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Theoretical Assessment of the Interaction Between Selected Quinolone Derivatives and RSK-4

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Abstract

Prostate cancer remains one of the most common causes of cancer-related mortality among men globally. Evidence indicates that ribosomal S6 p90 kinases (RSK 1–4), a group of highly conserved serine/threonine kinases, may be associated with elevated prostate cancer levels. This study aimed to theoretically evaluate the interaction between various quinolone derivatives (compounds 1–19) and RSK-4, utilizing the structure of the 6rv2 protein and the known RSK-14 inhibitor, LJH685, through molecular docking simulations. The results showed that specific derivatives—specifically compounds 12, 15, 17, and 18—exhibited distinct binding patterns on the surface of the 6rv2 protein compared to LJH685. This altered interaction may correspond to enhanced inhibition of RSK-14, potentially contributing to reduced prostate cancer activity. Based on these findings, the identified quinolone derivatives show promise as potential candidates for the treatment of prostate cancer.

Keywords: Prostate Cancer, Quinolone Derivatives, RSK-4, Molecular Docking

Introduction

Cancer remains a leading global cause of mortality, significantly reducing overall life expectancy [1]. Numerous molecular mechanisms contribute to cancer development and progression; for instance, prostate cancer advancement is closely linked to the activation of androgen receptors [2]. Although there are existing therapeutic agents targeting androgen receptors [3, 4], certain cases develop resistance to these treatments—commonly referred to as castration-resistant prostate cancer (CRPC) [5]—which has driven the exploration of alternative therapeutic approaches. In response to this need, several compounds have been developed and tested. One such compound is the benzenesulfonamide derivative Y08060, designed to inhibit bromodomain-containing protein 4 in prostate cancer cells [6]. Other studies have explored the potential of triazole-based analogs with antiandrogenic properties for prostate cancer therapy [7], and trioxane dimers, which were found to arrest human prostate cancer cells in the G0/G1 phase of the cell cycle [8]. Moreover, certain carboxamide derivatives have demonstrated efficacy against CRPC by inhibiting AKR1C3 (also known as type 5 17β-hydroxysteroid dehydrogenase/prostaglandin F synthase) [9]. Another promising compound, the quinolone derivative FPA-137, has shown activity as a proteasome inhibitor in prostate cancer cells [10].

Separately, ribosomal S6 p90 kinases (RSK 1–4), a group of conserved serine/threonine kinases [11], have been implicated in the progression of prostate cancer. For example, it has been shown that blocking RSK and YB-

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1 (Y-box protein, a regulator of androgen receptor expression) signaling pathways enhances the therapeutic effect of enzalutamide in prostate cancer models [12-14]. Further research revealed that PMD-026, a known RSK inhibitor, exhibited increased efficacy when used in combination with enzalutamide in CRPC patients [15]. Theoretical modeling has also identified bis-phenol pyrazole derivatives as potential inhibitors of the N-terminal kinase domain of RSK-2 [16]. Additionally, RSK-2 has been associated with the regulation of prostate-specific antigen (PSA), a key biomarker used in diagnosing prostate cancer. Interestingly, PSA levels were reduced in the presence of the RSK-2 inhibitor 3Ac-SL0101 [17, 18].

Despite these findings, there is still limited and often conflicting data in the literature concerning how certain drugs interact with RSK proteins in prostate cancer, likely due to the varying experimental setups focusing on different molecular pathways. Considering this, the current study aims to theoretically assess how 19 quinolone derivatives interact with RSK-4 using a molecular docking approach.

Materials And Methods

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

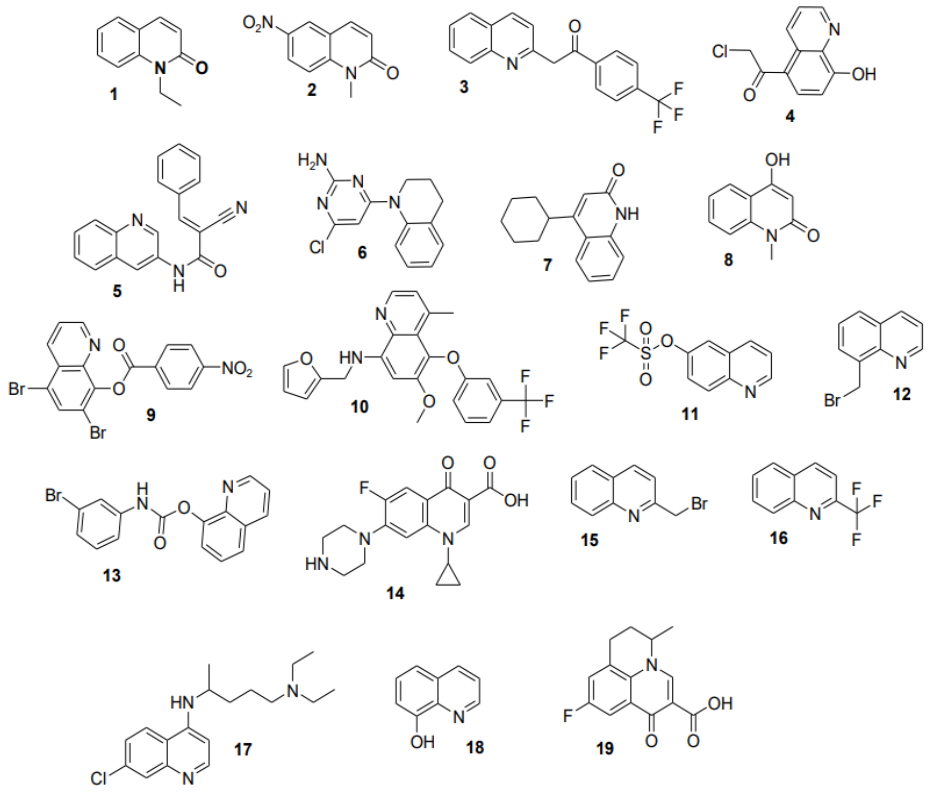

Figure 1. Chemical structure of dibenzo derivatives; 1 = 1-ethyl-2(1H)-quinolone [19], 2 = 1-methyl-6-nitro-2(1H)-quinolone [20], 3 = 2-(2-quinolinyl)-1-[4-(trifluoromethyl)phenyl]ethanone [21], 4 = 2-chloro-1-(8-hydroxy-5-quinolinyl)ethanone [22], 5 = 2-cyano-3-phenyl-N-(quinoline-3-yl)acrylamide [23], 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 = Cipriploxacine(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

To investigate the interaction between quinolone derivatives and RSK-4, the 6rv2 protein structure was utilized as the receptor model [38], with LJH685 (2,6-Difluoro-4-[4-[4-(4-methylpiperazin-1-yl)phenyl]pyridin-3-yl]phenol) serving as the reference inhibitor [39]. Additionally, Docking Server software was employed to examine the nature of binding energies contributing to the interaction between the quinolone compounds and the 6rv2 protein surface [40, 41].

Pharmacokinetic Parameters

Pharmacokinetic properties of the quinolone derivatives were predicted using the SwissADME platform [42], enabling an assessment of their drug-likeness and absorption characteristics.

Toxicity analysis

The potential toxicological effects of selected quinolone derivatives (12, 15, 17, and 18), along with the RSK-4 inhibitor LJH685, were estimated using GUSAR software [43].

Results and Discussion

Although various studies have pointed to the anticancer potential of quinolone derivatives [44, 45], the current understanding of their effects remains incomplete. Consequently, this study aimed to explore the theoretical interaction of 19 different quinolone derivatives with the RSK-4 protein using the 6rv2 structure and the known inhibitor LJH685 as reference molecules in a docking simulation [39, 41]. The findings (**Table 1** and **Figure 2**) revealed that LJH685 forms interactions with specific amino acid residues on the 6rv2 protein surface, including Phe84, Lys113, Arg197, Ser220, Lys221, Phe233, Cys234, Arg247, and His250. In contrast, the quinolone derivatives (compounds 1–19) displayed varying interaction profiles. These differences are likely attributed to the diverse functional groups present in the chemical structures of the quinolone derivatives (see **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}

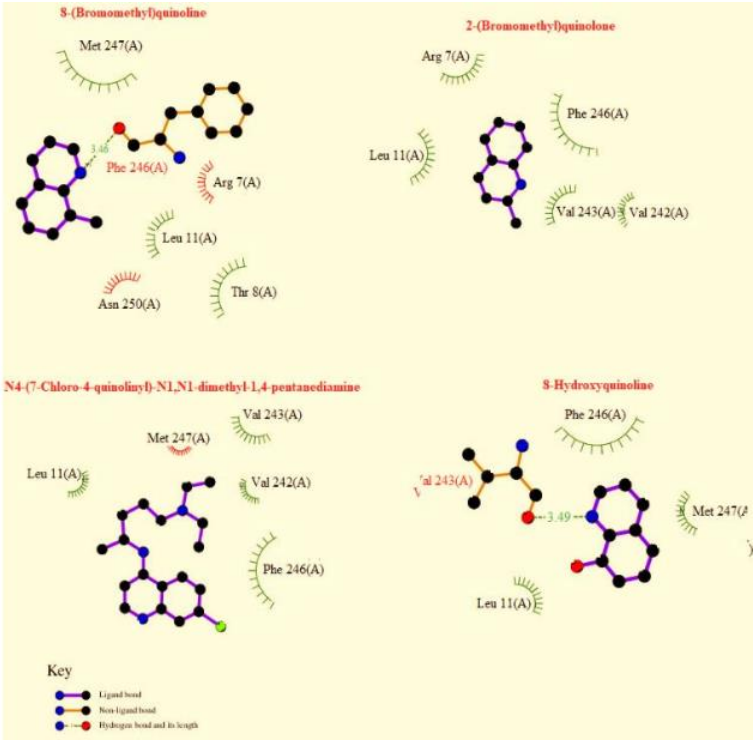

Figure 2. The scheme displayed the coupling site of amino acid residues involved in the interaction of quinolone derivatives with the 6rv2 protein surface; visualized with GL mol viewer, docking server

Conversely, it is noteworthy that some studies have indicated the stability of ligand-protein complexes is influenced by their associated energy levels [46]. Additionally, thermodynamic analyses have highlighted several key aspects: (i) the free binding energy reflects the energetic requirement for a molecule to associate with a protein in an aqueous environment; (ii) electrostatic energy arises from the interaction between electrical charges and electrostatic potentials within the ligand-protein complex; (iii) total intermolecular energy plays a significant role in modulating ligand–protein interactions; and (iv) the combined effects of van der Waals forces, hydrogen bonding, and desolvation energy can impact the displacement of water molecules within the complex system [46]. Based on this information, various thermodynamic properties governing the interaction between quinolone derivatives and the 6rv2 protein surface were assessed in this study. The findings (**Table 2**) demonstrated that compound 12 exhibited a lower inhibition constant than LJH685 and compounds 1–11 and 13–19, suggesting a stronger binding affinity to the 6rv2 protein. Furthermore, compounds 15, 17, and 18 also showed lower inhibition constants when compared to compounds 1–11, 13, 14, and 19. This enhanced binding could potentially alter RSK-4's biological activity, possibly contributing to a reduction in prostate cancer progression.

Table 2. Thermodynamic parameters involved in the interaction of quinolone derivatives with the 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

Pharmacokinetic evaluation

Numerous studies have employed various approaches to estimate pharmacokinetic parameters [47–49]. In the present study, key pharmacokinetic properties associated with the chemical structures of the quinolone derivatives were analyzed using the 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 findings revealed variations in gastrointestinal absorption and metabolism, particularly concerning different cytochrome P450 enzyme systems. These differences are likely attributed to the unique chemical structures of each quinolone derivative.

Toxicity analysis

Previous studies have indicated that quinolone compounds may exhibit toxic effects across various biological models [50]. Based on this, the potential toxicity of selected quinolone derivatives (12, 15, 17, and 18) was assessed using GUSAR software [43]. The analysis demonstrated that compounds 12, 15, and 18 exhibited higher LD50 values via the oral route compared to the RSK-14 inhibitor (LJH685), implying that their toxicity may be influenced by both dosage and route of administration (**Table 4**).

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

The theoretical assessment of quinolone derivatives interacting with the 6rv2 protein surface indicates that compounds 12, 15, 17, and 18 may exhibit stronger

binding affinity. This stronger interaction could enhance the inhibition of RSK-14, potentially contributing to a reduction in prostate cancer progression. Based on these findings, these specific quinolone derivatives show promise as potential therapeutic agents for the treatment of prostate cancer.

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Conflict of Interest: None

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Ethics Statement: None

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