Original Article

# Interaction of Thiophene and Their Derivatives with BRCA-1 Using a Theoretical Model


## Abstract

Several studies indicate that breast cancer has been associated with increases in mortality rates worldwide. There are several risk factors to developed breast cancer such as obesity, high fat diet, Lack of physical activity, alcohol, use of oral contraceptives, genetic mutations, and others. In addition, some reports suggesting that breast cancer gene 1 (BRCA1) has been related to breast cancer development. This research aimed to determine the possible interaction of thiophene (1) and their analogs (2 to 25) with BRCA-1 using the 3pxb protein and niraparib drug as controls in a docking model The results showed differences in the interaction of thiophene and its analogs with the surface of the 3pxb protein compared to niraparib drug. Besides, other data indicate that the inhibition constant (Ki) associated with thiophene-derivatives-protein complex formation for 11, 13, 16, 18, and 20 was similar manner to Ki for niraparib. These data suggest that compounds 11, 13, 16, 18, and 20 could inhibit the biological activity of BRCA-1; this phenomenon can be translated as a decrease in breast cancer cell growth.


**Keywords:** *Cancer, Thiophene, Derivatives, BRCA-1*


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## Introduction

For several years, breast cancer has increased drastically in women, which has increased the mortality rate worldwide.[1, 2] Some risk factors involved in the development of breast cancer have been detected, such as demographic, reproductive, hormonal, hereditary, and lifestyle parameters.[3] It should be noted that different drugs have been used to treat breast cancer such as tamoxifen (estrogen-receptor inhibitor),[4] trastuzu-mab,[5] pertuzumab,[6] margetuximab,[7] lapatinib,[8] neratinib/fulvestrant,[9] tucati-nib,[10] everolimus,[11] alpelisib,[12] capiva-sertib/fulvestrant,[13] and olaparib.[14] Nevertheless, some drugs produce some adverse effects such as nausea, diarrhea, and neutropenia.[15] In the search for new pharmacological alternatives, several drugs have been developed to treat breast cancer; for example, the preparation of niraparib (MK-4827) as an ADP-ribose polymerase inhibitory agent which is effective in BRCA-1 and BRCA-2 mutant tumors.[16] In addition, types of drugs such as olaparib and talazoparib were approved to treat breast cancers that express either BRCA-1 or BRCA-2 mutations.[17] Furthermore, a study in a phase III clinical trial showed that both olaparib and talazoparib drugs can produce beneficial effects in patients with breast cancer.[18] Other data showed that a benzo[a]pyrene and its epoxide diol can produce changes in BRCA-1 expression.[19] Furthermore, a study indicates that a carboxamide derivative has activity in a breast cancer cell line (MDA-MB-436; BRCA-1 mutated).[20]

On the other hand, some thiophene derivatives were synthesized to evaluate their biological activity against breast cancer; in this way, a study showed the preparation of a chloro-benzothiophene analog with biological activity against a breast cancer cell line (MCF-7).[21] Other report indicate that a thiophene derivative (4-Methyl-5-(phenyldiazenyl)-2-[((1-(thio-phen-2-yl) ethylidene)hydrazineylidene]-thiazol-3(2*H*)amine) decrease growth cancer using MCF-7 cells.[22] Other data displayed that a thiophene analog (pyrimido-thieno-pyrimidine derivative) decreases cancer cell line growth MCF-7 and A549 through epidermal growth factor receptor inhibition.[23] Besides, a dioxo-benzo[*b*]-thiophene derivative was developed as an agent YAP-TEAD (transcript-tional regulators) inhibitor for treating breast cancer using a cancer cell model.[24] Another report showed that a

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thiophene-triazine derivative decreased the growth of MCF-7 cancer cells through PI3K/mTOR (phosphoinositide 3-kinase/mammalian target of rapamycin) pathway inhibition.[25] All these experimental data indicate that some thiophene derivatives can inhibit breast cancer growth; nevertheless, its coupling with some biomolecules involved in cell growth in breast cancer patients is unclear. Therefore, this study aimed to determine the possible interaction of several thiophene (compound 1) and their analogs (2 to 25) with BRCA-1 (breast cancer gene 1) using a theoretical model.

## Materials and Methods

**Figure 1** shows the chemical structure of thiophene and its analogs which were used to determine its possible interaction with the BRCA-1 gene surface as follows:

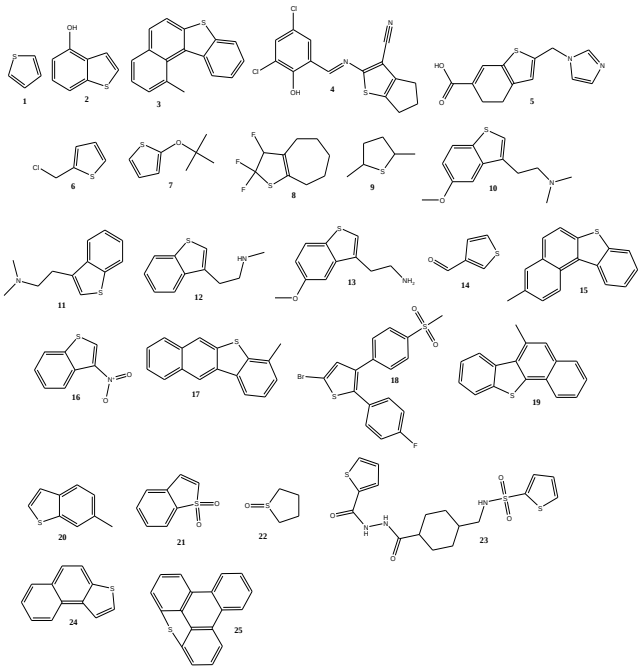

**Figure 1. Chemical structure of thiophene (1) and its derivatives (2-25).**
**1 = Thiophene**
**2 = 1-Benzothiophene-4-ol**
**3 = 1-Methylbenzo(b)naphtho(1,2-d)-thiophene**
**4= 2-([(E)-(3,5-Dichloro-2-hydroxyphenyl)methylidene]amino)-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile**
**5 = 2-(1H-Imidazol-1-ylmethyl)-4,5-dihydrobenzo(b)thiophene-6-carboxylic 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

Coupling of thiophene and its derivatives with **BRCA-1** was evaluated using **3pxb**[26] protein and niraparib (MK-4827) as theoretical tools in DockingServer software.[27]

### Pharmacokinetics parameter

Some pharmacokinetic parameters for thiophene derivatives (11, 13, 16, 18, and 20) were evaluated using the SwissADME software.[28]

### Toxicity analysis

Possible toxicity induced through different administration routes of thiophene derivatives (11, 13, 16, 18, and 20) and niraparib was evaluated using the GUSAR program.[29]

## Results and Discussion

Some reports indicate that several thiophene derivatives can exert biological activity against cancer cells;[21-25] nevertheless, experimental results are very confusing. Analyzing these data, this study aimed to evaluate the possible interaction of some thiophene and its derivatives with some biomolecules involved in cancer cell growth such as BRCA-1 using 3pxb protein and niraparib as theoretical tools in a Docking model. The results **(Table 1 and Figure 2)** showed that LJH685 interacts with different amino acid residues ($Leu_{1679}$; $Ile_{1680}$; $Arg_{1699}$; $Ala_{1700}$; $Leu_{1701}$; $Lys_{1702}$; $Leu_{1705}$; $Gln_{1779}$) involved in the 3pxb protein surface in comparison with thiophene (1) and its derivatives (2 to 25). This data indicates that the coupling of thiophene and its analogs with the 3pxb protein surface can depend on the chemical characteristic of each compound **(Table 1 and Figure 2)** or different thermodynamics parameters involved in the thiophene-protein complex formation.

**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 | $Ile_{1680}$; $Leu_{1701}$; $Lys_{1702}$; $Leu_{1705}$ |
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| 24 | $Arg_{1699}$; $Leu_{1701}$; $Phe_{1704}$; $Met_{1775}$; $Leu_{1839}$ |
| 25 | $Glu_{1698}$; $Arg_{1699}$; $Leu_{1701}$; $Met_{1775}$; $Leu_{1839}$ |

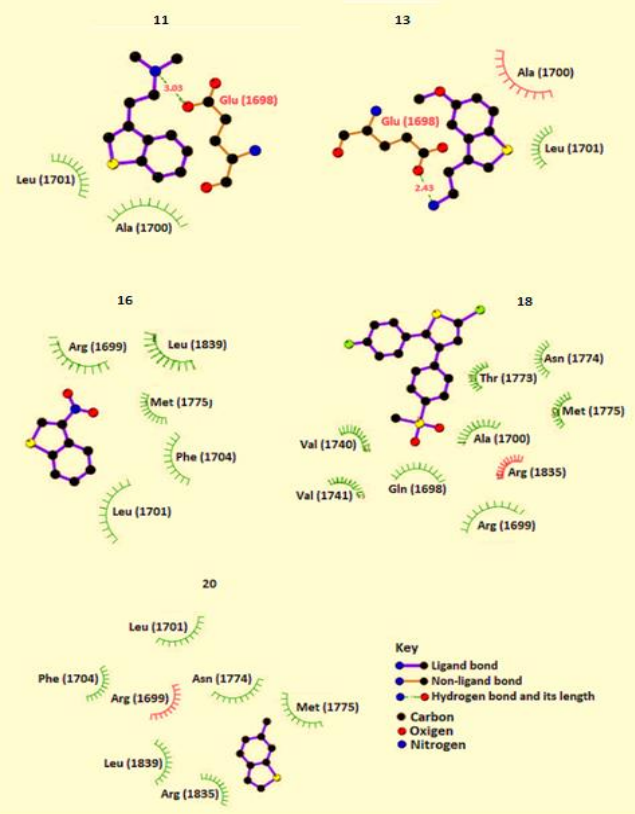


**Figure 2. Binding of thiophene analogs (11, 13, 16, 18, and 20) with the 3xpb protein surface. Visualized with GL mol viewer, DockingServer.**

## Thermodynamic parameters

There are theoretical studies that suggest that coupling of some drugs with several biomolecules may depend on different thermodynamic parameters, such as binding free energy, electrostatic energy, total intermolecular energy, Van Der Waals (vdW) + hydrogen bond (H bond) + desolvation energy.[29] For this reason, the study of these thermodynamic parameters involved in the interaction of thiophene and its analogs with the 3pxb protein surface was determined. The results **(Table 2)** displayed different energy levels for thiophene, and its analogs in comparison with niraparib. Furthermore, the inhibition constant (Ki) was higher for thiophene and its analogs 2-10, 12, 14, 15, 17, 19, and 21-25 compared to niraparib. However, Ki for thiophene analogs 11, 13, 16, 18, and 20 was very similar to the niraparib drug. These data suggest that thiophene derivatives 11, 13, 16, 18, and 20 could act as BRCA-1 inhibitory agents. However, it is important to mention that other types of biological experiments are required to verify this hypothesis.

**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)
F = Interact. Surface

## Pharmacokinetic evaluation

Several methods have been used to determine some pharmacokinetic parameters to evaluate the possible biological activity of different drugs.[30-33] For this reason, this research aimed to determine some pharmacokinetic parameters that could be involved in the administration of thiophene analogs 11, 13, 16, 18, 20, and nirapib using the SwissADME program **(Table 3)**. The results showed differences in gastrointestinal absorption degree and metabolism (which involves various types of cytochromes P450 enzymes) for thiophene 11, 13, 16, 18, and 20 compared to the niraparib drug. Possibly this process could be associated with the different chemical characteristics of each thiophene analog and differences in its lipophilicity degree.

**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 analysis

Some reports suggest that different thiophene derivatives may produce some toxicity degree using several biological models.[34-37] This research aimed to evaluate the possible toxicity produced by thiophene analogs (11, 13, 16, 18, and 20) using the GUSAR software.[28] The results suggest **(Table 4)** that thiophene derivative 18 possibly requires high doses to produce toxicity (LD50) via intraperitoneal, intravenous, oral, and subcutaneous compared to the niraparib drug. Besides, compound 16 requires a higher dose through the oral route compared to niraparib. All these data indicate that the toxicity degree would depend on the dose and administration route of each thiophene analog.

**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
SC - Subcutaneous route of administration

## Conclusion

In this study, the possible coupling of thiophene and its analogs with the 3pxb protein surface. The results indicate that thiophene derivatives 11, 13, 16, 18, and 20 may interact with some amino acid residues involved in the 3pxb protein surface. This data suggests that thiophene derivatives 11, 13, 16, 18, and 20 could act as BRCA-1 gene inhibitor agents; this phenomenon could be translated as a decrease in breast cancer cell growth. Analyzing these data these thiophene derivatives may be considered good pharmacological agents to treat breast cancer.

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## Conflict of interest

None.

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## Ethics statement

All procedures in this study were performed in accordance with protocols for Pharmacochemistry Laboratory of University Autonomous of Campeche.

## References

1. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with $^{18}$F-DCFPyL in prostate cancer patients (OSPREY). J Urol. 2021;206(1):52-61. doi:10.1097/JU.0000000000001698
2. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin. 2022;72(5):409-36. doi:10.3322/caac.21731
3. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/Black people 2022. CA Cancer J Clin. 2022;72(3):202-29. doi:10.3322/caac.21718
4. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer (Dove Med Press). 2019;11:151-64.
5. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023;401(10371):105-17. doi:10.1016/S0140-6736(22)02420-5
6. Loibl S, Jassem J, Sonnenblick A, Parlier D, Winer E, Bergh J, et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. Ann Oncol. 2022;33(9):986-7. doi:10.1016/j.annonc.2022.06.009
7. Royce M, Osgood CL, Amatya AK, Fiero MH, Chang CJG, Ricks TK, et al. FDA approval summary: Margetuximab plus chemotherapy for advanced or metastatic HER2-positive breast cancer. Clin Cancer Res. 2022;28(8):1487-92. doi:10.1158/1078-0432.CCR-21-3247
8. Yuan Y, Liu X, Cai Y, Li W. Lapatinib and lapatinib plus trastuzumab therapy versus trastuzumab therapy for HER2 positive breast cancer patients: An updated systematic review and meta-analysis. Syst Rev. 2022;11(1):264.
9. Ma CX, Luo J, Freedman RA, Pluard TJ, Nangia JR, Lu J, et al. The phase II MutHER study of neratinib alone and in combination with fulvestrant in HER2-mutated, non-amplified metastatic breast cancer. Clin Cancer Res. 2022;28(7):1258-67. doi:10.1158/1078-0432.CCR-21-3418
10. Curigliano G, Mueller V, Borges V, Hamilton E, Hurvitz S, Loi S, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): Final overall survival analysis. Ann Oncol. 2022;33(3):321-9. doi:10.1016/j.annonc.2021.12.005
11. Moreau-Bachelard C, Robert M, Gourmelon C, Bourbouloux E, Patsouris A, Frenel JS, et al. Evaluating everolimus for the treatment of breast cancer. Expert Opin Pharmacother. 2023;24(10):1105-11. doi:10.1080/14656566.2023.2214677
12. Batalini F, Xiong N, Tayob N, Polak M, Eismann J, Cantley L, et al. Phase 1b clinical trial with alpelisib plus olaparib for patients with advanced triple-negative breast cancer. Clin Cancer Res. 2022;28(8):1493-9. doi:10.1158/1078-0432.CCR-21-3045
13. Howell S, Casbard A, Carucci M, Ingarfield K, Butler R, Morgan S, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-

positive, HER2-negative breast cancer (FAKTION): Overall survival, updated progression-free survival, and expanded biomarker analysis from a randomized, phase 2 trial. Lancet Oncol. 2022;23(7):851-64. doi:10.1016/S1470-2045(22)00284-4
14. Geyer C, Garber J, Gelber R, Yothers G, Taboada M, Ross L, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol. 2022;33(12):1250-68. doi:10.1016/j.annonc. 2022.09.159
15. Jacobs AT, Martinez Castaneda-Cruz D, Rose MM, Connelly L. Targeted therapy for breast cancer: An overview of drug classes and outcomes. Biochem Pharmacol. 2022;204(3):115209. doi:10.1016/j.bcp.2022.115209
16. Jones P, Altamura S, Boueres J, Ferrigno F, Fonsi M, Giomini C, et al. Discovery of 2-{4-[(3 S)-piperidin-3-yl] phenyl}-2 H-indazole-7-carboxamide (MK-4827): a novel oral poly (ADP-ribose) polymerase (PARP) inhibitor efficacious in BRCA-1 and-2 mutant tumors. J Med Chem. 2009;52(22):7170-85.
17. Jerez Y, Márquez-Rodas I, Aparicio I, Alva M, Martín M, López-Tarruella S. Poly (ADP-ribose) polymerase inhibition in patients with breast cancer and BRCA 1 and 2 mutations. Drugs. 2020;80(2):131-46.
18. Lee A, Moon BI, Kim TH. *BRCA1*/*BRCA2* pathogenic variant breast cancer: Treatment and prevention strategies. Ann Lab Med. 2020;40(2):114-21. doi:10.3343/alm.2020.40.2.114
19. Jeffy BD, Schultz EU, Selmin O, Gudas JM, Bowden GT, Romagnolo D. Inhibition of BRCA-1 expression by benzo [a] pyrene and its diol epoxide. Mol Carcinog. 1999;26(2):100-18.
20. Chen X, Huan X, Liu Q, Wang Y, He Q, Tan C, et al. Design and synthesis of 2-(4,5,6,7-tetrahydrothienopyridin-2-yl)-benzoimidazole carboxamides as novel orally efficacious Poly(ADP-ribose) polymerase (PARP) inhibitors. Eur J Med Chem. 2018;145:389-403. doi:10.1016/j.ejmech.2018.01.018
21. Al-Owaidi MF, Mahdi MF. Synthesis and anti-breast cancer activity evaluation of the designed chlorobenzothiophene derivatives: Promising estrogen receptor alpha inhibitors. Egypt J Chem. 2023;66(10):431-41. doi:10.21608/EJCHEM.2023.153114.6633
22. Gomha SM, Riyadh SM, Huwaimel B, Zayed MEM, Abdellattif MH. Synthesis, molecular docking study, and cytotoxic activity against MCF cells of new thiazole-thiophene scaffolds. Molecules. 2022;27(14):4639. doi:10.3390/molecules27144639
23. Ahmed SA, Kamel MS, Aboelez MO, Ma X, Al-Karmalawy AA, Mousa SA, et al. Thieno [2, 3-b] thiophene derivatives as potential EGFRWT and EGFRT790M inhibitors with antioxidant activities: Microwave-assisted synthesis and quantitative in vitro and in silico studies. ACS Omega. 2022;7(49):45535-44. doi:10.1021/acsomega.2c06219
24. Son Y, Kim J, Kim Y, Chi SG, Kim T, Yu J. Discovery of dioxo-benzo [b] thiophene derivatives as potent YAP-TEAD interaction inhibitors for treating breast cancer. Bioorg Chem. 2023;131(6):106274. doi:10.1016/j.bioorg.2022.106274
25. Xu S, Luo L, Sun X, Yang Y, Guo Q, Jiang Z, et al. Design, synthesis and antitumor activity of novel thiophene- triazine derivatives bearing arylurea unit as potent PI3K/mTOR inhibitorss. Bioorg Med Chem. 2023;78:117133. doi:10.1016/j.bmc.2022.117133
26. Coquelle N, Green R, Glover JN. Impact of BRCA1 BRCT domain missense substitutions on phosphopeptide recognition. Biochemistry. 2011;50(21):4579-89. doi:10.1021/bi2003795
27. Figueroa-Valverde L, Diaz-Cedillo F, Nexticapa MR, Alvarez-Ramirez M, López-Ramos M, Melgarejo-Guttierrez M, et al. Biochemical interaction of twenty steroid derivatives with ribosomal protein kinase 4 S6 (RSK-4) surface using a theoretical model. Braz J Sci. 2024;3(2):66-81. doi:10.14295/bjs.v3i2.482
28. Lauro F, Francisco D, Ricardo G, Heidari A, Marcela Maria L. Design and synthesis of two Strychnidin-oxiran-naphthalenol derivatives and their theoretical evaluation as noradrenaline and serotonin reuptake inhibitors. Vietnam J Chem. 2022;60(2):245-56. doi:10.1002/vjch.202100128
29. Figueroa-Valverde L, Díaz-Cedillo F, Rosas-Nexticapa M, Alvarez-Ramirez M, Mateu-Armad M, López-Ramos M. Interaction of some amino-nitrile derivatives with vascular endothelial growth factor receptor 1 (VEGFR1) using a theoretical model. Drug Res. 2023;73(06):355-64. doi:10.1055/a-2062-3571
30. Vishal K, Singla C, Sharma A, Dhiman A. Prediction of environmental toxicity of active chemical constituents of ipomoea carnea through GUSAR software. Turk J Comput Math Educ. 2020;11(2):735-40.
31. Levitt DG. PKQuest: A general physiologically based pharmacokinetic model. Introduction and application to propranolol. BMC Clin Pharmacol. 2002;2(1):5. doi:10.1186/1472-6904-2-5
32. Ishaku SG, Bakare-Odunola MT, Musa A, Yakasai IA, Garba M, Adzu B. Effect of dihydro-artemisinin on the pharmacokinetics of gliclazide in diabetic subjects. Int J Biol Chem. 2020;14(6):2267-76. doi:10.4314/ijbcs.v14i6.27
33. 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.
34. Mohareb RM, Ibrahim RA. Design, cytotoxicity and toxicity of new thiophene and thieno [2, 3-b] pyridine derivatives. Med Chem Res. 2017;26(3):587-602.
35. Lisboa T, Silva D, Duarte S, Ferreira R, Andrade C, Lopes AL, et al. Toxicity and antitumor activity of a thiophene-acridine hybrid. Molecules. 2019;25(1):64. doi:10.3390/molecules25010064
36. Jaladanki C, Taxak N, Varikoti R, Bharatam P. Toxicity originating from thiophene-containing drugs: Exploring the mechanism using quantum chemical methods. Chem Res Toxicol. 2015;28(12):2364-76. doi:10.1021/acs.chemrestox.5b00364
37. Mosier PD, Jurs PC, Custer LL, Durham SK, Pearl GM. Predicting the genotoxicity of thiophene derivatives from molecular structure. Chem Res Toxicol. 2003;16(6):721-32. doi:10.1021/tx020104