}) on a Perkin Elmer Spectrum-II FT-IR spectrometer.

Starting material

Preparation of phenyl urea

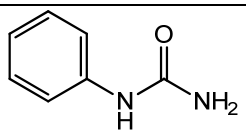
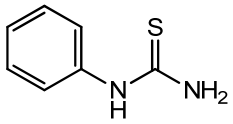
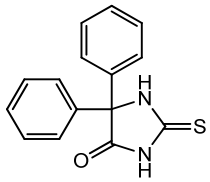
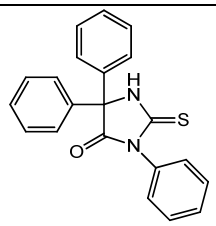
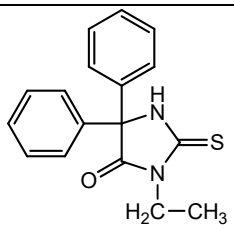
A molar ratio ca 1:2, 3.087 g (0.024 mol) of aniline hydrochloride and 5.700 g (0.095 mol) of urea were taken in 10 mL of water in a 1-litre round bottom flask, and the solution was filtered for a small number of suspensions. 0.20 mL of concentrated hydrochloric acid and 0.20 mL of glacial acetic acid were added to this clear solution. Before fitting the reflux condenser, a few fragments of broken porcelain were added to this solution, and the mixture was boiled for about 30 minutes. After 15 min, fine white crystals were found and slowly increased in amount as the refluxing was continued. After cooling the flask in ice, it was filtered with suction. The filtrate was discarded after collecting the residues. These residues were then added to 25 mL of distilled water and boiled for 10 min. A preheated Buchner funnel was used to filter this hot solution into a warm flask. The filtration was collected carefully and placed in an ice bath to cool. Fine white crystals of phenyl urea were found and dried well in the steam oven.

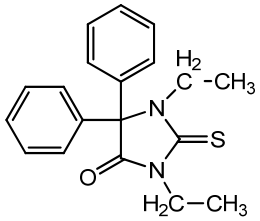
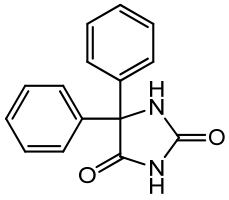
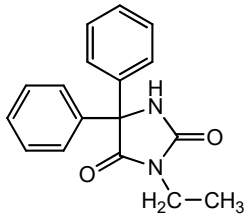
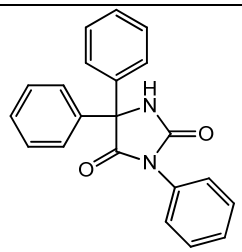
Preparation of phenyl thiourea

Concentrated HCl (5 mL) was added to aniline (5 mL) in a round bottom flask, and the solution was warmed at about 60-70°C for about 1 h. In the above solution, a saturated solution of ammonium thiocyanate in water (6 g in 12 mL) was applied slowly from a burette. The solution was boiled until it became turbid. The turbid solution was poured into cold water. The precipitated phenyl thiourea was filtered and crystallized from aqueous ethanol (80%) so as to obtain pure compound.

General procedure for the synthesis of hydantoin and thiohydantoin derivatives

In a two-necked 100-mL round-bottomed flask, Benzil was mixed with substituted urea or thiourea in the molar ratio of ca 1:2. 30% aqueous sodium hydroxide and absolute ethanol were added to these reactants. The reaction mixture was continuously stirred with the help of a magnetic bar. A condenser was attached after wrapping the ground glass joint with grease, and the mixture was refluxed at about 70-80°C for 3-4 h. Then the reaction mixture was allowed to cool at room temperature, and added 15 mL of water. The solution was filtrated due to the presence of some suspended solids in it. After that, the clear solution was carefully acidified with concentrated hydrochloric acid, and the product was collected by vacuum filtration and washed with water. The product was then recrystallized with ethanol and dried in the oven.

Table S1 — Spectral data of the compounds	
Phenyl urea	
	5.45 gm, 44%; m. p. 147-149°C; IR (ν, KBr, cm-1): 3381 (w, νN-H amide, CO-NH-Ph); 3340 and 3190 (m, νN-H, amide, NH_2-CO-); 3036 (w, νC-H aromatic); 1668 (s, sh, νC=O amide); 1598 (w), 1594 (sh), 1532 (m, sh) (νC=C, benzene); 1356 (s, sh,νC-N).
Phenyl thiourea	
	6.12 gm, 58%; m. p. 152-154°C; IR (ν, KBr, cm-1): 3424 (sh, νN-H amide, CS-NH-Ph); 3274 and 3178 (m, νN-H, amide, NH_2-CS-); 3002 (w, νC-H aromatic); 1610 (sh, νN-H amide),); 1589 (sh), 1531 (m), 1520 (m) (νC=C, benzene); 1318 (s, sh,νC-N); 1169 (sh, νC=S).
5,5-Diphenyl-2-thioxoimidazolidine-4-one (L1)	
	0.595 gm, 92%; m. p. 235-237°C (Lit.[1] 234-235; Lit.[2] 232-234); IR (ν, KBr, cm^{-1}):3265 (m, νN-H amide, CO-NH-CS);3162 (m, νN-H, amide, CPh_2-NH-CS); 3025 (s, νC-Haromatic); 1749 (s, sh, νC=O amide); 1584 (sh, νN-H amide), 1533 (s, sh), 1495 (sh), 1447 (s, sh)(νC=C, benzene); 1382 (s, sh νC-N); 1157 (m, νC=S).
3,5,5-Triphenyl-2-thioxoimidazolidine-4-one (L2)	
	0.928 gm, 52%; m. p. 263-264°C; IR (ν, KBr, cm^{-1}):3301 (s, sh, νN-H amide, CPh_2-NH-CS); 3062 (w, νC-Haromatic); 1740 (s, sh, νC=O amide); 1603 (w, νN-H amide), 1497 (sh), 1484 (sh), 1444 (sh) (νC=C, benzene); 1398 (s, sh νC-N); 1176 (sh, νC=S).
3-Ethyl-5,5-diphenyl-2-thioxoimidazolidine-4-one (L3)	
	0.889 gm, 59%; m. p. 185-187°C; IR (ν, KBr, cm^{-1}):3258 (m, νN-H amide, CPh_2-NH-CS); 3028 (w, νC-Haromatic); 1741 (s, sh, νC=O amide); 1642 (w, νN-H amide), 1493 (sh), 1449 (sh), 1402 (m) (νC=C, benzene); 1168 (w, νC=S).

1,3-Diethyl-5,5-diphenyl-2-thioxoimidazolidine-4-one (L4)	
	0.551 gm, 45%; m. p. 118-120°C; IR (ν, KBr, cm^{-1}):3106 (w, νC-Haromatic); 2832 (w, νC-H, aliphatic); 1737 (s, sh, νC=O amide); 1658 (w, νN-H amide), 1498 (m), 1451 (sh), 1404 (m) (νC=C, benzene); 1168 (w, νC=S).
5,5-Diphenylimidazolidine-2,4-dione (L5)	
	0.768 gm, 64%; m. p. 293-295°C (Lit.[2] 288-290; Lit.[3] 295-299)IR (ν, KBr, cm^{-1}):3273 (m, νN-H amide, CO-NH-CO);3209 (m, νN-H, amide, CPh_2-NH-CO); 3087 (w, νC-Haromatic); 1773(s, sh, νC=O amide, NH-CO-CPh_2); 1741 (s, sh, νC=Oamide, NH-CO-NH); 1635 (w, νN-H amide), 1495 (sh), 1449 (sh), 1403 (m)(νC=C, benzene); 1309 (w,νC-N).
3-Ethyl-5,5-Diphenylimidazolidine-2,4-dione (L6)	
	0.852 gm, 62%; m. p. 140-143°C (Lit.[4]137.9-139.2)IR (ν, KBr, cm^{-1}):3228 (m, νN-H, amide, CPh_2-NH-CO); 3055 (w, νC-Haromatic);2827 (w, νC-H, aliphatic); 1774(s, sh, νC=O amide); 1742 (s, sh, νC=Oamide); 1602 (w, νN-H amide), 1495 (sh), 1450 (sh), 1403 (m) (νC=C, benzene); 1311 (w,νC-N).
3,5,5-Triphenylimidazolidine-2,4-dione (L7)	
	0.079 gm, 50%; m. p. 199-201°C (Lit.[4] 204.2-204.9) IR (ν, KBr, cm^{-1}):3348 (b, νN-H, amide, CPh_2-NH-CO); 3060 (w, νC-Haromatic);1776 (sh, νC=O amide, NPh-CO-CPh_2); 1718 (s, sh, νC=Oamide, NH-CO-NPh); 1667 (w, νN-H amide), 1497 (sh), 1447 (sh), 1411 (m) (νC=C, benzene); 1314 (m,νC-N).

References

1. Faghihi K, Zamani K and Mallakpour S, *Iranian Polymer J,* 11 **(**2002) 340.
2. Arani N M and Safari J, *Ultrasonics Sonochem,* 18 (2011) 640.
3. Safari J, Naeimi H, Ghanbari M M, and Fini O S, *Russian J Org Chem,* 45 (2009) 477.
4. Muccioli G G, Fazio N, Scriba G K E, Poppitz W, Cannata F, Poupaert J H, Wouters J and Lamber D M, *J Med Chem,* 49 (2006) 417.

Table S1 — Binding affinity of 9 commercially available PCa drugs with Androgen receptor

Commercially available drugs for PCa	First pocket	Second pocket	Third pocket
Abiraterone	-8.7	-6.2	-6.3
Bicalutamide	-9.7	-6.9	-6.1
Enzalutamide	-8.1	-6.5	-5.7
Flutamide	-7.6	-5.2	-6.0
Carbazitaxel	-7.1	-2.9	-4.3
Darolutamide	-9.6	-6.7	-6.3
Degarelix	-4.2	6.0	9.5
Leuprorelin	-6.0	-4.9	-3.1
Nilutamide	-8.4	-5.5	-6.1

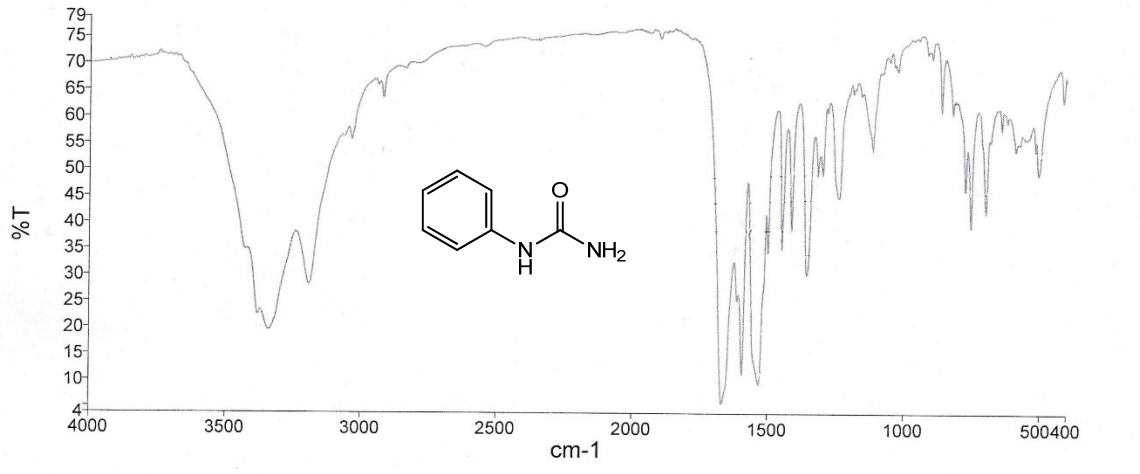


Fig. S1 — IR spectrum of phenyl urea

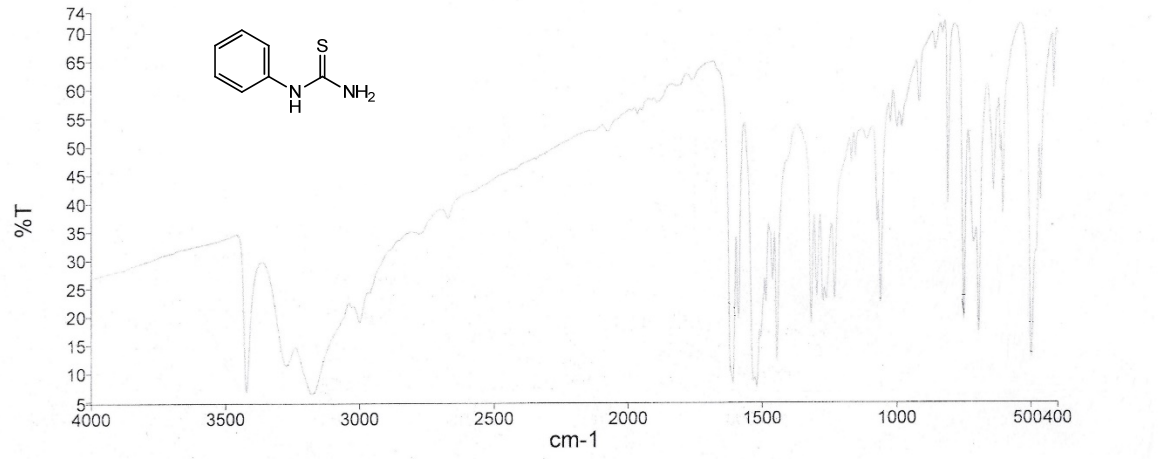


Fig. S2 — IR spectrum of phenyl thiourea

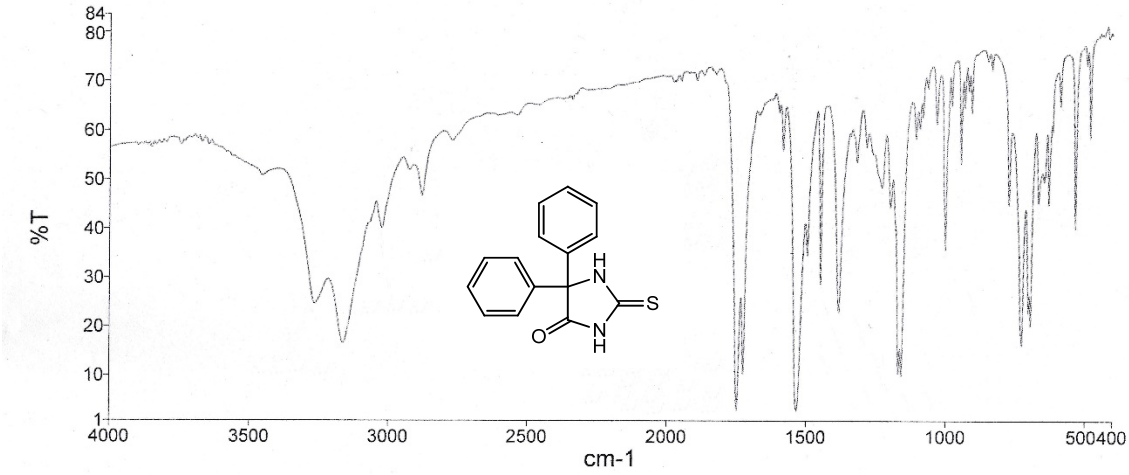


Fig. S3 — IR spectrum of **L1**

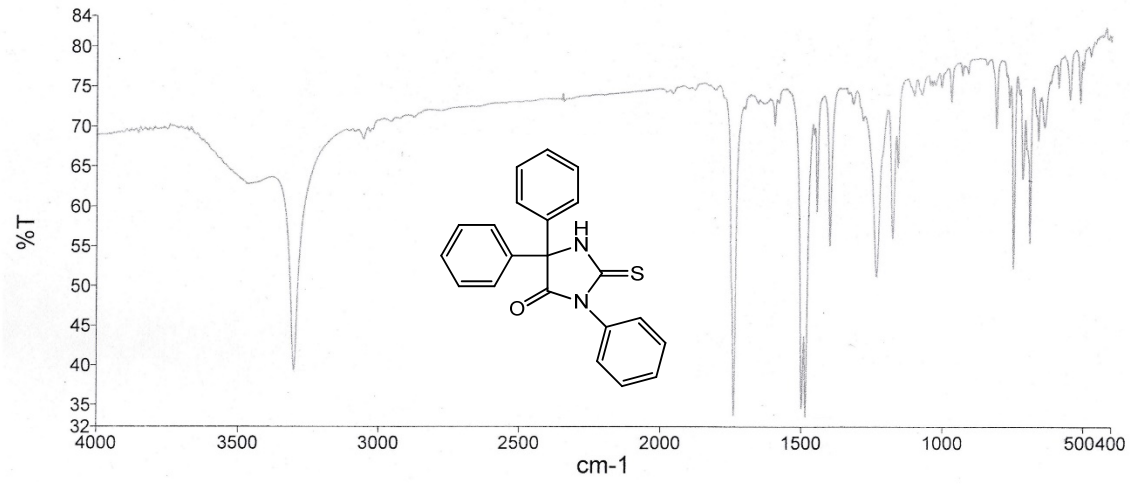


Fig. S4 — IR spectrum of **L2**

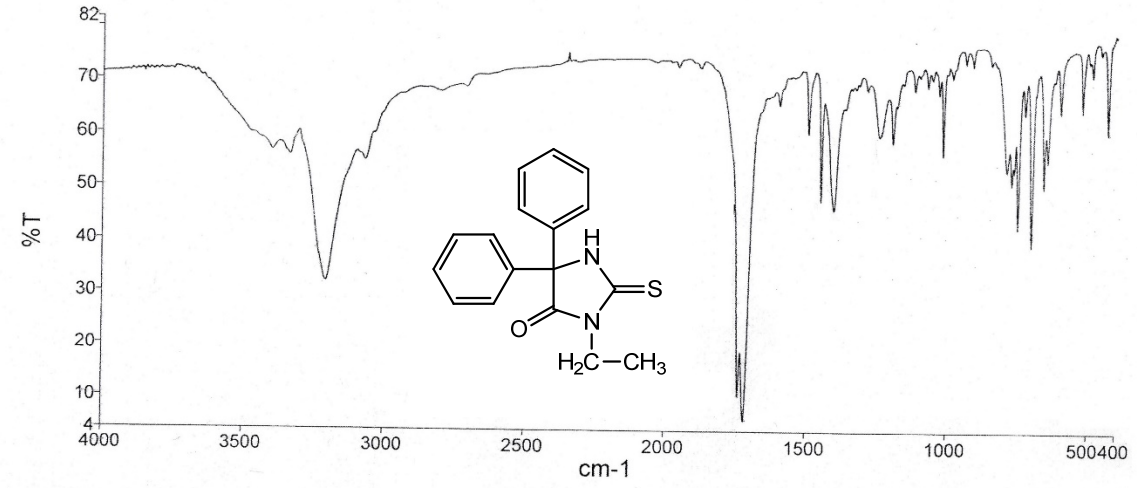


Fig. S5 ─ IR spectrum of **L3**

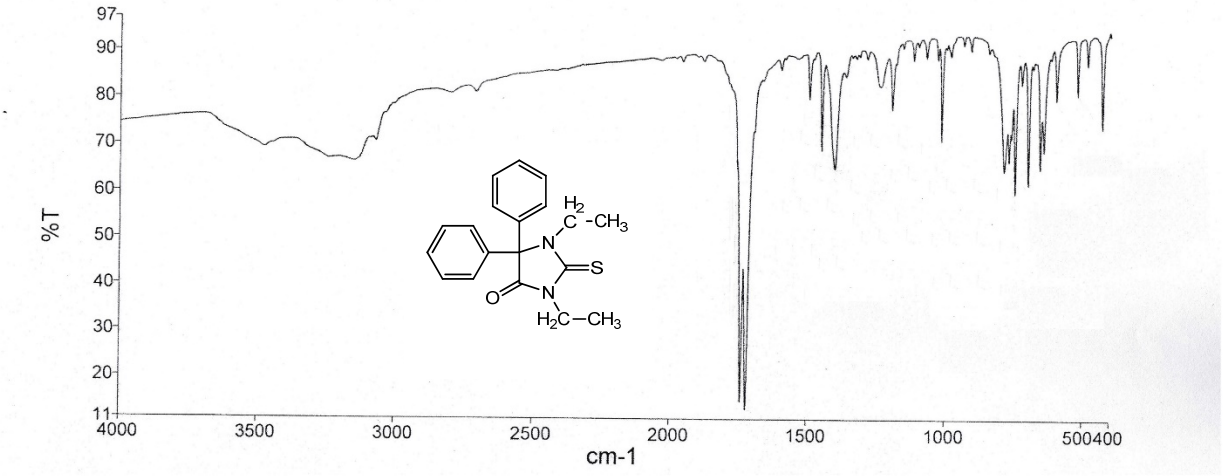


Fig. S6 ─ IR spectrum of **L4**

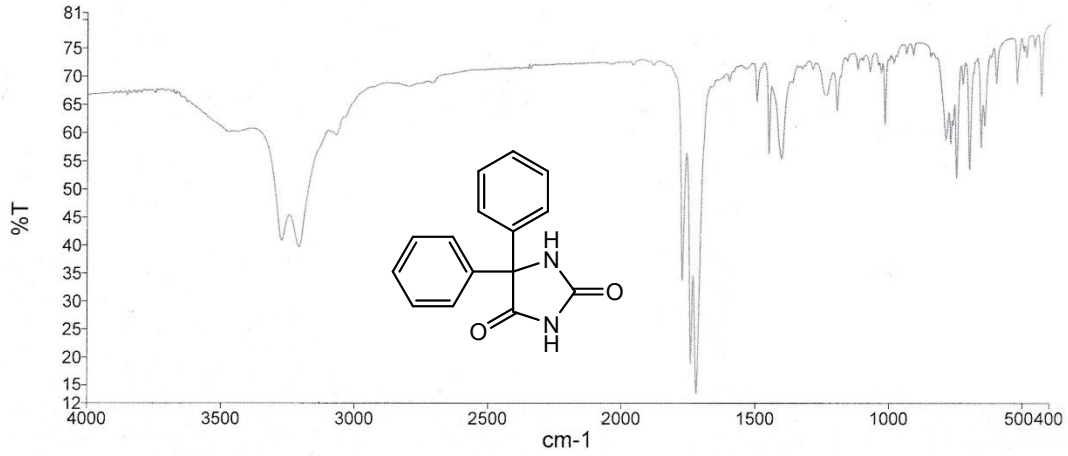


Fig. S7 ─ IR spectrum of **L5**

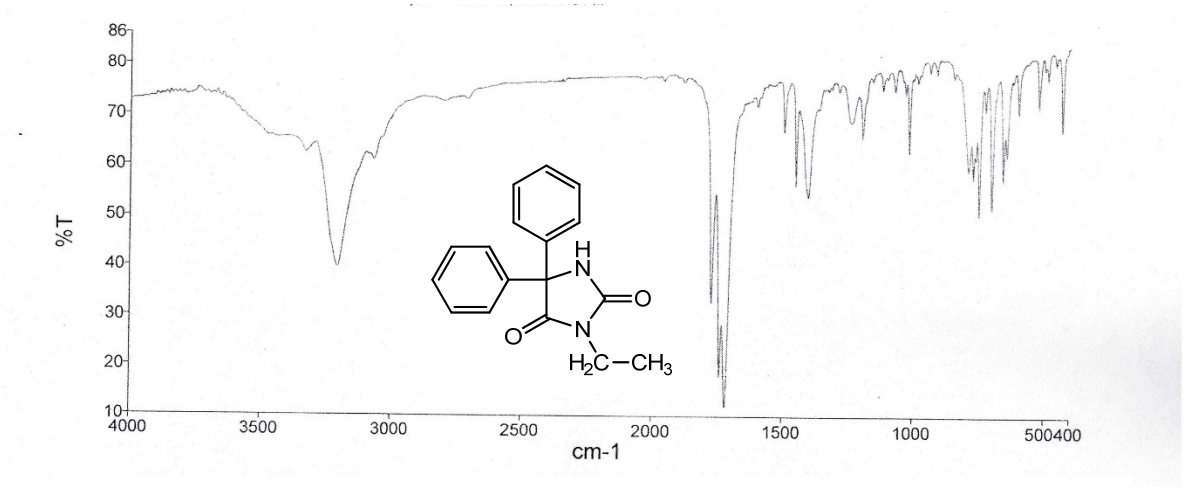


Fig. S8 ─ IR spectrum of **L6**

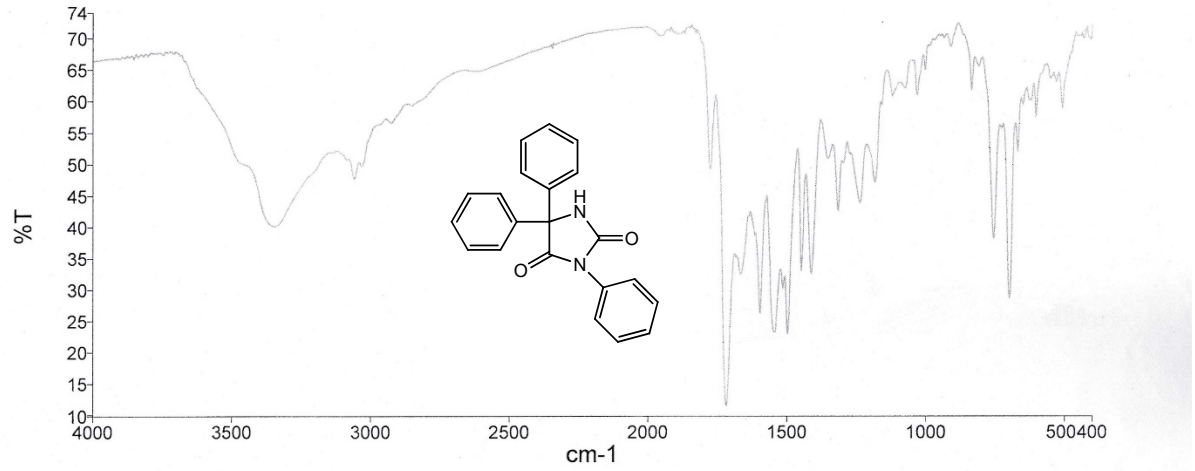
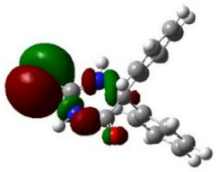
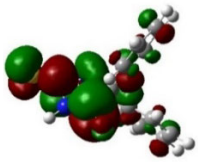
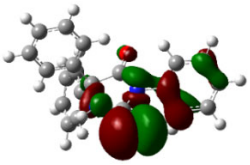
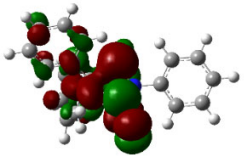
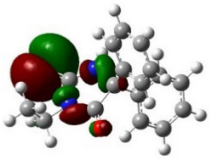
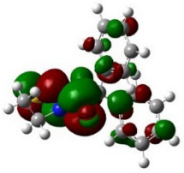
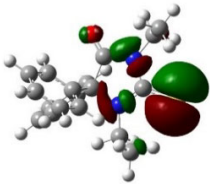
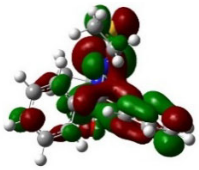
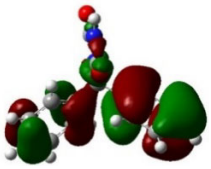
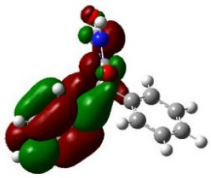
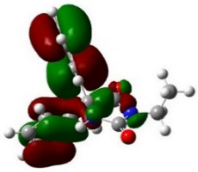
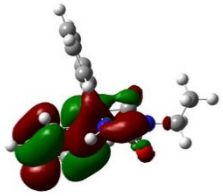


Fig. S9 ─ IR spectrum of **L7**

	HOMO	LUMO
L1		
L2		
L3		
L4		
L5		
L6		

L7

Fig. S10 — Frontier molecular orbitals of the synthesized compounds

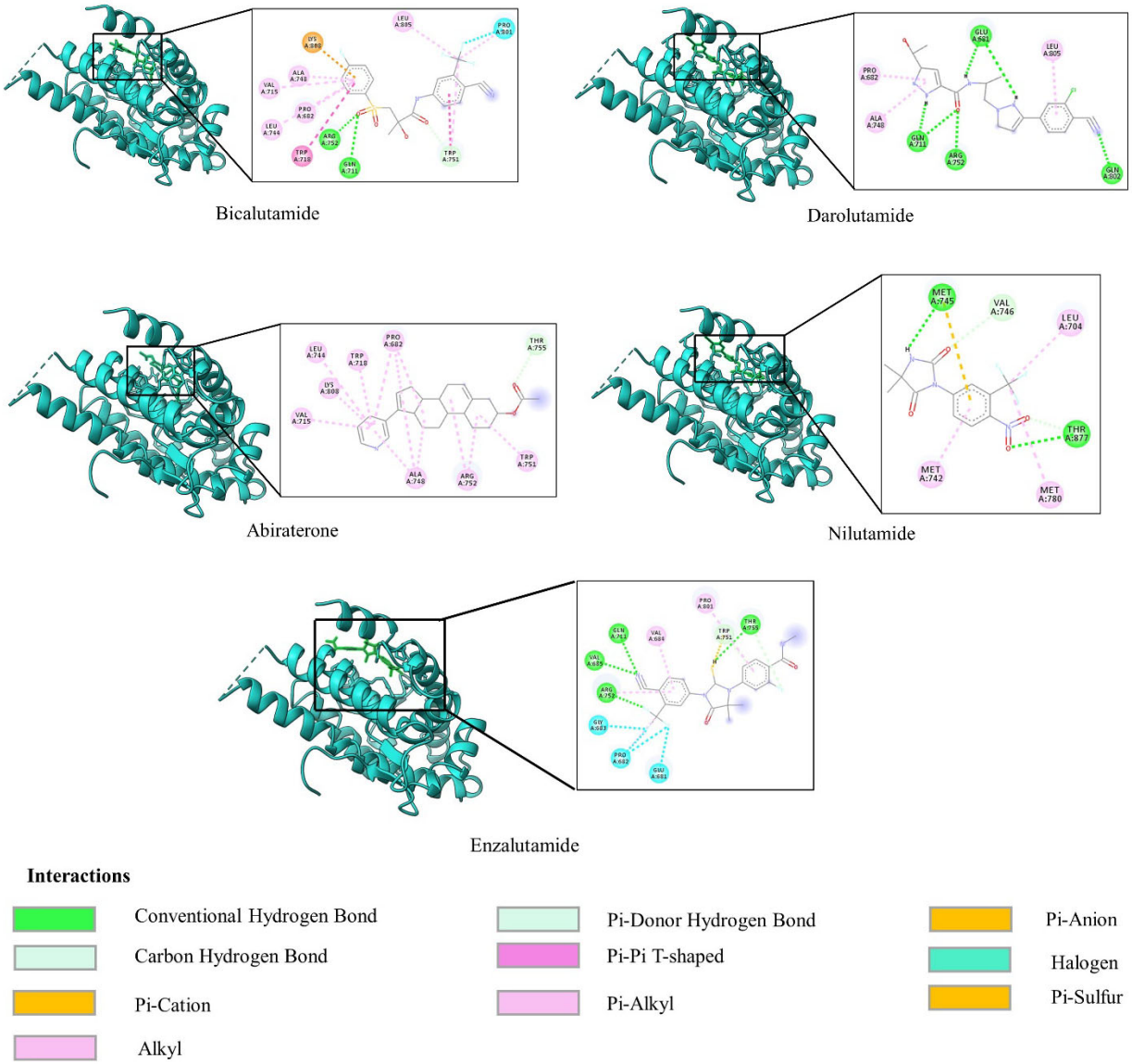


Fig. S11 — Nonbonding interactions of some commercially available PCa drugs with Androgen receptor

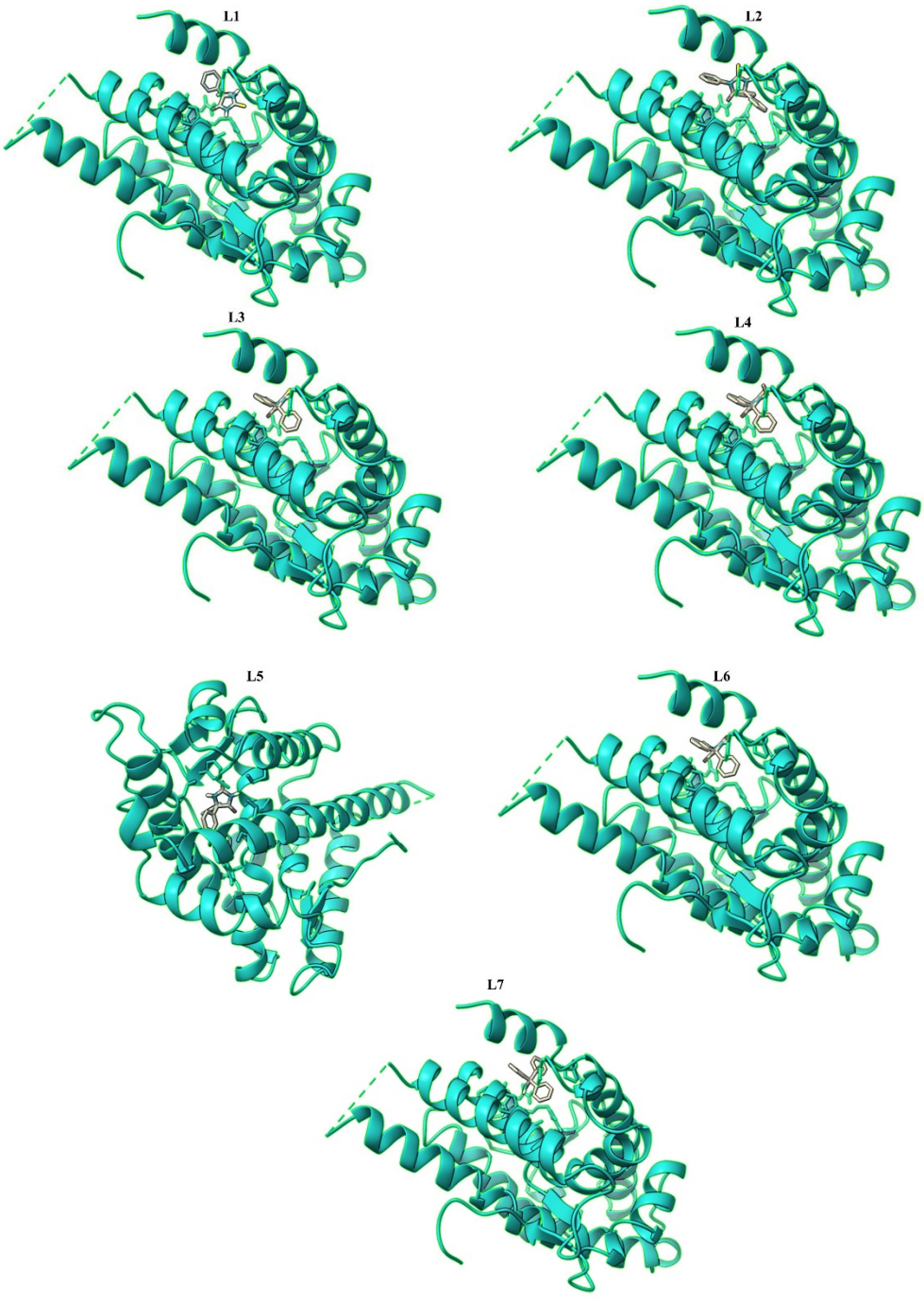


Fig. S12 — Docking pose of compounds **L1-L7** with Androgen receptor