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Theoretical Model of Thiophene and Its Derivatives Interaction with BRCA-1

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ABSTRACT

Research indicates a growing association between breast cancer and increased mortality rates across the globe. Various risk factors, such as obesity, high-fat diets, lack of physical exercise, alcohol use, oral contraceptive consumption, genetic mutations, and others, contribute to the development of breast cancer. In addition, some studies have pointed to the role of the breast cancer gene 1 (BRCA1) in breast cancer onset. The objective of this study was to investigate how thiophene (1) and its derivatives (2 to 25) interact with BRCA-1, using the 3pxb protein and niraparib as control compounds in a docking simulation. The results showed changes in the interaction of thiophene and its analogs with the 3pxb protein surface when compared to the niraparib drug. In addition, the inhibition constants (Ki) of thiophene-derivative-protein complexes for compounds 11, 13, 16, 18, and 20 showed similar patterns to that of niraparib. These findings suggest that these specific compounds may inhibit the activity of BRCA-1, which could lead to a reduction of breast cancer cell proliferation.

Keywords: BRCA-1, Cancer, Thiophene, Derivatives

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Introduction

Breast cancer has become increasingly prevalent in women over the years, leading to a rise in mortality rates globally [1, 2]. A range of risk factors have been identified as contributing to the onset of breast cancer, including demographic, reproductive, hormonal, genetic, and lifestyle factors [3]. Various therapeutic agents are currently used in breast cancer treatment, such as tamoxifen (a drug targeting estrogen receptors) [4], trastuzumab [5], pertuzumab [6], margetuximab [7], lapatinib [8], neratinib/fulvestrant [9], tucatinib [10], everolimus [11], alpelisib [12], capivasertib/fulvestrant [13], and olaparib [14]. However, some of these treatments come with side effects, such as diarrhea, nausea, and neutropenia [15]. To find new therapeutic options, several drugs have been developed, including niraparib (MK-4827), an ADP-ribose polymerase inhibitor that shows effectiveness against tumors with BRCA-1 and BRCA-2 mutations [16]. Additionally, drugs like olaparib and talazoparib have been approved for treating breast cancers harboring BRCA-1 or BRCA-2 mutations [17]. Phase III clinical trials have demonstrated that both olaparib and talazoparib offer significant benefits to breast cancer patients [18]. Other studies have shown that compounds like benzo[a]pyrene and its epoxide diol can influence BRCA-1 expression [19]. Moreover, a carboxamide derivative has demonstrated activity against the MDA-MB-436 breast cancer cell line, which carries the BRCA-1 mutation [20].

In addition, several thiophene derivatives have been synthesized to evaluate their potential anti-cancer effects. One study highlighted a chloro-benzothiophene analog that exhibited biological activity against the MCF-7 breast

cancer cell line [21]. Another study found that a thiophene derivative (4-Methyl-5-(phenyldiazenyl)-2-[((1-(thiophen-2-yl) ethylidene)hydrazineylidene]-thiazol-3(2H)amine) inhibited growth in MCF-7 cancer cells [22]. Further findings showed that a pyrimido-thieno-pyrimidine thiophene derivative reduced the growth of both MCF-7 and A549 cancer cell lines by targeting the epidermal growth factor receptor [23]. In addition, a dioxo-benzo[b]-thiophene derivative was identified as a YAP-TEAD (transcriptional regulators) inhibitor in breast cancer, demonstrating activity in a cancer cell model [24]. Additionally, a thiophene-triazine derivative inhibited MCF-7 cancer cell growth through the PI3K/mTOR (phosphoinositide 3-kinase/mammalian target of rapamycin) pathway [25]. These results suggest that certain thiophene derivatives may hold promise as inhibitors of breast cancer growth, but their specific interactions with molecules involved in cell proliferation in breast cancer remain unclear. Consequently, this study sought to investigate the potential interactions between several thiophene compounds (1) and their analogs (2 to 25) with BRCA-1 (breast cancer gene 1) using a theoretical modeling approach.

Materials and Methods

The chemical structures of thiophene and its derivatives, which were utilized to explore their potential interaction with the BRCA-1 gene surface, are depicted in **Figure 1**.

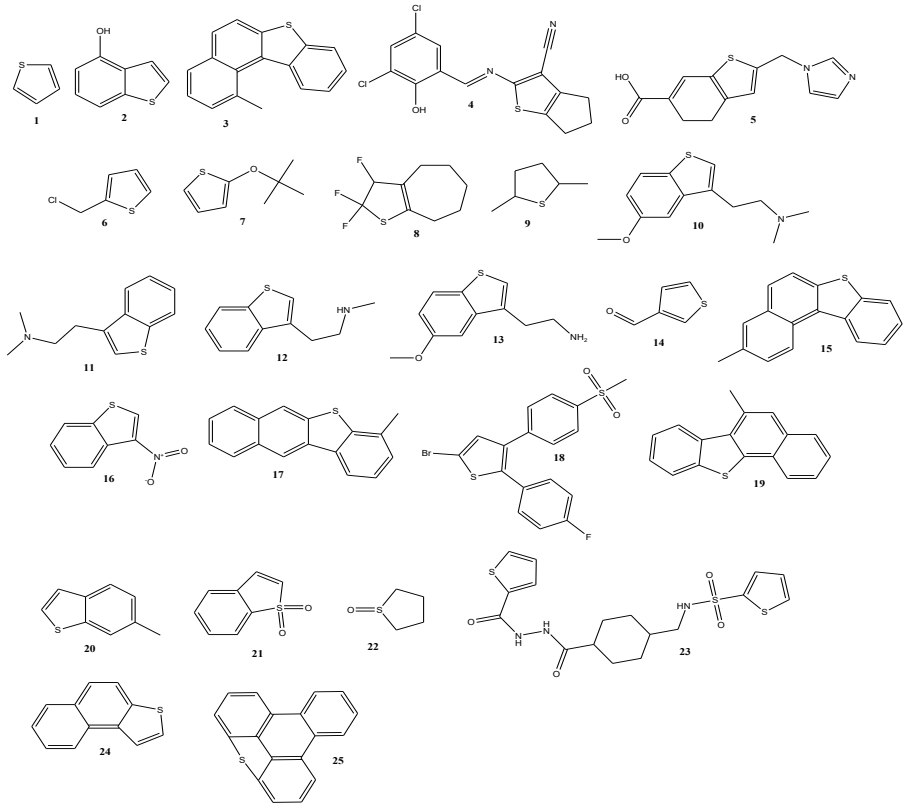

Figure 1. Chemical structure of thiophene (1) and its derivatives (2-25); 1 = thiophene, 2 = 1-benzothiophene-4-ol, 3 = 1-methylbenzo(b)naphtho(1,2-d)-thiophene, 4 = 2-([(E)-(3,5-Dichloro-2-hydroxyphenyl)methylidene]amino)-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile, 5 = 2-(1H-imidazol-1-ylmethyl)-4,5-dihydrobenzo(b)thiophene-6-carboxylic acid, 6 = 2-(Chloromethyl)-thiophene, 7 = 2-(tert-butoxy)thiophene, 8 = 2,2,3-trifluoro-2,4,5,6,7,8-hexahydrocyclohepta(b)thiophene, 9 = 2,5-dimethyltetrahydrothiophene, 10 = 3-(2-(Dimethylamino)ethyl)-5-methoxybenzo(b)thiophene, 11 = 3-(2-(dimethylamino)ethyl)benzo(b)thiophene, 12 = 3-(2-(methylamino)ethyl)benzo(b)thiophene, 13 = 3-(2-aminoethyl)-5-methoxybenzo(b)thiophene, 14 = 3-formylthiophene, 15 = 3-methylbenzo(b)naphtho(1,2-d)thiophene, 16 = 3-nitrobenzo(b)thiophene, 17 = 4-methylbenzo(b)naphtho(2,3-d)thiophene, 18 = 5-bromo-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-thiophene, 19 = 6-methylbenzo(b)naphtho(2,1-d)thiophene, 20 = 6-methylbenzo(b)thiophene, 21 = -benzothiophene 1,1-dioxide, 22 = tetrahydro-thiophene-1-oxide, 23 = N-[[4-[(thiophene-2-carbonylamino)carbamoyl]cyclohexyl]methyl]thiophene-2-sulfonamide, 24 = naphtho(2,1-b)thiophene, 25 = 19-thiapentacyclo[14.2.1.05,18.06,11.012,17]nonadeca-

1,3,5(18), 6,8,10, 12(17),13,15-nonaene

Ligand-protein complex

The interaction between thiophene and its derivatives with the BRCA-1 gene was assessed by modeling their binding to the 3pxb [26] protein and using niraparib (MK-4827) as a reference in the DockingServer software [27].

Pharmacokinetics parameter

The pharmacokinetic properties of thiophene derivatives (11, 13, 16, 18, and 20) were analyzed through the SwissADME software [28].

Toxicity analysis

The potential toxicity of thiophene derivatives (11, 13, 16, 18, and 20), as well as niraparib, was evaluated by considering various administration routes using the GUSAR program [29].

Results and Discussion

Previous research indicates that several thiophene derivatives have shown potential biological activity against cancer cells [21-25]; however, these findings have often been inconsistent. In light of these varying results, this study focused on exploring how thiophene and its analogs might interact with specific biomolecules related to cancer progression, like BRCA-1, using the 3pxb protein and niraparib in a docking simulation. The outcomes **(Table 1; Figure 2)** revealed that LJH685 engages with a variety of amino acid residues (Leu1679, Ile1680, Arg1699, Ala1700, Leu1701, Lys1702, Leu1705, Gln1779) on the 3pxb protein's surface, which was not observed with thiophene (1) or its other derivatives (2 to 25). This indicates that the binding of thiophene and its analogs to the 3pxb protein depends on the distinct chemical structures of each compound **(Table 1; Figure 2)** and various thermodynamic factors that influence the formation of the thiophene-protein complex.

Table 1. Theoretical interaction of thiophene (1) and its analogs (compounds 2-25) with 3pxb protein surface

Compound	Aminoacid residues
Niraparib	Leu_{1679}; Ile_{1680}; Arg_{1699}; Ala_{1700}; Leu_{1701}; Lys_{1702}; Leu_{1705}; Gln_{1779}
1	Ile_{1680}; Leu_{1701}; Lys_{1702}; Leu_{1705}; Gln_{1779}
2	Glu_{1698}; Arg_{1699}; Val_{1740}; Val_{1741}
3	Glu_{1698}; Arg_{1699}; Ala_{1700}; Asn_{1774}; Met_{1775}; Arg_{1699}; Leu_{1839}
4	Arg_{1699}; Ala_{1700}; Leu_{1701}; Lys_{1702}; Asn_{1774}; Met_{1775}
5	Ser_{1655}; Ala_{1700}; Leu_{1701}; Lys_{1702}; Phe_{1704}; Asn_{1774}; Met_{1775}; Arg_{1835}; Leu_{1839}
6	Arg_{1699}; Phe_{1704}; Asn_{1774}; Met_{1775}; Arg_{1835}; Leu_{1839}
7	Leu_{1701}; Phe_{1704}; Asn_{1774}; Met_{1775}; Arg_{1835}; Leu_{1839}
8	Arg_{1699}; Leu_{1701}; Phe_{1704}; Met_{1775}; Leu_{1839}
9	Phe_{1704}; Asn_{1774}; Met_{1775}; Arg_{1835}; Leu_{1839}
10	Glu_{1698}; Arg_{1699}; Phe_{1704}; Met_{1775}
11	Glu_{1698}; Ala_{1700}; Leu_{1701}
12	Glu_{1698}; Arg_{1699}; Phe_{1704}; Met_{1775}; Leu_{1839}
13	Glu_{1698}; Ala_{1700}; Leu_{1701}
14	Ile_{1680}; Leu_{1701}; Lys_{1702}; Leu_{1705}
15	Glu_{1698}; Arg_{1699}; Ala_{1700}; Met_{1775}; Leu_{1839}
16	Arg_{1699}; Leu_{1701}; Phe_{1704}; Met_{1775}; Leu_{1839}

17	Ala_{1700}; Leu_{1701}; Met_{1775}; Arg_{1835}; Leu_{1839}
18	Glu_{1698}; Arg_{1699}; Ala_{1700}; Val_{1740}; Val_{1741}; Thr_{1773}; Asn_{1774}; Met_{1775}; Arg_{1835}
19	Arg_{1699}; Ala_{1700}; Leu_{1701}; Met_{1775}; Leu_{1839}
20	Arg_{1699}; Leu_{1701}; Phe_{1704}; Asn_{1774}; Met_{1775}; Arg_{1835}; Leu_{1839}
21	Arg_{1699}; Phe_{1704}; Asn_{1774}; Met_{1775}; Leu_{1839}
22	Ile_{1680}; Leu_{1701}; Lys_{1702}; Leu_{1705}
23	Ser_{1655}; Glu_{1698}; Arg_{1699}; Ala_{1700}; Leu_{1701}; Asn_{1774}; Met_{1775}
24	Arg_{1699}; Leu_{1701}; Phe_{1704}; Met_{1775}; Leu_{1839}
25	Glu_{1698}; Arg_{1699}; Leu_{1701}; Met_{1775}; Leu_{1839}

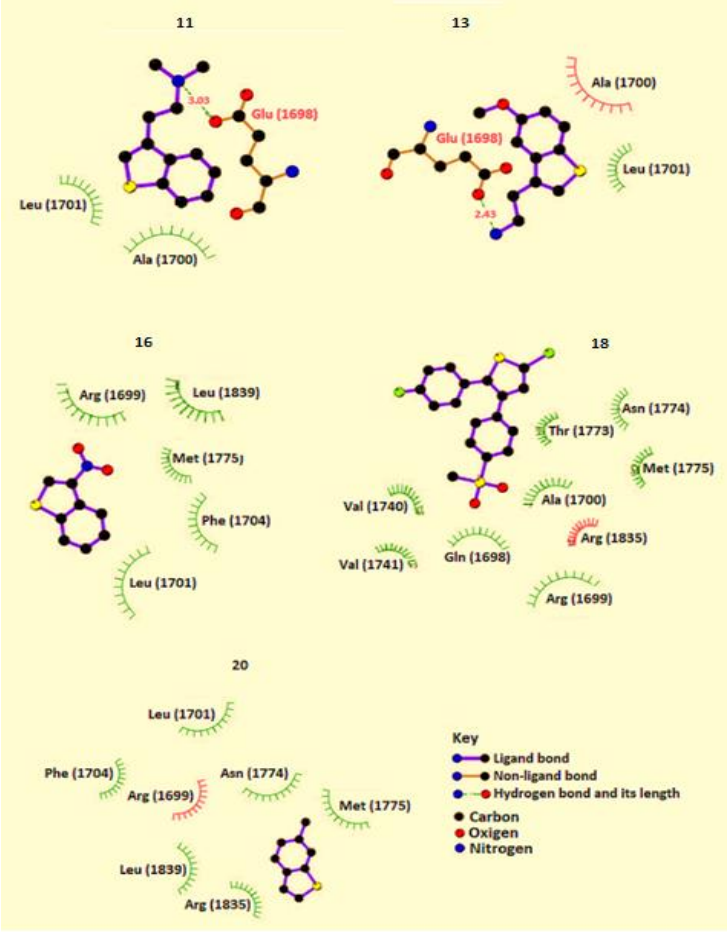

Figure 2. Binding of thiophene analogs (11, 13, 16, 18, and 20) with the 3xpb protein surface; visualized with GL mol viewer, DockingServer.

Thermodynamic parameters

The binding of drugs to biomolecules has been theorized to be influenced by various thermodynamic factors such as binding free energy, electrostatic interactions, total intermolecular energy, and contributions from Van der Waals (vdW) forces, hydrogen bonding, and desolvation effects [29]. To explore the role of these parameters in the interaction between thiophene and its derivatives with the 3pxb protein, a detailed analysis was conducted. The outcomes, as shown in **Table 2**, demonstrated notable variations in the energy levels of thiophene derivatives compared to niraparib. Additionally, the inhibition constant (Ki) for most of the thiophene derivatives (2-10, 12, 14, 15, 17, 19, 21-25) was found to be higher than that of niraparib. In contrast, derivatives 11, 13, 16, 18, and 20 exhibited Ki values very similar to that of niraparib. These results suggest that compounds 11, 13, 16, 18, and 20 may have the potential to inhibit BRCA-1, although further experimental validation is necessary.

Table 2. Thermodynamic parameters for thiophene-3pxb-protein complex formation

Compound	A	B	C	D	E	F
Niraparib	-3.97	1.23	-4.45	0.17	-4.28	566.74
1	-2.69	10.64	-2.69	-0.01	-2.69	262.81
2	-3.20	4.52	-3.30	-0.19	-3.50	361.44
3	-5.71	65.54	-5.70	-0.01	-5.71	507.69
4	-5.15	166.84	-6.00	0.05	-5.95	639.36
5	-4.89	259.58	-5.42	-0.36	-5.78	502.05
6	-3.12	5.17	-3.41	-0.01	-3.42	324.30
7	-3.02	6.15	-3.70	0.01	-3.69	394.77
8	-5.29	132.58	-5.20	-0.09	-5.29	366.08
9	-3.09	5.39	-3.10	0.01	-3.09	312.43
10	-4.46	540.66	-4.50	-0.97	-5.47	479.82
11	-4.00	1.17	-3.98	-0.77	-4.76	410.80
12	-4.44	560.34	-4.11	-1.15	-5.26	426.31
13	-3.92	1.33	-3.92	-1.17	-5.09	434.79
14	-2.87	7.87	-3.12	-0.05	-3.17	293.08
15	-5.00	216.89	-4.99	0.00	-5.00	507.79
16	-3.77	1.74	-4.01	-0.05	-4.06	368.70
17	-5.09	186.30	-5.09	0.00	-5.09	493.21
18	-4.07	1.04	-5.12	-0.03	-5.14	559.29
19	-5.01	211.98	-5.01	0.00	-5.01	485.12
20	-3.72	1.89	-3.69	-0.02	-3.72	383.12
21	-3.40	3.22	3.38	-0.02	-3.40	372.32
22	-2.67	11.10	-2.65	0.02	-2.67	276.73
23	-2.30	20.55	-4.32	0.10	-4.21	616.39
24	-4.16	888.00	-4.15	-0.01	-4.15	402.99
25	-5.48	96.79	-5.47	0.00	-5.48	497.96

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), and F = Interact. surface.

Pharmacokinetic assessment

Various approaches have been employed to assess pharmacokinetic parameters to evaluate the potential biological effects of different pharmaceutical compounds [30-33]. Therefore, this study aimed to analyze certain pharmacokinetic properties of thiophene analogs 11, 13, 16, 18, 20, and niraparib using the SwissADME tool **(Table 3)**. The findings revealed notable variations in gastrointestinal absorption and metabolism, involving different cytochrome P450 enzymes, between thiophene analogs 11, 13, 16, 18, and 20 and the niraparib drug. These differences are likely linked to the unique chemical features and varying lipophilicity of each thiophene derivative.

Table 3. Theoretical analysis of some pharmacokinetic factors for thiophene analogs and niraparib drug

Parameter	Niraparib	11	13	16	18	20
GI absorption	High	High	High	High	Low	High
BBB permeant	Yes	Yes	Yes	Yes	No	Yes
P-GP substrate	Yes	No	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	Yes	Yes	Yes	Yes	Yes
CYP2C9 inhibitor	No	No	No	No	Yes	No
CYP2D6 inhibitor	Yes	Yes	No	No	No	No

CYP3A4 inhibitor	No	No	No	No	No	No
Consensus $LogP_{O/W}$	2.29	3.14	2.49	2.02	5.17	3.19

Toxicity evaluation

Previous studies have indicated that certain thiophene derivatives can induce toxicity to varying degrees, depending on the biological models used for assessment [34-37]. In this study, the potential toxicity of thiophene analogs (11, 13, 16, 18, and 20) was evaluated using the GUSAR software [28]. The findings, as shown in **Table 4**, suggest that compound 18 might require significantly higher doses to achieve toxicity (LD50) through different administration routes, including intraperitoneal, intravenous, oral, and subcutaneous, compared to niraparib. Furthermore, thiophene analog 16 requires a higher oral dose to induce toxicity than niraparib. These observations imply that the toxicity levels of thiophene derivatives vary based on the dosage and route of administration for each compound.

Table 4. Theoretical analysis of toxicity for thiophene derivatives (11, 13, 16, 18, and 20) and niraparib drug using GUSAR software.

Compound	IP LD50 (mg/kg)	IV LD50 (mg/kg)	Oral LD50 (mg/kg)	SC LD50 (mg/kg)
Niraparib	423.10	104.50	366.00	158.60
11	90.10	31.09	190.60	150.50
13	189.80	75.37	1154.00	374.60
16	216.20	115.80	868.40	181.00
18	586.60	285.20	465.80	307.50
20	227.60	63.58	1232.00	416.20

IP = intraperitoneal route of administration, IV = intravenous route of administration, Oral = oral route of administration, and SC = subcutaneous route of administration

Conclusion

This research explored the interaction between thiophene derivatives and the 3pxb protein surface. The findings suggest that compounds 11, 13, 16, 18, and 20 might interact with various amino acid residues on the 3pxb protein, positioning them as potential inhibitors of the BRCA-1 gene. Such inhibition may translate into reduced breast cancer cell proliferation, indicating that these thiophene derivatives could hold promise as therapeutic agents for breast cancer treatment.

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Conflict of Interest: None

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Ethics Statement: All experimental procedures adhered to the ethical guidelines established by the Pharmacochemistry Laboratory of the University Autonomous of Campeche.

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