Research Article

Evaluation of Interaction of Some Quinolone Derivatives on RSK-4 Using a Theoretical Model

Abstract

Prostate cancer is one of the leading causes of death among men worldwide; Some data suggest that ribosomal S6 p90 kinase (RSK 1-4), which belongs to the group of highly conserved Ser/Thr kinases, has been related to an increase in prostate cancer levels. For this reason, the aim of this study was to evaluate the theoretical interaction of some quinolone derivatives (compounds 1-19) with RSK-4 using 6rv2 protein and RSK-14 inhibitor (LJH685) in a docking model. The results showed that some quinolone derivatives (12, 15, 17, and 18) could interact with the 6rv2 protein surface in a different manner than LJH685. This phenomenon could be translated as greater RSK-14 inhibition, resulting in a decrease in prostate cancer levels. Analyzing these data, these quinolone derivatives could be considered good compounds to treat prostate cancer.

Keywords: *Cancer, Quinolone, RSK-4, Docking*

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

[1]Nutrition Laboratory, Faculty of Nutrition, University of Veracruz, Doctors and Dentists 910210, Forest Unit, Xalapa, Mexico. [2]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.

Address for correspondence:
Virginia Mateu-Armand, Laboratory of Pharmacoquímica Inestigation, faculty of Biological-Chemical Sciences, University Autonomous of Campeche; Humberto Lanz Cárdenas s/n, Colonia Ex Hacienda Kalá, C.P. 24085.
E-mail: lfiguero@uacam.mx

Introduction

Cancer is one of the main causes of death worldwide, which translates into a decrease in the life expectancy population.[1] There are several molecular mechanisms involved in the proliferation of cancer; for example, prostate cancer progression is related to androgen receptor activation.[2] It is important to mention that although there are some androgen receptor inhibitor drugs,[3,4] in some cases, resistance to drug therapy (castrate-resistant prostate cancer)[5] has led to the search for new treatments for this clinical pathology. In this way, a benzenesulfonamide derivative (Y08060) was developed as a bromodomain-containing protein 4 inhibitor for treating prostate cancer.[6] Furthermore, several triazole analogs were synthesized with antiandrogenic activity for prostate cancer.[7] Another study showed that some trioxane dimers interfere with the G0/G1 cell cycle using human prostate cancer cell lines.[8] In addition, a report showed that some carboxamide analogs could be used for castration-resistant prostate cancer through AKR1C3 inhibition (type 5 17β-hydroxysteroid dehydrogenase/prostaglandin F synthase.[9] Another study showed that quinolone derivative (FPA-137) might act as a proteasome inhibitor in human prostate cancer cells.[10]

On the other hand, some studies suggest that ribosomal S6 p90 kinase (RSK 1-4), which belongs to the group of highly conserved Ser/Thr kinases,[11] has been related to an increase in prostate cancer. For example, a study showed the Inhibition of RSK and YB-1 (Y-box; regulates androgen receptor expression)[12, 13] signaling enhances the anti-cancer effect of enzalutamide in prostate cancer.[14] In addition, a report showed that S6 PMD-026 drug acts as an inhibitor of RSK in combination with enzalutamide in castration-resistant prostate cancer patients.[15] Another theoretical study showed that a bis-phenol pyrazole derivative could be used as an inhibitor of the N-terminal kinase of RSK-2 in cancer cells.[16] In addition, other reports showed that RSK-2 is related to changes in the levels of prostate-specific antigen (a diagnostic marker for prostate cancer); however, in the presence of 3Ac-SL0101 (sk2 inhibitor), the expression of prostate-specific antigen is decreased.[17, 18]

All this data suggests that some drugs produce effects on prostate cancer; however, the data that exists in the literature on the interaction of some drugs with RSK in prostate cancer are few and very confusing. Perhaps this is due to the

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diverse experimental designs that focus on multiple molecular mechanisms involved in this clinical pathology. Analyzing these data, the objective of this study was to evaluate the interaction of 19 quinolone derivatives on RSK-4 using a theoretical model.

Materials and Methods

Some quinolone derivatives **(Figure 1)** were used to evaluate the possible interaction with both the androgen receptor and RSK-4 as follows:

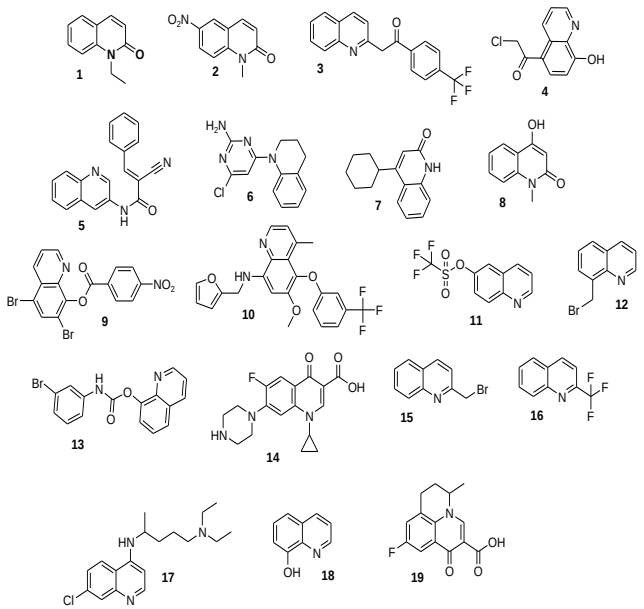

Figure 1. Chemical structure of Dibenzo derivatives

1= 1-ethyl-2(1H)-quinolone[19]
2= 1-methyl-6-nitro-2(1H)-quinolone[20]
3= 2-(2-quinolinyl)-1-[4-(trifluoromethyl)phenyl]ethanone[21]
4= 2-chloro-1-(8-hydroxy-5-quinolinyl)ethanone[22]
5= 2-cyano-3-phenyl-N-(quinoline-3-yl)acrylamide[23]
6= 4-chloro-6-(3,4-dihydro-1(2h)-quinolinyl)-2-pyrimidinamine[24]
7= 4-cyclohexyl-2(1h)-quinolone[25]
8= 4-Hydroxy-1-methyl-2(1H)-quinolone[26]
9= 5,7-dibromo-8-quinolinyl 4-nitrobenzoate[27]
10=6-methoxy-8-[(2-furanylmethyl)amino]-4-methyl-5-(3-trifluoromethylphenyloxy)quinolone[28]
11= 6-Quinolinyl trifluoromethanesulfonate[29]
12= 8-(Bromomethyl)quinoline[30]
13= 8-quinolinyl n-(3-bromophenyl)carbamate[31]
14=Ciprifloxacine(1-cyclopropyl-6-fluoro-4-oxo-7-piperazine-1-ylquinoline-3-carboxylic acid)[32]
15 = 2-(Bromomethyl)quinolone[33]
16 = 2-(Trifluoromethyl)quinolone[34]
17= N4-(7-Chloro-4-quinolinyl)-N1,N1-dimethyl-1,4-pentanediamine[35]
18= 8-Hydroxyquinoline[36]
19=Flumequine (7-fluoro-12-methyl-4-oxo-1-azatricyclo[7.3.1.0][5,13]trideca-2,5,7,9(13)-tetraene-3-carboxylic acid)[37]

Ligand-protein complex

The interaction of quinone derivatives with RSK-4 was evaluated using 6rv2[38] protein and LJH685 (2,6-Difluoro-4-[4-[4-(4-methylpiperazin-1-yl)phenyl]pyridin-3-yl]phenol)[39] as theoretical tools. Besides, to evaluate the types of binding energy involved in the interaction of quinolone derivatives with the 6rv2[40] protein surface, the Docking Server software was used.[41]

Pharmacokinetics parameter

Pharmacokinetic parameters were determined using the Swiss ADME software.[42]

Toxicity analysis

Toxicity produced by quinolone derivatives (12, 15, 17, and 18) and RSK-14 inhibitor (LJH685) were evaluated using GUSAR software.[43]

Results and Discussion

There are several studies that indicate that quinolone derivatives could exert anti-cancerogenic activity;[44,45] however, these data are not very clear. Therefore it is necessary to delve deeper into the possible anticancerigenic activity of these compounds. In this way, in this study, the interaction of 19 quinolone derivatives on RSK-4 was evaluated using 6rv2 protein and LJH685 (RSK-4 inhibitor)[39] as a theoretical tool in a Docking model.[41] The results **(Table 1 and Figure 2)** showed that LJH685 interacts with different amino acid residues (Phe_{84}; Lys_{113}; Arg_{197}; Ser_{220}; Lys_{221}; Phe_{233}; Cys_{234}; Arg_{247}; His_{250})involved in the 6rv2 protein surface compared with quinolone derivatives (1 to 19); this data suggest that this interaction is due to different functional groups involved in the chemical structure of each quinolone derivatives **(Table 1 and Figure 2)**.

Table 1. Aminoacid residues involved in the interaction of LJH685 and quinolone derivatives (compounds 1-19) with 6rv2-protein surface.

Compound	Aminoacid residues
LJH685	Phe_{84}; Lys_{113}; Arg_{197}; Ser_{220}; Lys_{221}; Phe_{233}; Cys_{234}; Arg_{247}; His_{250}
1	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
2	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
3	Arg_{7}; Ala_{10}; Leu_{11}; Cys_{14}; Phe_{246}; Met_{249}
4	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
5	Arg_{7}; Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
6	Arg_{3}; Arg_{7}; Leu_{11}; Phe_{246}; Met_{249}
7	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Met_{249}; Asn_{250}
8	Arg_{3}; Val_{6}; Arg_{7}; Met_{249}
9	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
10	Arg_{7}; Thr_{8}; Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{249}; Asn_{250}
11	Arg_{7}; Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
12	Arg_{7}; Thr_{8}; Leu_{11}; Phe_{246}; Met_{247}; Asn_{250}
13	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{249}
14	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Met_{249}; Asn_{250}
15	Arg_{7}; Leu_{11}; Val_{242}; Val_{243}; Phe_{246}
16	Arg_{7}; Leu_{11}; Phe_{246}; Met_{247}; Asn_{250}
17	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}
18	Leu_{11}; Val_{243}; Phe_{246}; Met_{247}
19	Arg_{3}; Arg_{7}; Ala_{10}; Leu_{11}; Cys_{14}; Phe_{246}; Met_{249}

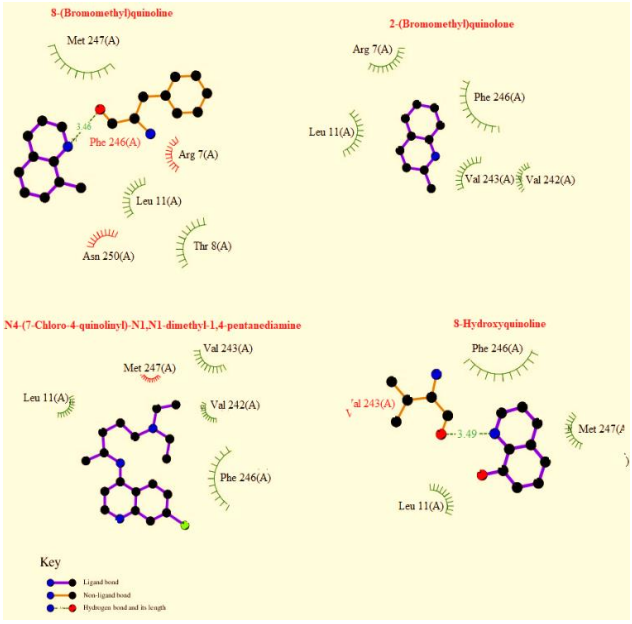

Figure 2. The scheme displayed the coupling site of amino acid residues involved in the interaction of quinolone derivatives with the 6rv2 protein surface. Visualized with GL mol viewer, docking server

On the other hand, it is important to mention that there are some reports which suggest that the interaction protein-ligand complex depends on energy levels which may determine their stability.[46] Besides, some thermodynamics reports showed the following; *i*) free energy of binding can determine 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 may exert changes in the interaction protein-ligand, 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).[46] Analyzing these data, several thermodynamic parameters involved in the interaction of quinolone derivatives with the 6rv2 protein surface were evaluated in this investigation. The results **(Table 2)** displayed that the inhibition constant for compound 12 is lower than LJH685, compounds 1-11, and 13-19, which may result in greater interaction with the 6rv2 protein surface. In addition, the inhibition constant for compounds 15, 17, and 18 was lower compared to 1-11, 13, 14, and 19. This phenomenon could produce changes in the biological activity of RSK-4, translated as a possible decrease in prostate cancer levels.

Table 2. Thermodynamic parameters involved in the interaction of quinolone derivatives with 6rv2-protein surface.

Compound	A	B	C	D	E	F
LJH685	-7.60	2.67	-6.39	-1.28	-7.67	624.82
1	-4.12	951.24	-4.43	+0.01	-4.42	444.59
2	-4.75	330.89	-5.02	-0.02	-5.05	459.08
3	-5.32	125.58	-5.80	-0.03	-5.83	559.86
4	-4.61	420.50	-4.66	+0.00	-4.66	473.39
5	-5.06	196.85	-6.20	+0.00	-6.20	604.06
6	-5.69	67.14	-5.96	-0.03	-5.99	553.31
7	-5.31	127.42	-5.63	+0.02	-5.61	519.25
8	-4.39	609.13	-3.31	-1.08	-4.39	398.90
9	-6.08	35.14	-6.53	+0.00	-6.52	530.45
10	-6.32	23.21	-6.74	+0.01	-6.73	660.84
11	-4.31	697.92	-5.31	-0.03	-5.34	478.36
12	-3.94	1.30	-4.23	-0.00	-4.23	410.80
13	-5.44	103.59	-5.93	-0.01	-5.94	570.68
14	-5.09	186.23	-5.97	-0.09	-6.06	607.72
15	-3.70	1.93	-4.00	+0.00	-4.00	406.73
16	-4.45	544.70	-4.69	-0.06	-4.75	410.04
17	-2.85	8.10	-4.87	+0.25	-4.62	563.56
18	-3.13	5.09	-3.40	-0.03	-3.43	371.03
19	-5.40	110.30	-4.69	-1.01	-5.70	499.25

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

Pharmacokinetic evaluation

There are several reports to predict some pharmacokinetic parameters using different methods.[47-49] In this research, some pharmacokinetic parameters involved in the chemical structure of quinolone derivatives were evaluated using Swiss ADME software **(Table 3)**.

Table 3. Pharmacokinetic parameters involved in the chemical structure of quinolone derivatives

Parameter	LJH685	12	15	17	18
GI absorption	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	Yes
P-GP substrate	Yes	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes	No	No
CYP2C9 inhibitor	No	No	No	No	No
CYP2D6 inhibitor	Yes	No	No	Yes	No
CYP3A4 inhibitor	Yes	No	No	Yes	No
Consensus LogPO/W	3.76	2.98	2.98	4.15	1.76

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 quinolone derivative.

Toxicity analysis

Some data in the literature indicate that quinolone can produce toxicity in different biological models.[50] Analyzing this data, the possible toxicity produced by some quinolone derivatives (12, 15, 17, and 18) was evaluated using the GUSAR software.[43] The results showed that compounds 12, 15, and 18 require a higher dose to produce toxicity (LD50) via oral compared with RSK-14 inhibitor (LJH685). This data suggest that toxicity could be dose-dependent and the routes of administration for each quinolone derivative.

Table 4. Possible toxicity involved in the administration of quinolone derivatives (12, 15, 17, and 18) and LJH685 using Gusar Software.

Compound	IP LD50 (mg/kg)	IV LD50 (mg/kg)	Oral LD50 (mg/kg)	SC LD50 (mg/kg)
LJH685	339.70	78.62	291.30	353.70
12	218.00	60.73	502.90	315.10
15	174.80	57.35	650.70	511.10
17	102.50	48.29	33.60	342.40
18	245.30	63.77	1028.00	593.00

Conclusion

Theoretical evaluation of the interaction of quinolone derivatives with the 6rv2 protein surface suggests that quinoline derivatives 12, 15, 17, and 18 may have a higher affinity for the 6rv2 protein. This phenomenon could be translated as greater RSK-14 inhibition, resulting in a decrease in prostate cancer levels. Analyzing these data, these quinolone derivatives could be considered good compounds to treat prostate cancer.

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None.

Conflict of interest
None.

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None.

Ethics statement
None.

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