Original Research Article

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Evaluation of the Anticancer Potentials of some Quercetin Derivatives - An *in Silico* Approach

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ABSTRACT

***Background*:** Quercetin has been reported to possess anticancer activities. This study was aimed at designing some derivatives of quercetin and evaluating their binding affinities to target proteins implicated in cancer.

***Methodology*:** Derivatives of quercetin were designed with ChemDraw. The targets: Phosphodiesterases (PDEs; 1XMU), Cyclooxygenase-1 (COX-1; 4O1Z); Cyclooxygenase-2 (COX-2; 4M11); Epidermal growth factor receptor (EGFR, 6DUK); α-glucosidase (5KZW); and TNF-α-inducing protein (TNFA, 3VNC) were downloaded from the Protein data bank. Ligands and targets were converted to pdbqt format using PyRx. Carboplatin, carmustine, dacarbazine, dexamethasone, doxorubicin, floxuridine, hydroxyurea, imatinib, lomustine, methotrexate, prednisone, valrubicin and vincristine were used as reference drugs. Molecular docking of the ligands with each of the target proteins was done using Autodock Vina. Discovery Studio was used to visualise ligand-protein binding interactions. Calculated molecular and pharmacokinetic properties were obtained from molinspiration and pKCM websites, respectively.

***Results*:** Ligand 1 (quercetin) had a binding energy of -9.5 kcal/mol. While ligands 10, 39, 34 and 38 had binding energy of -9.6. -9.7, -9.8 and -9.9 kcal/mol, respectively, on PDE. On COX-1 ligand 1 (Quercetin) had a binding energy of -9.8 kcal/mol while ligands 17 and 26 had better binding energy of -10.0 and -10.2 kcal/mol, respectively. On COX-2, the binding energy for ligands 1 (quercetin), 15 and 25 were -10.0, -10.4 and -10.5 kcal/mol, respectively. While binding energy for ligand 1 (quercetin) on EGFR was -8.8 kcal/mol those for ligands 3, 15 and 27 were -9.4 kcal/mol; ligands 37 and 39 were -9.7 kcal/mol. None of the ligands in this study had a better binding energy than quercetin (-7.4 kcal/mol) on TNF. Imatinib and valrubicin had a good binding affinity to all the protein targets.

***Conclusion*:** Some of the derivatives of quercetin (ligands) exhibited better binding affinities to the various cancer target proteins studied in this work. These derivatives have good anticancer potential.

Keywords: Quercetin, cancer, molecular docking, *in silico*

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled cell growth and proliferation that can invade and destroy healthy tissues in the body. It is a major public health concern globally and is responsible for millions of deaths each year [1, 2, 3]

Cancer arises from genetic mutations that disrupt the normal control mechanisms of cell growth and division. These mutations can be inherited or acquired, and they can affect various genes that regulate cell proliferation, differentiation,

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and apoptosis (programmed cell death). The accumulation of these mutations can lead to the formation of a tumour, which can be benign (non-cancerous) or malignant (cancerous) [4, 5, 6, 7].

Malignant tumours can invade nearby tissues and metastasize to other parts of the body, making them more difficult to treat. Cancer cells also have unique characteristics that distinguish them from normal cells, such as altered metabolism, immune evasion, and resistance to apoptosis. These characteristics make cancer cells a challenging target for anticancer drugs [5,7,8,9].

Anticancer drugs are an important part of cancer treatment, and they work by targeting and killing cancer cells while minimizing damage to healthy cells. In this essay, we will explore the biology of cancer, the mechanisms of action of anticancer drugs, and the challenges of developing effective and safe anticancer drugs. Anticancer drugs are a diverse group of compounds that can target different aspects of cancer biology, including DNA synthesis, cell division, and signalling pathways. They can be classified into several categories based on their mode of action, including cytotoxic agents, targeted therapies, and immunotherapies. There are numerous anticancer drugs used in the treatment of various types of cancer, and their effectiveness can vary depending on the cancer type, stage, and other factors. [1, 2, 10, 11, 12]

Quercetin is a flavonoid, a type of plant pigment with potent antioxidant and anti-inflammatory properties. Several studies have reported on its potential anticancer properties, including its ability to inhibit cancer cell growth and induce apoptosis (programmed cell death). Moreover, researchers have studied the structure-activity relationships (SARs) of quercetin and its derivatives to better understand their biological activities and develop more potent anticancer agents [13, 14, 15]. This study was undertaken to evaluate the in silico anticancer activity of some derivatives of quercetin.

METHODOLOGY

The method of Eseyin et al (2022) [16] was followed. Derivatives of quercetin were designed with ChemDraw Pro 12.0 (CambridgeSoft Corporation, USA) and saved in SDF format. The target proteins - Phosphodiesterases (PDEs; 1XMU), Cyclooxygenase-1 (COX-1; 4O1Z); Cyclooxygenase-2 (COX-2; 4M11); Epidermal growth factor receptor (EGFR, 6DUK); α-glucosidase (5KZW); and TNF-α-inducing protein (TNFA, 3VNC) were downloaded in PDB format from the Protein data bank (http://www.rcsb.org/pdb/home/home.do).
Ligands and targets were converted to pdbqt format using PyRx (https://pyrx.sourceforge.io/). Molecular docking of the ligands with each of the target proteins was done using Autodock Vina (http://vina.scripps.edu/), to obtain their respective binding affinity. The identity of the ligands studied in this work was earlier reported [16]. The grid box parameters are shown in Table 1.
Discovery Studio (Dassault Systèmes), and Ligplot (https://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/) were used to analyse ligand-protein binding interactions. Calculated molecular properties were obtained from the molinspiration website (https://www.molinspiration.com/cgi-bin/properties), while pharmacokinetic properties from pKCMwebsite (http://biosig.unimelb.edu.au/pkcsm/prediction).

Table 1: Grid box parameters

S/N	Target	center_x	center_y	center_z	size_x	size_y	size_z
1	EGFR	37.6235	93.5838	-61.1114	31.7551	35.5583	30.9252
2	COX1	200.4908	99.1732	40.4314	80.8286	80.0598	80.9848
3	COX2	9.2499	37.9687	34.3301	63.9623	76.2313	59.3606
4	PDE	2.1790	2.9501	49.0644	44.1863	42.9283	44.9889
5	TNF	33.1364	1.2824	16.0331	32.1929	49.9880	51.1111

EGFR- Epidermal growth factor receptor. COX1- Cyclooxygenase-1. COX2 - Cyclooxygenase-2. PDE - Phosphodiesterases. TNF - TNF-α-inducing protein

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RESULTS

Table 2: Binding affinity (kcal/mol) of the ligands and reference compounds obtained from Autodock vina

Ligand	EGFR	COX-1	COX-2	TNF	PDE
1	-8.8	9.8	-10	-7.4	-9.5
2	-8.8	7.9	-8.6	-7.1	-9.0
3	-9.4	8.9	-9.7	-7.1	-9.2
4	-8.4	8.8	-10.0	-7.2	-9.2
5	-8.4	8.8	-9.6	-6.9	-9.2
6	-8.8	9.1	-10.0	-7.5	-9.5
7	-8.8	9.7	-9.8	-7.3	-9.4
8	-8.7	9.2	-9.9	-7.3	-9.4
9	-8.6	9.1	-9.7	-7.1	-9.3
10	-8.8	9.3	-9.4	-7.2	-9.6
11	-8.5	9.7	-9.6	-7.2	-9.4
12	-8.2	8.4	-9.1	-6.7	-9.3
13	-8.1	8.2	-8.9	-6.6	-8.9
14	-8.6	9.6	-9.6	-7.2	9.0
15	-9.4	9.0	-10.4	-7.2	-9.2
16	-8.9	8.9	-10.1	-7.3	-9.6
17	-8.4	10.0	-9.3	-6.6	-9.5
18	-8.8	8.7	-10.1	-6.7	-9.5
19	-8.8	8.5	-10.1	-6.7	-9.2
20	-8.8	9.3	-10	-7.0	-9.1
21	--8.9	9.5	-9.7	-6.7	-9.0
22	-8.9	9.6	-9.5	-6.9	-9.1
23	-8.6	8.5	-10.3	-6.9	-9.1
24	-8.4	8.3	-10.0	-6.9	-9.3
25	-8.6	8.7	-10.5	-7.0	-8.6
26	-9.0	10.2	-8.8	-7.1	-8.8
27	-9.4	8.3	-8.3	-6.8	-8.6
28	-8.6	8.8	-9.8	-7.3	-9.4
29	-8.4	7.7	-8.7	-6.6	-9.1

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30	-8.5	8.4	-10.2	-7.0	-9.4
31	-9.2	8.9	-8.6	-7.2	-8.8
32	-8.5	8.7	-8.7	-6.3	-8.1
33	-9.0	9.8	-9.7	-7.0	-9.6
34	-9.2	6.7	-9.5	-7.3	-9.8
35	-7.8	7.7	-9.8	-6.9	-8.7
36	-7.7	7.5	-9.7	-6.9	-9.0
37	-9.7	7.8	-9.2	-7.3	-8.8
38	-9.2	7.8	-9.8	-6.8	-9.9
39	-9.7	7.6	-8.7	-7.4	-9.7
40	-7.8	9.4	-9.5	-6.3	-8.4
41	-8.1	7.9	-8.4	-6.5	-8.5
42	-7.9	9.8	-9.4	-6.3	-9.0
43	-7.7	8.1	-9.7	-6.0	-9.0
44	-8.9	7.5	-9.3	-6.1	-8.8
45	-8.9	8.1	-9.1	-6.3	-8.3
46	-7.8	7.8	-9.3	-6.3	-8.8
47	-8.8	9.9	-8.3	-6.9	-8.8
48	-8.7	7.1	-7.0	-5.6	-8.8
49	-8.1	6.5	-8.0	-6.7	-8.7
50	-8.3	9.6	-9.5	-7.1	-9.0
51	-8.2	7.8	-8.1	-6.6	-8.6
52	-8.1	9.7	-7.8	-6.3	-8.6
53	-7.7	9.1	-9.6	-6.0	-8.3
54	-8.1	7.5	-9.2	-6.6	-8.6
55	-8.1	9.0	-9.9	-6.8	-9.0
56	-8.9	7.1	-8.2	-5.4	-8.8
57	-9.6	7.2	-8.7	-5.2	-8.9
58	-8.2	7.9	-8.3	-6.6	-8.8
59	-8.7	7.4	-8.0	-5.7	-8.7
60	-9.3	6.4	-8.6	-6.8	-8.0
61	-8.7	6.2	-8.3	-6.8	-7.4

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62	-8.6	9.0	-8.2	-6.2	-9.3
63	-8.0	8.3	-9.5	-6..5	-8.7
64	-9.0	5.1	-8.3	-6.4	-7.7
65	-8.0	9.1	-8.1	-6.6	-9.2
66	-8.4	9.3	-9.0	-6.4	-8.9
Carboplatin	-5.3	4.3	-5.3	-4.5	-5.1
Carmustine	-5.0	4.2	-5.1	-4.4	-4.8
Dacarbazine	-5.8	5.7	-6.5	-5.1	-5.9
Dexamethasone	-7.7	7.4	-7.7	-6.8	-9.7
Doxorubicin	-9.7	9.5	-9.1	-7.3	-9.2
Floxuridinie	-6.6	5.0	-7.7	-5.8	-7.2
Hydroxyurea	-4.5	3.4	-4.5	-3.7	-4.2
Imatinib	-9.8	11.1	-10.8	-8.5	-11.0
Lomustine	-5.8	5.7	-6.2	-4.9	-5.5
Methotrexate	-9.7	7.3	-8.3	-7.7	-9.0
Prednisone	-8.4	6.8	-7.8	-6.5	-9.4
Valrubicin	-10.3	10.0	-9.9	-8.5	-9.4
Vincristine	-8.0	8.2	-9.4	-8.2	-8.5

EGFR- Epidermal growth factor receptor. COX1- Cyclooxygenase-1. COX2 - Cyclooxygenase-2. PDE - Phosphodiesterases. TNF - TNF-α-inducing protein

The results of the biological and pharmacokinetic properties of the ligands are as earlier reported [16]

The structures of the various target proteins and their interactions with quercetin and some ligands are shown in figures 1-5.

Phosphodiesterases (PDEs; 1XMU)

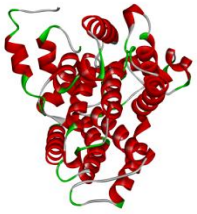

Figure 1a: Phosphodiesterases (PDEs; 1XMU)

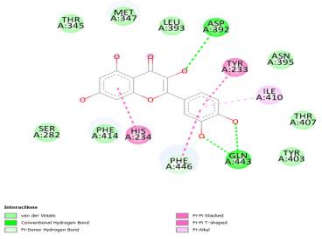

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Figure 1b: PDE-ligand 1(Quercetin) interactions

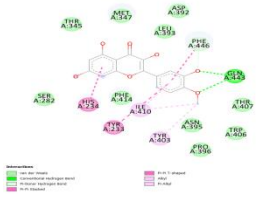

Figure 1c: PDE-ligand 10 interactions

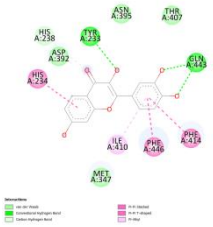

Figure 1d: PDE-ligand 35 interactions

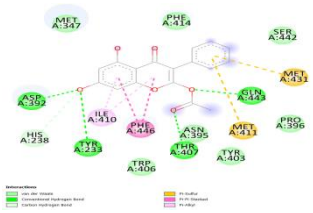

Figure 1e: PDE - ligand 36 interactions

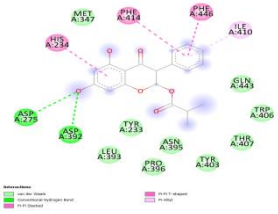

Figure 1f: PDE - ligand 40 interactions

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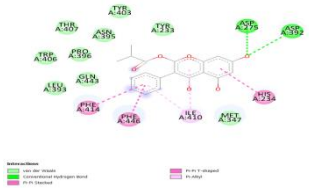

Figure 1g: PDE - ligand 41 interactions

Cyclooxygenase-1 (COX-1; 4O1Z)

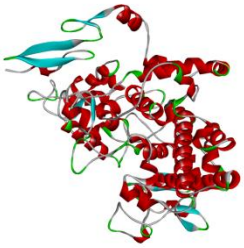

Figure 2a: Cyclooxygenase-1 (COX-1; 4O1Z)

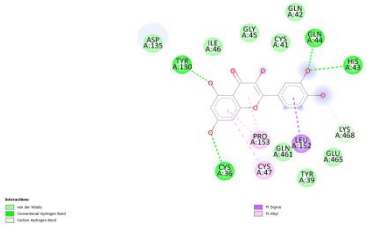

Figure 2b: COX14o1z-ligand 1(Quercetin) interactions

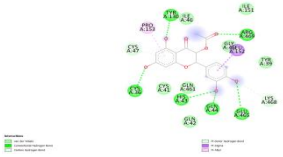

Figure 2c: COX14o1z-ligand 17 interactions

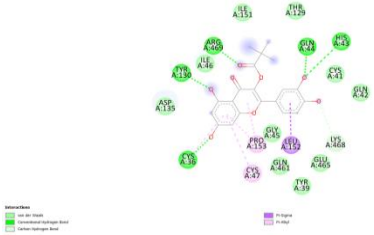

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Figure 2d: COX14o1z-ligand 26 interactions

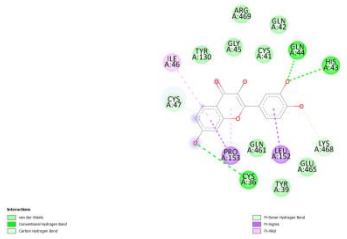

Figure 2e: COX14o1z-ligand 33 interaction

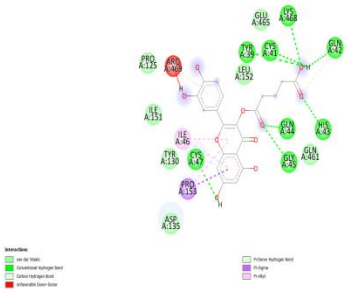

Figure 2f: COX14o1z-ligand glutaric interactions Cyclooxygenase-2 (COX-2; 4M11)

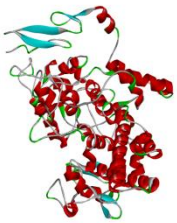

Figure 3a: Cyclooxygenase-2 (COX-2; 4M11)

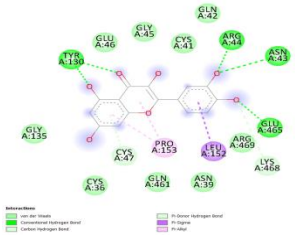

Figure 3b: Cox2-ligand 1(Quercetin) interactions

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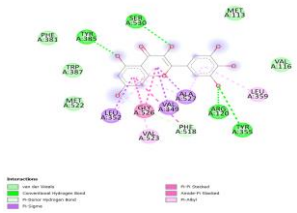

Figure 3c: COX2-ligand 16

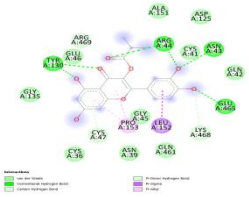

Figure 3d: COX2-ligand 26

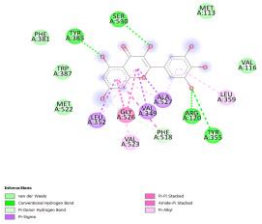

Figure 3e: COX2-ligand 39

Epidermal growth factor receptor (EGFR, 6DUK)

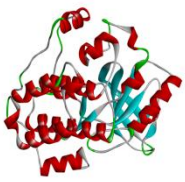

Figure 4a: Epidermal growth factor receptor (EGFR, 6DUK)

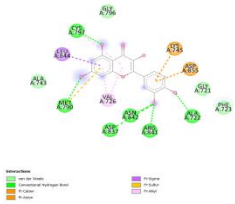

Figure 4b: EGFR-ligand 1(quercetin) interactions

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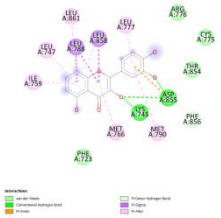

Figure 4c: EGFR-ligand 3

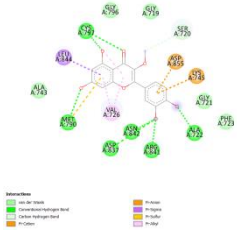

Figure 4d: EGFR-ligand 15

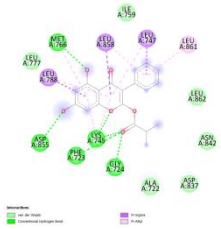

Figure 4e: EGFR-ligand 39 TNF-α-inducing protein (TNFA, 3VNC)

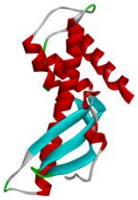

Figure 5a: TNF-α-inducing protein (TNFA, 3VNC)

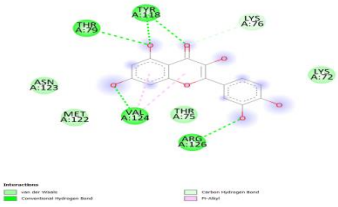

Figure 5b: TNF-ligand 1(Quercetin) interactions

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Table 3: Protein amino acid residues involved in binding interactions with Quercetin

Target protein	H-bonding	Pi anion/Pi sigma	Pi Sulfur	Pi-pi stacked	Pi alkyl
EGFR	Met790, Cys797, Ala722, Arg841, Asn842, Asp837	Lys745, Asp855/Leu844	Met790		Val726
COX1	Cys36, Tyr130, His43, Gln44	Leu152		Lys468	Cys47, Pro153
COX2	Tyr130, Arg44, Asn43, Asn44, Gln465, Lys468				Leu152
PDE	Gln443, Asp392, Phe446			His234, Tyr233, Phe446	Ile410
TNF	Thr79, Tyr118, Val124, Arg126, Lys76				Val124

DISCUSSION

Phosphodiesterases (PDEs)

Ligand 1 (quercetin) had a binding energy of -9.5 kcal/mol. While ligands 10, 39, 34 and 38 had a binding energy of -9.6. -9.7, -9.8 and -9.9 kcal/mol, respectively. In addition to hydrogen bonding between Gln 443 and Oxygen at C3' and C4' which is common to all, Ligand 38 which had the best binding energy, also had hydrogen bonding between Thr407 and the side chain carbonyl oxygen, Tyr233 and C7 oxygen, Asp392 and C7 oxygen, and His238 and C7 oxygen. Furthermore, ligand 38 had a pi - sulfur bond between ring C and Met411 and 431. These additional interactions seemed to enhance the binding energies of ligands.

Phosphodiesterases (PDEs) comprise a large family of enzymes that catalyze the hydrolysis of cAMP or cGMP and are implicated in various diseases. These cocrystal structures reveal a common scheme of inhibitor binding to the PDEs: (i) a hydrophobic clamp formed by highly conserved hydrophobic residues that sandwich the inhibitor in the active site; (ii) hydrogen bonding to an invariant glutamine that controls the orientation of inhibitor binding. A scaffold can be readily identified for any given inhibitor based on the formation of these two types of conserved interactions. The interactions in the study between ligands and amino acid residues is in tandem with this report.

PDEs play important roles in cancer cell proliferation, survival, and metastasis. For example, PDE4, which is upregulated in various types of cancer, has been linked to tumour growth and resistance to chemotherapy [17]. Similarly, PDE5 and PDE6, which are downregulated in certain types of cancer, have been associated with tumour progression and poor prognosis [18, 19]. PDE inhibitors have been developed as potential anti-cancer agents, based on their ability to increase intracellular levels of cyclic nucleotides, which can inhibit tumour growth and promote apoptosis in cancer cells.

Among the reference compounds only dexamethasone (-9.7 kcal/mol) and imatinib(-11.0 kcal/mol) had better binding energies than quercetin. The binding energy of ligands 34 (-9.8) and 38 (-9.9) are in between the two. These two ligands may be useful as antitumour agents.

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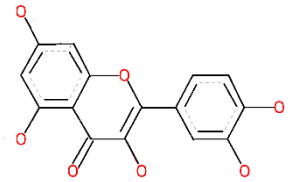
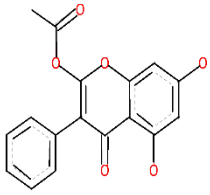
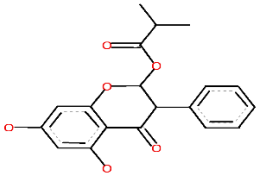


Ligand 1 (Quercetin)



Ligand 34



Ligand 38

Cyclooxygenase-1

Ligand 1 (Quercetin) had a binding energy of -9.8 kcal/mol. Ligands 17 and 26 had better binding energy of -10.0, and -10.2 kcal/mol. They all shared the same ligand-protein interactions I.e hydrogen bonding: Cys36 - C7 oxygen, His 43-C3' oxygen, Gln44-C' oxygen, and Tyr130-C5 oxygen. However, ligands 17 and 26 had additional hydrogen bonding between Arg469 and Aryl Carbonyl oxygen. The carbonyl group of the side chain, therefore, conferred a better binding property on the two ligands than on quercetin. Again, among the reference compounds, the binding energies of Valrubicin (-10.2 kcal/mol) and Imatinib(-11.1 kcal/mol) were the best. The binding energy of ligand 26 was the same as Valrubicin and lower than that of Imatinib.

Cyclooxygenase-1 (COX-1) is an enzyme involved in the synthesis of prostaglandins, which are important signalling molecules involved in various physiological processes, including inflammation, pain, and blood clotting. Dysregulation of COX-1 expression and activity has been implicated in various diseases, including cancer. The role of COX-1 in cancer may be related to its ability to modulate the tumour microenvironment. For example, COX-1-derived prostaglandins can promote angiogenesis (the formation of new blood vessels), which is important for tumour growth and metastasis. In addition, COX-1 can modulate the immune response in the tumour microenvironment, which can affect tumour growth and metastasis [20].

The use of COX-1 inhibitors as cancer therapies have been investigated in preclinical and clinical studies, with mixed results. While some studies have suggested that COX-1 inhibitors may have anti-tumour effects, others have found no significant benefit [21].

The results of this study show that ligands 17 and 26 which had better binding energies than Quercetin could be useful as anticancer agents by serving as COX-1 inhibitors.

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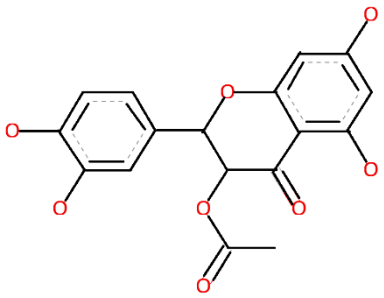
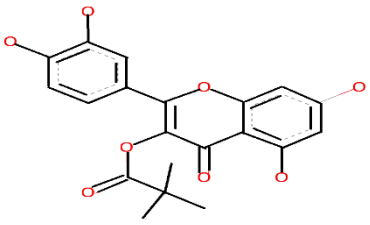


Ligand 17



Ligand 26

Cyclooxygenase-2

The binding energy for ligands 1 (quercetin), 15 and 25 were -10.0, -10.4 and -10.5 kcal/mol, respectively. Quercetin and ligand 25 had the same Hydrogen bonding interactions between the ligands and amino acid residues in the target protein. But in ligand 25 there were pi-alkyl interactions between Pro153 and rings A and B; and pi-sigma interactions between Leu152 and ring C. These additional interactions gave ligand 25 a better binding property than quercetin.

COX-2 is induced in response to inflammatory stimuli and is responsible for the production of prostaglandins that mediate inflammation. Dysregulation of COX-2 expression and activity has been implicated in various diseases, including cancer.

In cancer, the role of COX-2 is complex and context-dependent. COX-2 expression is upregulated in many types of cancer, including breast, colorectal, lung, and prostate cancer (Wang D, Dubois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010;10(3):181-193.). COX-2 has been shown to promote tumour growth, survival, angiogenesis, and metastasis, as well as to inhibit immune responses to tumours [22, 23]. Inhibition of COX-2 has been shown to have anti-tumour effects in preclinical and clinical studies, suggesting that COX-2 may be a promising target for cancer therapy [24].

The mechanisms by which COX-2 promotes cancer are multifaceted. COX-2-derived prostaglandins can promote cell proliferation, survival, and angiogenesis, as well as inhibit apoptosis (programmed cell death) [25]. In addition, COX-2 can modulate the immune response in the tumour microenvironment, leading to immune evasion by cancer cells [21]. COX-2 has also been shown to promote cancer stem cell self-renewal and maintenance, which may contribute to tumour progression and therapy resistance [26].

Ligands 15(-10.4 kcal/mol) and 25 (-10.5 kcal/mol) had better binding properties than quercetin (10.0 kcal/mol) and valrubicin (-9.9 kcal/mol). Their binding property was almost at par with that of imatinib (-10.8 kcal/mol). These results show that ligands 15 and 25 possess COX-2 inhibitory activity which makes them potential anticancer agents.

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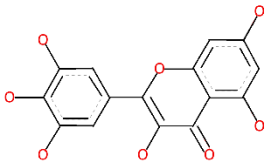
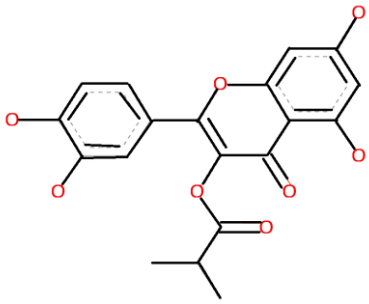


Ligand 15



Ligand 25

Epidermal growth factor receptor (EGFR)

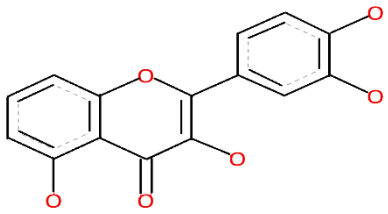
While binding energy for ligand 1 (quercetin) was -8.8 kcal/mol those for ligands 3, 15 and 27 were -9.4 kcal/mol; ligands 37 and 39 were -9.7 kcal/mol. Imatinib and valrubicin had -9.8 and -10.3 kcal/mol. These results showed that ligands 3, 15, 27, 37 and 39 had better binding properties than quercetin. The binding energy of ligands 37 and 39 were comparable to that of imatinib and a little lower than that of valrubicin.

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase that plays a critical role in cell proliferation, differentiation, and survival. Dysregulation of EGFR signalling has been implicated in various types of cancer, including lung, breast, and colon cancer.

Targeted therapies that inhibit EGFR signalling have been developed as cancer treatments, particularly for lung cancer. EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, are effective in treating non-small cell lung cancer (NSCLC) with EGFR mutations [27]. However, resistance to EGFR TKIs can develop over time, leading to disease progression [28].

In addition, EGFR is a potential target for cancer immunotherapy. EGFR is expressed on the surface of many cancer cells, and targeting EGFR with immune checkpoint inhibitors, such as pembrolizumab, has shown promise in the treatment of certain types of cancer, particularly NSCLC [29].

The results obtained from this study showed that ligands 3, 15, 27, 37 and 39 could serve as anticancer agents through their inhibitory activity of EGFR.



Ligand 3

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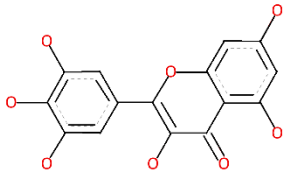
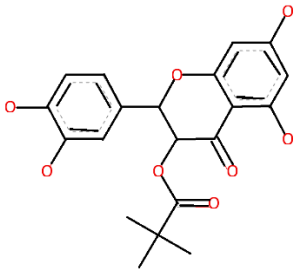
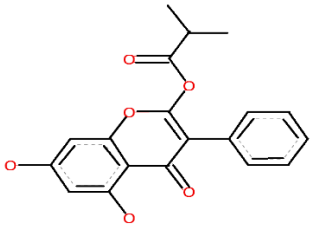


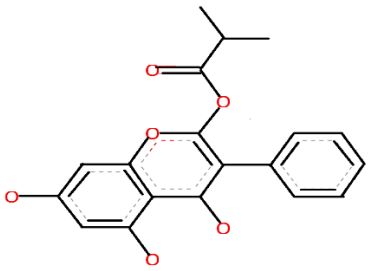
Ligand 15



Ligand 27



Ligand 37



Ligand 39

Tipα (TNF-α-inducing protein)

Tipα (TNF-α-inducing protein) is a member of the TNF-α family of cytokines that are produced by various cell types, including cancer cells. Tipα has been shown to have pro-tumorigenic effects and is involved in the regulation of cell growth, survival, and invasion in various types of cancer.

None of the ligands in this study had better binding energy than quercetin (-7.4). Consequently, none of them is a potential TNF inhibitor.

Reference Drugs

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The reference drugs used in this study are carboplatin, carmustine, dacarbazine, dexamethasone, doxorubicin, floxuridine, hydroxyurea, imatinib, lomustine, methotrexate, prednisone, valrubicin, vincristine. Imatinib had the best binding affinity towards all the target proteins. Valrubicin was next to imatinib.

Imatinib is a tyrosine kinase inhibitor used to treat several leukaemias, myelodysplastic/myeloproliferative disease, systemic mastocytosis, hypereosinophilic syndrome, dermatofibrosarcoma protuberans, and gastrointestinal stromal tumours. It is a small molecule kinase inhibitor that revolutionized the treatment of cancer, particularly chronic myeloid leukaemia, in 2001. It was deemed a "miracle drug" due to its clinical success. The discovery of imatinib also established a new group of therapy called "targeted therapy", since treatment can be tailored specifically to the unique cancer genetics of each patient (https://go.drugbank.com/drugs/DB00619).

Valrubicin is a semisynthetic analogue of doxorubicin an anthracycline that affects a variety of interrelated biological functions, most of which involve nucleic acid metabolism. It readily penetrates cells, where after DNA intercalation, it inhibits the incorporation of nucleosides into nucleic acids, causes extensive chromosomal damage, and arrests the cell cycle in G2. Although valrubicin does not bind strongly to DNA, a principal mechanism of its action, mediated by valrubicin metabolites, is interference with the normal DNA breaking-resealing action of DNA topoisomerase II (https://go.drugbank.com/drugs/DB00385).

The binding properties of imatinib and valrubicin EGFR, COX-1, COX-2, PDE and TNF proteins as shown in this study show their good potential in the treatment of cancers through diverse mechanisms of action.

Pharmacokinetics and biological activities of ligands

The results of the calculated molecular and pharmacokinetic properties of the ligands were obtained from molinspiration and pKCM websites and were earlier reported [16].

CONCLUSION

Some of the derivatives of quercetin (ligands) exhibited better binding affinities to the various cancer target proteins studied in this work. These derivatives have good anticancer potential.

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