Original Article

Theoretical evaluation of interaction of some dibenzo derivatives on both androgen receptor and 5α-reductase enzyme

Abstract

There are several drugs to treat cancer; nevertheless, some can produce adverse effects, such as hypertension, hepatic injury, and erectile dysfunction. In the search for new therapeutic alternatives, some Dibenzo derivatives have been used for treating cancer; however, other data suggest that Dibenzo derivatives can increase this clinical pathology. All these data are confusing; perhaps this phenomenon is due to the different chemical structures of each Dibenzo-derivative. Analyzing this data, this research aimed to evaluate the possible interaction of some Dibenzo derivatives (compounds 1 to 15) on some biomolecules involved in prostate cancer, such as androgen receptor and 5*α*-reductase enzyme using flutamide, dutasteride, and finasteride drugs as theoretical tools in a Docking model. The results showed that some Dibenzo derivatives (9, 11, and 15) could interact with the androgen receptor surface. Besides, the Dibenzo derivatives 2, 5, and 13 may interact with the 5*α*-reductase enzyme surface. In conclusion, these data suggest that some Dibenzo derivatives could be good candidates for the treatment of prostate cancer.

Keywords: *Cancer, Dibenzo, Androgen, 5α-reductase*

Lauro Figueroa-Valverde[1], Marcela Rosas-Nexticapa[2], Magdalena Alvarez-Ramirez[2], Maria Lopez-Ramos[1], Virginia Mateu-Armand[2*]

[1]Pharmacochemistry Research Laboratory, Faculty of Biological-Chemical Sciences, University Autonomous of Campeche; Humberto Lanz Cárdenas s/n, Ex Hacienda Kalá, C.P. 24085, Campeche, Mexico. [2]Nutrition Laboratory, Faculty of Nutrition, University of Veracruz, Medicos y s/n Odontologos 910210, Unidad del Bosque, Xalapa, Mexico.

Introduction

Prostate cancer is one of the leading causes of death among men worldwide; this clinical pathology has been increasing in recent years and has been directly related to aging in men.[1] There are several drugs for treating prostate cancer, such as androgen receptor inhibitors (flutamide,[2] nilutamide,[3] bicalutamide,[4] enzalutamide,[5] and apalutamide[6]) and 5-alpha-reductase inhibitors (finasteride[7] and dutasteride[8]). However, some drugs can produce some secondary effects, such as hot flashes,[9] hypertension,[10] hepatic injury,[11] and erectile dysfunction.[12] In the search for new alternative therapeutics for treating prostate cancer, some compounds have been prepared; in this way, ERGi-USU-6 was developed from ERGi-USU as an ERG protein inhibitor to treat prostate cancer.[13] Another study showed the synthesis of Y08060 drug as bromodomain-containing protein 4 (BRD4) inhibitors for the treatment of prostate cancer.[14] Besides, a series of 1,4-substituted triazoles were prepared with antiandrogenic activity as possible prostate cancer inhibitors.[15] Another study showed the preparation of a phosphatidylinositol-3-kinase inhibitor from a quercetin derivative (LY294002) and peptide Mu-LEHSSKLQL that induce apoptosis in C4-2 cells translated as prostate cancer inhibition.[16] Another report showed the biological activity of three trioxane dimers on human prostate cancer (LNCaP) cell lines through G0/G1 cell cycle arrest.[17] Recently, a study showed the preparation of a carboxamide derivative as AKR1C3 inhibitors (type 5 17β-hydroxysteroid dehydrogenase/ prostaglandin F synthase) to treat castration-resistant prostate cancer.[18] In addition, quinolone thiosemicarbazone (FPA-137) was reported as a proteasome inhibitor in human prostate cancer cells.[19]

On the other hand, some studies indicate that several compounds may decrease prostate cancer through androgen receptor inhibition; for example, a study showed that lupeol acts as an androgen receptor antagonist, which could be used as a prostate cancer agent.[20] In addition, a report showed that some curcumin analogs act as androgen receptor antagonists, translated as prostate cancer agents.[21] It is noteworthy that recently has been developed the JNJ-63576253 drug for castration-resistant prostate cancer through

Address for correspondence:
Virginia Mateu-Armand, Nutrition Laboratory, Faculty of Nutrition, University of Veracruz, Medicos y s/n Odontologos 910210, Unidad del Bosque, Xalapa, Mexico.
E-mail: lfiguero@uacam.mx

Access this article online

Website: www.ccij-online.org

DOI: 10.51847/flVMfELA7I

Quick Response Code:

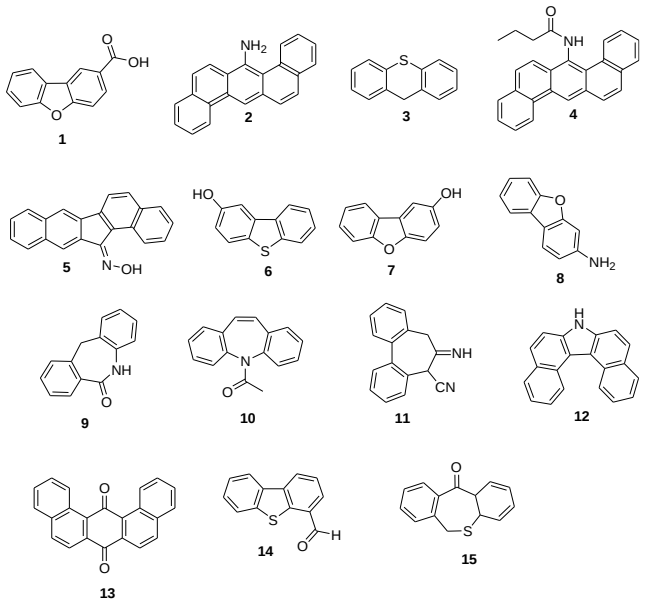
How to cite this article: Figueroa-Valverde L, Rosas-Nexticapa M, Alvarez-Ramirez M, Lopez-Ramos M, Mateu-Armand V. Theoretical evaluation of interaction of some dibenzo derivatives on both androgen receptor and 5α-reductase enzyme. Clin Cancer Investig J. 2022;11(5):11-6. https://doi.org/10.51847/flVMfELA7I

receptor androgen inhibition.[22] Besides, a report showed that urolithins, hydroxylated derivatives of 6 H-dibenzo[b;d]pyran-6-one, reduce LNCaP cell proliferation compared with some antiandrogens drugs.[23] All this data suggests that several drugs produce effects on prostate cancer; however, the effect produced by these compounds involves different mechanisms of action; this phenomenon could be due to the different chemical structures of each drug.

The objective of this investigation was to evaluate the possible interaction of some Dibenzo derivatives on both androgen receptor and 5α-reductase enzyme using flutamide, dutasteride, and finasteride drugs as theoretical tools in a Docking model through the analysis of this data.

Materials and Methods

Fifteen Dibenzo derivatives **(Figure 1)** were used to evaluate the possible interaction with both the androgen receptor and 5α-reductase enzyme as follows:



1 = Dibenzo[b,d]furan-2-carboxylic acid[24]
2 = 10H-Dibenzo[a,h]anthracen-7-ylamine[25]
3 = 10H-Dibenzo[b,e]Thiopyran[26]
4 = 1n-Dibenzo[a,h]anthracen-7-yl-Butamide[27]
5 = 1n-Dibenzo[a,h]fluoren-13-one oxime[28]
6 = 1n-Dibenzo[b,d]Thiophen-2-ol[29]
7 = 1n-Dibenzo[b,d]furan-2-ol[30]
8 = 1n-Dibenzo[b,d]furan-3-amine[31]
9 = 5,11-Dihydro-6H-dibenzo[b,e]azepin-6-one[32]
10 = 5-acetyl-5H-dibenzo[b,f]azepine[33]
11 = 6-imino-6,7-dihydo-5H-dibenzo[a,c]cycloheptene-5-carbonitrile[34]
12 = 7H-Dibenzo[c,g]carbazole[35]
13 = Dibenzo[a,j]Anthracene-7,14-dione[36]
14 = Dibenzo[b,d]thiophene-4-carbaldehyde[37]
15 = Dibenzo[b,e]thiepin-11(6H)-one[38]

Figure 1. Chemical structure of Dibenzo derivatives.

Ligand-protein interaction

The interaction of Dibenzo derivatives with both androgen receptor and 5α-reductase enzyme surface was evaluated using either 4fdh[39] or 7bw1[40] proteins as theoretical models. In addition, to evaluate the types of binding energy involved in the interaction of Dibenzo derivatives with either 4fdh or 7bw1 proteins surface, the DockingServer software was used.[41]

Pharmacokinetics parameter

Pharmacokinetic parameters were determined using the SwissADME software.[42]

Toxicity evaluation

Possible toxicity produced by either Dibenzo[b,e]thiophen-11(6H)-one was determined using GUSAR software.[43]

Results and Discussion

It is important to mention that several reports in the literature indicate that Dibenzo derivatives can exert anti-cancerogenic activity;[44] however, contrary to this data, some studies indicate that different Dibenzo derivatives may produce mutagenic effects using some biological models.[45] All these data are confusing; perhaps this phenomenon is due to i) differences in the chemical structure of each Dibenzo derivative, ii) different sites of its action, or iii) different concentrations and routes of administration. Analyzing all these data and other studies which indicates that some dibenzo-*p*-dioxins may increase the incidence of prostate cancer by interacting with the androgen receptor.[20-22] For this reason, in this study, the interaction of fifteen Dibenzo derivatives on androgen receptors was evaluated using 4fdh protein[39] and flutamide (Androgen receptor inhibitor)[2] as a theoretical tool in a Docking model.[41]

Table 1. Aminoacid residues involved in the coupling of Dibenzo derivatives (compounds 1-5) with 4fdh protein surface.

Flutamide	Leu_{701}; Leu_{704}; Asn_{705}; $Gln_{711;}$ $Trp_{741;}$ $Met_{745;}$ Val_{746}; Met_{749}; Phe_{764};Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
1	Leu_{704}; Asn_{705}; Gln_{711}; Met_{745}; Met_{749}; Arg_{752}; Phe_{764}; Met_{895}
2	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Leu_{873}; Phe_{876}; Thr_{877}
3	Asn_{705}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Met_{749}; Arg_{752}: Phe_{764}; Met_{895}
4	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Trp_{741}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; $Met_{787;}$ Leu_{873}; Phe_{876}; Thr_{877}; Leu_{880}; Met_{895}
5	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Met_{742}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Leu_{873}; Phe_{876}; Thr_{877}; Leu_{880}
6	Asn_{705}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{787}; Met_{895}
7	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Phe_{764}; Met_{780}; Leu_{873}; Phe_{876}; Thr_{877}
8	Leu_{704}; $Leu_{707;}$ Gln_{711}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Leu_{873}

9	Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Thr_{877}; Met_{895}
10	Leu_{704}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}
11	Leu_{704}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}
12	Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; $Thr_{877;}$ Met_{895}
13	Asn_{705}; Leu_{707}; Gln_{711}; Met_{742}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
14	Asn_{705}; Leu_{707}; Gln_{711}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{787}; Met_{895}
15	Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}

The results **(Table 1 and Figure 2)** showed that flutamide interacts with different amino acid residues involved in the 4fdh protein surface compared with Dibenzo derivatives (1 to 15); this data suggest that this interaction is due to different functional groups involved in the chemical structure of each Dibenzo derivatives **(Tables 1-3 and Figure 2)**.

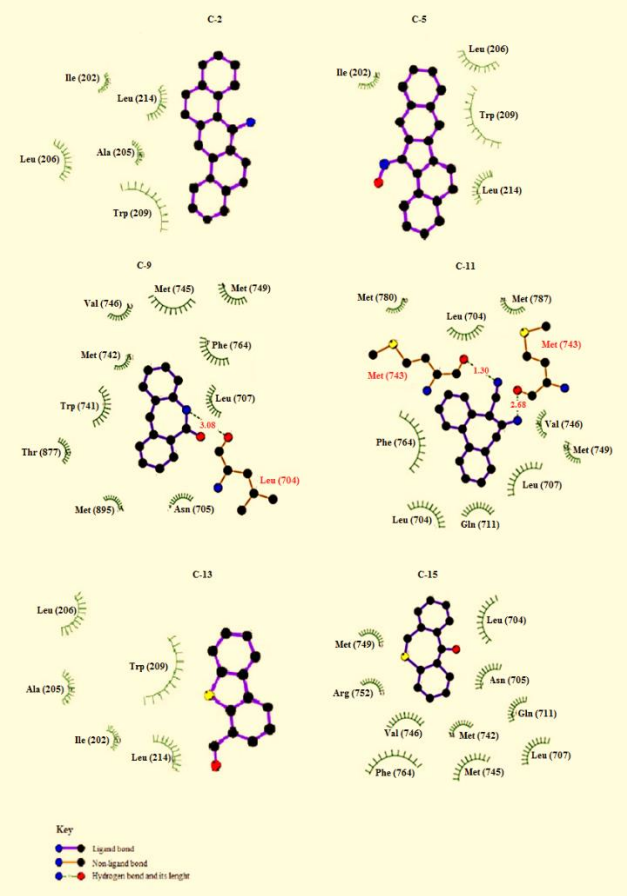


Figure 2. The scheme showed the binding site of amino acid residues involved in the interaction of Dibenzo derivatives (9, 11, and 15) with the 4fdh protein surface and compounds 11, 13 and 15 which could interact with 7bw1 protein surface. Visualized with GL mol viewer, docking server

However, it is important to mention that several reports suggest that the energy levels involved in the interaction protein-ligand must be considered to determine the stability of the protein-ligand complex.[41] In this way, some studies indicate that *i*) free energy of binding, which determines the energy value that requires a molecule to interact with a protein in a water environment; *ii*) Electrostatic energy is the product of electrical charge and electrostatic potential, which are involved in the ligand-protein system; *iii*) total intermolecular energy; and *iv*) van der Waals (vdW) + hydrogen bond (H-bond) + desolvation energy (which have an influence on the movement of water molecules into or out of the ligand-protein system).[41] This research determined different thermodynamic factors involved in the interaction of Dibenzo-derivatives with 4fdh protein surface using an androgen receptor inhibitor (flutamide) as control. The results **(Table 2)** showed that the inhibition constant for compounds 9, 11, and 14 was lower compared to flutamide, compounds 1-8, 10, and 12-14, which may result in greater interaction with the 4fdh protein surface. This phenomenon could produce changes in the biological activity of androgen receptors, translating into a possible decrease in prostate cancer levels.

Table 2. Thermodynamic parameters involved in the interaction of Dibenzo derivatives (1-15) and flutamide with the 4fdh-protein surface

Compound	A	B	C	D	E	F
Flutamide	-7.35	4.09	-8.51	-0.01	-8.51	443.01
1	-6.89	8.95	-6.87	-0.32	-7.19	410.76
2	-10.81	11.86	-11.09	-0.02	-11.11	530.21
3	-7.11	6.14	-7.11	+0.00	-7.11	400.69
4	-7.07	6.55	7.98	+0.01	-7.97	589.60
5	-9.77	68.60	-9.73	-0.34	-10.07	528.70
6	-6.55	15.79	-6.78	-0.07	-6.85	390.97
7	-5.83	53.23	-6.07	-0.06	-6.13	382.26
8	-6.83	9.77	-7.06	-0.07	-7.13	391.66
9	-7.65	2.47	-7.63	-0.02	-7.65	415.67
10	-8.27	859.79	-8.28	+0.01	-8.27	450.91
11	-8.03	1.29	-8.19	-0.14	-8.33	454.20
12	-10.10	39.73	-10.10	+0.00	-10.10	490.81
13	-8.48	612.25	-8.50	+0.02	-8.48	525.38
14	-7.14	5.89	-7.45	+0.01	-7.43	406.69
15	-8.03	1.31	-8.03	+0.00	-8.03	423.60

A = Est: Free Energy of Binding (kcal/mol)
B = Est. Inhibition Constant, Ki (mM)
C = vdW + Hbond + desolv Energy (kcal/mol)
D = Electrostatic Energy (kcal/mol)
E = Total Intermolec. Energy (kcal/mol)
F = Interact. Surface

However, it is important to mention that other biomolecules, such as the 5(-reductase enzyme, are involved in the development of prostate cancer. In this way, a study showed that some Dibenzo derivatives could modulate the 5α-reductase enzyme levels in a human prostatic carcinoma cell line.[46] In this research, the theoretical activity of Dibenzo derivatives was determined using 7bw1 protein,[40] dutasteride, and finasteride drugs (5α-reductase enzyme inhibitors)[7] as a theoretical tool on DockingSever software. The results show different amino acid residues involved in the

interaction between Dibenzo derivatives (compound 1 to 15) with 7bw1 protein surface compared with dutasteride and finasteride **(Table 3 and Figure 2)**.

Table 3. Aminoacid residues involved in the coupling of Dibenzo derivatives (compounds 1-15) with 7bw1 protein surface.

Dutasteride	Arg_{145}; Leu_{14}; Leu_{152}; Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
Finasteride	Tyr_{129}; Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
1	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
2	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
3	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
4	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
5	Ile_{202}; Leu_{206}; Trp_{209}; Leu_{214}
6	Ala_{205}; Trp_{209}; Leu_{214}
7	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
8	Ile_{202}; Ala_{205}; $Leu_{206;}$ Trp_{209}; Leu_{214}
9	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}
10	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
11	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
12	Ala_{205}; Leu_{206}; Trp_{209}; Ser_{210}; Leu_{214}
13	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
14	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
15	Tyr_{129}; Ala_{134}; Tyr_{136}; Pro_{137}; Trp_{140}; Trp_{209}

Finally, the thermodynamic analysis of Dibenzo derivatives **(Table 4)** showed that the inhibition constant of compound 13 was lower compared with finasteride. In addition, compounds 2, 5 and 13 showed differences in constant inhibition levels compared with dutasteride. All these data suggest that 2, 5, and 13 could have higher affinity by 7bw1 protein surface, which may translate as 5α-reductase enzyme inhibition resulting in decreasing prostate cancer levels.

Table 4. Thermodynamic parameters involved in the interaction of Dibenzo derivatives (1-15), finasteride, and dutasteride with 7bw1-protein surface.

Compound	A	B	C	D	E	F
Dutasteride	-9.81	64.59	-10.48	-0.03	-10.51	702.17
Finasteride	-7.48	3.30	-8.04	0.02	-8.02	639.91
1	-5.68	68.99	-5.95	-0.03	-5.98	450.84
2	-7.30	4.44	-7.60	-0.00	-7.60	533.59
3	-5.95	43.16	-5.97	0.01	-5.95	444.85
4	-6.92	8.40	-7.40	-0.00	-7.40	570.32
5	-7.39	3.84	-7.83	0.15	-7.69	539.21
6	-5.70	66.20	-6.00	0.01	-6.00	427.17
7	-4.99	218.52	-5.33	0.03	-5.29	424.95
8	-5.33	88.66	-5.83	0.01	-5.83	442.09
9	-5.98	41.23	-5.97	-0.01	-5.98	460.19
10	-6.11	33.33	-6.10	-0.00	-6.11	463.63
11	-5.05	200.14	-5.48	0.14	-5.35	463.14
12	-6.96	7.93	-6.94	-0.02	-6.96	470.67
13	-7.52	3.08	-7.52	0.01	-7.52	503.48
14	-5.97	42.33	-6.26	-0.01	-6.26	451.99
15	-6.44	19.10	-6.39	-0.05	-6.44	454.90

A = Est: Free Energy of Binding (kcal/mol)
B = Est. Inhibition Constant, Ki (mM)
C = vdW + Hbond + desolv Energy (kcal/mol)
D = Electrostatic Energy (kcal/mol)
E = Total Intermolec. Energy (kcal/mol)
F = Interact. Surface

Pharmacokinetic evaluation

For several years, different protocols have been used to predict some pharmacokinetic parameters, such as PKQuest,[47] PharmPK,[48] and SwissADME.[49] In this study, some pharmacokinetic factors involved in Dibenzo derivatives were analyzed usingSwissADME software **(Table 5)**.

Table 5. Pharmacokinetic parameters involved in the chemical structure of Dibenzo derivatives

Parameter	2	5	9	11	13	15
GI absorption	High	High	High	High	High	High
BBB permeant	No	Yes	Yes	Yes	Yes	Yes
P-GP substrate	No	Yes	Yes	Yes	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	No	No	No	Yes	Yes
CYP2C9 inhibitor	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No

The results displayed differences in gastrointestinal absorption and metabolism (involving different types of cytochrome P450 systems). This phenomenon could depend on the chemical structure of each Dibenzo derivative.

Toxicity analysis

Some data in the literature indicate that some Dibenzo derivatives can produce toxicity in different biological models.[50] Analyzing this data, the possible toxicity produced by some Dinenzo derivatives (2, 5, 9, 11, 13, and 15) was evaluated using the GUSAR software.[49] The results showed that compound 5 require higher dose to produce toxicity (LD50) via oral (2182 mg/kg) and intravenous (110.10 mg/kg) compared with compounds 2 (oral, 66.17 mg/kg; intravenous 1086 mg/kg), 9 (oral, 1621 mg/kg; intravenous 61.34 mg/kg), 11(oral, 1496 mg/kg; intravenous 88.69 mg/kg), 13 (oral, 1496 mg/kg; intravenous 89.69 mg/kg) and 15 (oral, 305.20 mg/kg; intravenous 73.18 mg/kg). This data suggest that toxicity could be dose-dependent and the routes of administration for each Dibenzo derivative.

Conclusion

Theoretical analyzes on the interaction of Dibenzo derivatives with the 4fdh protein surface suggest that Dibenzo derivatives 9, 11, and 15 might have a higher affinity for 4fdh translated as greater androgen receptor inhibition, possibly resulting in the decrease of prostate cancer levels. Besides, other studies

suggest that Dibenzo derivatives such as 2, 5, and 13 could act as 5α-reductase inhibitors in prostate cancer.

Acknowledgments
None.

Conflict of interest
None.

Financial support
None.

Ethics statement
None.

References

1. Pienta K, Gorin M, Rowe S, Carroll P, Pouliot F, Probst S. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate-specific membrane antigen PET/CT with 18F-DCFPyL in prostate cancer patients (OSPREY). J Urol. 2021;206(1):52-61.
2. Lowrance W, Breau R, Chou R, Chapin B, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline part I. J Urol. 2021;05(1):14-21.
3. Akhter S, Zain N, Shalauddin M, Singh V, Misnon I, Sharma R, et al. Tri-metallic Co-Ni-Cu based metal organic framework nanostructures for the detection of an anticancer drug nilutamide. Sens Act A Phys. 2021;325:112711.
4. Kim G, Song C, Yang Y, Lee N, Yoo H, Son S, et al. Chemical Degradation of Androgen Receptor (AR) Using Bicalutamide Analog–Thalidomide PROTACs. Molecules. 2021;26(9):2525.
5. Leach D, Mohr A, Giotis E, Cil E, Isac A, Yates L, et al. The antiandrogen enzalutamide downregulates TMPRSS2 and reduces cellular entry of SARS-CoV-2 in human lung cells. Nat Comm. 2021;12(1):1-12.
6. Smith M, Saad F, Chowdhury S, Oudard S, Hadaschik B, Graff J, et al. Apalutamide and overall survival in prostate cancer. Eur Urol. 2021;79(1):150-8.
7. Goodman P, Tangen C, Darke A, Lucia M, Ford L, Minasian L, et al. Long-term effects of finasteride on prostate cancer mortality. New Eng J Med. 2019;380(4):393-4.
8. Hou Z, Huang S, Li Z. Androgens in prostate cancer: A tale that never ends. Cancer Lett. 2021;516:1-12.
9. Delaere K, Thillo E. Flutamide monotherapy as primary treatment in advanced prostatic cancer. Sem Oncol. 1991;18 (suppl 1):13-8.
10. Gomez J, Dupont A, Cusan L, Tremblay M, Tremblay M, Labrie F. Simultaneous liver and lung toxicity related to the nonsteroidal antiandrogen nilutamide (Anandron): a case report. Am J Med. 1992;92(5):563-6.
11. Boelsterli U, Ho H, Zhou S, Yeow K. Bioactivation and hepatotoxicity of nitroaromatic drugs. Curr Drug Metab. 2006;7(7):715-27.
12. Silva M, Souza J. Vulnerability of patients with prostatic hyperplasia treated with dutasteride and finasteride. Rev Bioética. 2021;29:394-400.
13. Eldhose B, Pandrala M, Xavier C, Mohamed A, Srivastava S, Sunkara A, et al. New Selective Inhibitors of ERG Positive Prostate Cancer: ERGi-USU-6 Salt Derivatives. Med Chem Lett. 2021;12(11):1703-9.
14. Xiang Q, Zhang Y, Li J, Xue X, Wang C, Song M, et al. Y08060: a selective BET inhibitor for treatment of prostate cancer. Med Chem Lett. 2018;9(3):262-7.
15. Ferroni C, Pepe A, Kim Y, Lee S, Guerrini A, Parenti M, et al. 1, 4-Substituted triazoles as nonsteroidal anti-androgens for prostate cancer treatment. Med Chem Lett. 2017;60(7):3082-93.
16. Baiz D, Pinder T, Hassan S, Karpova Y, Salsbury F, Welker M et al. Synthesis and characterization of a novel prostate cancer-targeted phosphatidylinositol-3-kinase inhibitor prodrug. J Med Chem. 2012;55(18):8038-46.
17. Alagbala A, McRiner A, Borstnik K, Labonte T, Chang W, D'Angelo J, et al. Biological mechanisms of action of novel C-10 non-acetal trioxane dimers in prostate cancer cell lines. J Med Chem. 2006;49(26):7836-42.
18. Endo S, Oguri H, Segawa J, Kawai M, Hu D, Xia S, et al. Development of novel AKR1C3 inhibitors as new potential treatment for castration-resistant prostate cancer. J Med Chem. 2020;63(18):10396-411.
19. Adsule S, Barve V, Chen D, Ahmed F, Dou Q, Padhye S, et al. Novel Schiff base copper complexes of quinoline-2 carboxaldehyde as proteasome inhibitors in human prostate cancer cells. J Med Chem. 2006;49(24):7242-6.
20. Siddique H, Mishra S, Karnes R, Saleem M. Lupeol, a Novel Androgen Receptor Inhibitor: Implications in Prostate Cancer TherapyLupeol, a Novel Androgen Receptor Inhibitor. Clin Cancer Res. 2011;17(16):5379-91.
21. Ohtsu H, Xiao Z, Ishida J, Nagai M, Wang H, Itokawa H, et al. Antitumor agents. 217. Curcumin analogues as novel androgen receptor antagonists with potential as anti-prostate cancer agents. J Med Chem. 2002;45(23):5037-42.
22. Zhang Z, Connolly P, Lim H, Pande V, Meerpoel L, Teleha C, et al. Discovery of JNJ-63576253: a clinical stage androgen receptor antagonist for F877L mutant and wild-type castration-resistant prostate cancer (mCRPC). J Med Chem. 2021;64(2):909-24.
23. Stanisławska I, Granica S, Kiss A. Comparison of anti-proliferative effects of urolithins, ellagitannin gut metabolites, and non-steriodal antiandrogens on androgen-dependant prostate cancer cell line LNCaP. Planta Med. 2014;80(16):LP46.
24. Melkonyan F, Gevorgyan V. Catalytic Transformations via C-H Activation. Thieme. 2015;XV:5-69.
25. Yamada Y, Tanaka H, Kubo S, Sato S. Unveiling bonding states and roles of edges in nitrogen-doped graphene nanoribbon by X-ray photoelectron spectroscopy. Carbon. 2021;185:342-67.
26. Kargi F. Biological oxidation of thianthrene, thioxanthene and dibenzothiophene by the thermophilic organism Sulfolobus acidocaldarius. Biotechnol Lett. 1987;9(7):478-82.
27. Turner L. Interaction of Carmustine Tautomers with Adenine-DFT Study. Earth J Chem Sci. 2021;5(1):63-76.
28. Higgins S, Morris D, Muir K, Ryder K. The chiral oxime of 13 H-dibenzo (a, i) fluoren-13-one. Can J Chem. 2004;82(11):1625-8.
29. Aranda E, Kinne M, Kluge M, Ullrich R, Hofrichter M. Conversion of dibenzothiophene by the mushrooms Agrocybe aegerita and Coprinellus radians and their extracellular peroxygenases. Appl Microbiol Biotechnol. 2009;82(6):1057-66.
30. Jonas U, Hammer E, Schauer F, Bollag J. Transformation of 2-hydroxydibenzofuran by laccases of the white rot fungi Trametes versicolor and Pycnoporus cinnabarinus and characterization of oligomerization products. Biodegradation. 1997;8(5):321-7.
31. Khoshtariy T, Kakhabrishvili M, Kurkovskaya L, Suvorov N. Indolobenzofurans. 1. Synthesis of isomeric indolobenzo [b] furans. Chem Heter Comp. 1984;20(10):1123-7.
32. PatentScope (WIPO) SID 388542872. Available from: https://pubchem.ncbi.nlm. nih.gov/substance/388542872
33. PatentScope (WIPO) SID 388418871. Available from: https://pubchem.ncbi.nlm. nih.gov/substance/388418871
34. Available from: https://pubchem.ncbi.nlm.nih.gov/#query=dibenzo%5Ba%2Cc%5Dcycloheptene-5-carbonitrile
35. Vondráček, J, Švihálková-Šindlerová L, Pěnčíková K, Krčmář P, Andrysík Z, Chramostová K, et al. 7H-Dibenzo [c, g] carbazole and 5, 9-dimethyldibenzo [c, g] carbazole exert multiple toxic events contributing to tumor promotion in rat liver epithelial 'stem-like'cells. Mutat Res/Fund Mol Mech Mutagen. 2006;596(1-2):43-56.
36. Moriconi E, Taranko L. Ozonolysis of Polycyclic Aromatics. XI. 1a 3-Methylcholanthrene2. J Org Chem. 1963;28(10):2526-9.
37. Sorrentino J, Orsi D, Altman R. Acid-Catalyzed Hydrothiolation of gem-Difluorostyrenes to Access α, α-Difluoroalkylthioethers. J Org Chem. 2021;86(3):2297-311.
38. Mihai D, Nitulescu G, Smith J, Hirsch A, Stecoza C. Dengue virus replication inhibition by dibenzothiepin derivatives. Med Chem Res. 2019;28(3):320-8.
39. Li J, Yu N, Guo H, Shi Y, Chen X, Wu J, et al. Combining virtual screening and in vitro evaluation for the discovery of potential CYP11B2 inhibitors. Future Med Chem. 2022;14(17):1239-50.
40. Prabhakar M, Mohanty A, Meena S. In silico screening of effective inhibitor of 5α-reductase type 1 for androgenic alopecia treatment. Nat Prod Res. 2021:1-6.

41. Figueroa L, Rosas M, Montserrat M, Díaz F, López M, Alvarez M, et al. Synthesis and Theoretical Interaction of 3-(2-oxabicyclo [7.4. 0] trideca-1 (13), 9, 11-trien-7-yn-12-yloxy)-steroid Deriva-tive with 17β-hydroxysteroid Dehydrogenase Enzyme Surface. Biointerface Res Appl Chem. 2023;13(3):266.
42. Lauro F, Marcela R, Maria L, Magdalena A, Virginia M, Francisco D, et al. Evaluation of Biological Activity of a Diazocine Derivative against Heart Failure Using an Ischemia-Reperfusion Injury Model. Drug Res. 2021;72(07):404-11.
43. Gorla U, Rao K, Kulandaivelu U, Alavala R, Panda S. Lead finding from selected flavonoids with antiviral (SARS-CoV-2) potentials against COVID-19: An in-silico evaluation. Comb Chem High Thr Scr. 2021;24(6):879-90.
44. Sadashiva M, NanjundaSwamy S, Li F, Manu K, Sengottuvelan M, Prasanna D, et al. Anti-cancer activity of novel dibenzo [b, f] azepine tethered isoxazoline derivatives. BMC Chem Biol. 2012;12(1):1-11.
45. Desbois N, Pertuit D, Moretto J, Cachia C, Chauffert B, Bouyer F. cis-Dichloroplatinum (II) complexes tethered to dibenzo [c, h][1, 6] naphthyridin-6-ones: Synthesis and cytotoxicity in human cancer cell lines in vitro. Eur J Med Chem. 2013;69:719-27.
46. Lian J, Gao Y, Tang J, Chen X, Liu Y, Wu D, et al. Response of prostate cancer to addition of dutasteride after progression on abiraterone. Asian J Androl. 2021;23(2):222.
47. Levitt D. PKQuest: a general physiologically based pharmacokinetic model. Introduction and application to propranolol. BMC Clin Pharmacol. 2012;2(1):1-21.
48. Bourne D. Using the Internet as a pharmacokinetic resource. Clin Ppharmacokinet. 1997;33(3):153-60.
49. Sicak Y. Design and antiproliferative and antioxidant activities of furan-based thiosemicarbazides and 1, 2, 4-triazoles: their structure-activity relationship and SwissADME predictions. Med Chem Res. 2021;30(8):1557-68.
50. Poland A, Glover E. Studies on the mechanism of toxicity of the chlorinated dibenzo-p-dioxins. Environ Health Perspect. 1973;5:245-51.