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Synthesis and Anticancer Activity of Benzimidazole and Benzothiazole Derivatives Bearing Furan Moiety by CAN as a Catalyst Under Ultrasonic Irradiation and Molecular Docking Studies

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A practical method for the synthesis of 2-(5-arylfuran-2-yl)-1*H*-benzo[d]imidazole and 2-(5-arylfuran-2-yl)benzothiazole using cerium(IV) ammonium nitrate (CAN) as an inexpensive and readily available catalyst, under ultrasonic conditions is described. With the help of molecular docking studies, the anticancer properties of these compounds were studied and investigated for the first time. The docking study results revealed that the synthesized compounds significantly interacted with the target protein 5WS1. The synthesized compound 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole achieved the highest docking score. Finally, the MTT assay was conducted on the best compound identified through molecular docking, revealing an IC50 value of 44.5 µg/mL. The results showed that the benzimidazole derivatives bearing furan are useful as a template for the future design of potent inhibitors against breast cancer cell lines (MCF7).

1. Introduction

Cancer remains a formidable challenge in global healthcare and is a leading cause of mortality worldwide.[1] Breast cancer is the most common type of cancer among women, accounting for about 18% of all female cancer cases, with more than half a million new cases diagnosed globally each year.[2–4] Breast cancer is targeted by a new class of drugs known as poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors. PARP-1 is a nuclear enzyme crucial in repairing breaks in single-stranded DNA.[5–7]

Due to their unique properties, benzimidazole and its derivatives have captured attention for many years.[8] Benzothiazole (BTA) is a type of fused benzo heterocyclic compound found in numerous naturally occurring substances, playing a key role in their medicinal and pharmaceutical uses.[9–11] Exploring biological activity and developing pharmaceuticals rely on the investigation of N-containing heterocyclic compounds.[12–15] Compounds containing benzimidazole and benzothiazole moieties display a wide array of biological activities, such as antimicrobial, antifungal, anticancer, antihistaminic, antihelminthic, anti-inflammatory, antihypertensive, and anti-HIV effects. Some of the medicinal compounds featuring benzimidazole and benzothiazole derivatives with anticancer properties are detailed in Scheme 1.[16–19]

Cerium(IV) ammonium nitrate (CAN) is a homogeneous catalyst.[20–24] It is distinguished among lanthanide reagents as a leading one-electron oxidant, extensively applied in various oxidative transformations within organic chemistry.[24–29] Recent advancements have developed protocols that use CAN for achieving mild reaction conditions, swift conversions, and efficient clean-up processes, establishing it as an essential tool for environmentally conscious and safer chemical methodologies. Additionally, CAN catalyzes a range of organic transformations, leveraging both its Lewis acidic properties and electron transfer capabilities.[30–35] Molecular docking has emerged as a crucial tool in in-silico drug design in recent years. This method focuses on predicting the atomic-level interactions between a protein and a small molecule.[36–39]

Recently, Sharghi et al.[9] introduced a method for synthesizing novel 2-(5-arylfuran-2-yl)-1*H*-benzo[d]imidazole and 2-(5-arylfuran-2-yl)benzothiazole utilizing Cu(II) complex nanoparticles supported on silica. However, this approach has several drawbacks, including the use of costly reagents, prolonged reaction times, and the need for silica gel column chromatography for purification. Furthermore, the biological activities of the synthesized compounds were not explored. Therefore, in this research, we synthesized 2-(5-arylfuran-2-yl)-1*H*-benzo[d]imidazole and 2-(5-arylfuran-2-yl) benzothiazole in the presence of cerium(IV) ammonium nitrate under ultrasonic conditions. We performed molecular docking studies on these compounds using Schrödinger software to evaluate their binding energy and interactions with the target protein PARP-1 (PDB ID: 5WS1). In addition, the cytotoxicity of compound 3f was assessed on a breast cancer cell line using the MTT assay.

The impact of various solvents was investigated to determine the optimal reaction conditions. As indicated in Table 1, protic solvents exhibited superior performance, with ethanol (EtOH) showing particularly promising results in terms of both yield and reaction time. When CAN was utilized as the catalyst in EtOH, the

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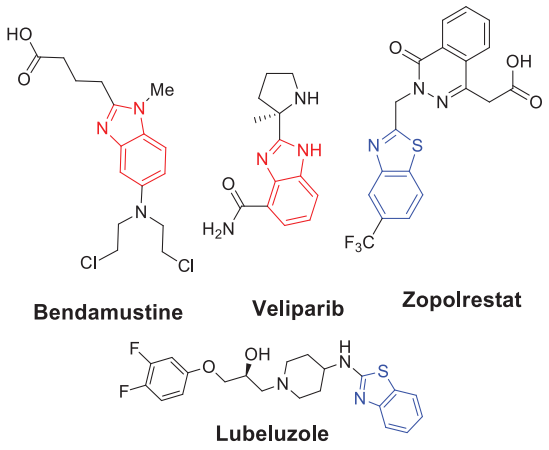


Scheme 1. Relevant anticancer compounds containing benzimidazole and benzothiazole.

Table 1. The effects of the solvent on the synthesis of 2-(5-(4-chlorophenyl) furan-2-yl)-1*H*-benzo[d]imidazole.[a)]

Entry	Solvent	Catalyst	Time (min)	Yield[b)]%
1	H_2O	CAN	10	45
2	EtOH/H_2O	CAN	10	64
3	THF	CAN	10	–
4	CH_3CN	CNA	10	39
5	MeOH	CAN	10	82
6	EtOH	CAN	10	90

[a)] Reaction conditions: *O*-phenylenediamine (1.0 mmol) and 5-(4-chlorophenyl) furan-2-carbaldehyde (1.0 mmol) in the presence of CAN (0.05 mol %) under ultrasound irradiation at 50 °C.
[b)] Isolated yield.

product obtained an excellent yield within a remarkably short period (Table 1, entry 7).

Comparison with various catalysts from previous studies, as depicted in Table 2, highlighted CAN's efficiency, especially when employed under ultrasonic conditions, yielding the desired derivative in just 10 min with a 90% yield (Table 2, entry 2).

2. Results and Discussion

2.1. Comparison of the Efficiency of Solvent, Amount of CAN, and Other Catalysts on the Synthesis of 2-(5-(4-Chlorophenyl) furan-2-yl)-1*H*-benzo[d]imidazole

The catalytic efficacy of CAN was evaluated in synthesizing benzimidazole and benzothiazole derivatives. A range of experiments with varying parameters like reaction conditions and temperature were conducted. The base reaction involved *o*-phenylenediamine 1a (1.0 mmol) and 5-(4-chlorophenyl) furan-2-carbaldehyde 2a (1.0 mmol) to produce 2-(5-(4-chlorophenyl) furan-2-yl)-1*H*-benzo[d]imidazole 3a (refer to Table 3). Initially, the reaction was performed without any catalyst, yielding only 20% of the product under catalyst-free conditions (Table 3, entry 1). Subsequently, the reaction was tested with 0.02 mol% CAN in an ethanol solvent, resulting in a 45% yield after 20 min (Table 3, entry 2). Increasing the catalyst to 0.05 mol% significantly boosted the yield (Table 3, entry 3). Further increase in catalyst concentration, however, did not lead to any additional gains in efficiency (Table 3, entry 4).

Product efficiency was evaluated using different methodologies, including thermal conditions and ultrasonic conditions. Reflux in ethanol without a catalyst resulted in a 10% efficiency (Table 4, entry 1), while ultrasonic conditions without a catalyst yielded a 20% reaction efficiency (Table 4, entry 2). The most optimal results were achieved under ultrasonic conditions with the CAN catalyst in just 10 min (Table 4, entry 3). Following the optimization of these conditions, a series of 2-(5-substituted phenylfuran-2-yl)-1*H*-benzo[d]imidazole and benzothiazole derivatives were synthesized. This involved the reaction of heterocyclic aromatic aldehydes with o-phenylenediamines or 2-aminothiophenol in the presence of 0.05 mol% CAN as a homogeneous catalyst, leading to the desired products. As illustrated in Table 5, various heterocyclic aromatic aldehydes bearing substituents such as Cl, Br, and OMe reacted with *o*-phenylenediamine, yielding the targeted benzimidazole derivatives in good to excellent yields. Furthermore, *o*-phenylenediamines containing substituents like Cl and Me were reacted with different heterocyclic aromatic aldehydes, resulting in corresponding products with good yields. The reaction conducted under ultrasonic conditions in ethanol solvent proved to be the most effective method, achieving a 90% efficiency for synthesizing 2-(5-(4-chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole derivatives.

A plausible mechanism as supported by the literature[35] has been reported (Scheme 2). First, 5-(4-chlorophenyl) furan-2-carbaldehyde (I) was activated using CAN. Next, *o*-phenylenediamine (II) attacks the carbonyl group, which, after the elimination of H_2O, leads to the formation of intermediate (III). Subsequently, intermediate (IV) is generated via intramolecular cyclization. Finally, the product is produced through the oxidative dehydrogenation of intermediate (IV).

2.2. Molecular Docking Calculations of Synthesized Benzimidazole and Benzothiazole Derivatives

The results of the molecular docking calculations for the synthesized compounds are shown in Table 6. The docking scores of all synthesized molecules are presented in Table 7. All derivatives except 3o, 3n, 3q, 3m, and 3p have better docking scores than the two standard drugs, namely Olaparib and Veliparib.

The docking energy measures the strength of the interaction between the ligand and the receptor (PDB ID:5WS1). The analysis of these docking results, according to Lee Pinsky's rules, is illustrated below (Figure 1).

In studying kinetic effects with the help of computer software, which is one of the ways to analyze kinetic parameters, ADME (absorption, distribution, metabolism, and excretion) is examined. This evaluation helps determine whether compounds exhibit drug-like properties. For instance, one parameter mea-

Table 2. Reported catalytic system for the formation of benzimidazole derivatives.

Entry	Catalyst	Time (min)	Method	Yield[a] (%)	Ref.
1	–	180	Reflux	45	This work
2	CAN	10	Ultrasound	90	This work
3	CAN-PEG	120	Reflux	98	[35]
4	H_3PO_4	15	Reflux	90	[40]
5	$Ce(NO_3)_3.6H_2O$	90	Reflux	98	[41]
6	Schiff-base-Cu(II)@SiO_2	120	r.t	90	[9]
7	Schiff-base-Cu(II)	120	r.t	88	[9]

[a] Isolated yield.

Table 3. Optimization of catalyst amount for the formation of 2-(5-(4-chlorophenyl) furan-2-yl)-1*H*-benzo[d]imidazole.[a]

Entry	Solvent	Amount of Catalyst (mol %)	Time (min)	Yield[b] %	Method
1	EtOH	0	10	20	Ultrasound
2	EtOH	0.02	10	45	Ultrasound
3	EtOH	0.05	10	90	Ultrasound
4	EtOH	0.1	10	90	Ultrasound

[a] Reaction conditions: *O*-phenylenediamine (1.0 mmol), 5-(4-chlorophenyl) furan-2-carbaldehyde (1.0 mmol), and CAN catalyst were added to EtOH as the solvent (5 mL) under ultrasound irradiation.
[b] Isolated yield.

Table 4. Optimization of reaction condition for the formation of 2-(5-(4-chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole.[a]

Entry	Catalyst	Time (min)	Method	Yield[b] (%)
1	–	10	Reflux (78 °C)	10
2	–	10	Ultrasound (50 °C)	20
3	CAN	10	Ultrasound (50 °C)	90
4	CAN	10	30 °C	45
5	CAN	10	35 °C	48
6	CAN	10	40 °C	50
7	CAN	10	45 °C	55
8	CAN	10	50 °C	60
9	CAN	10	Reflux (78 °C)	84

[a] Reaction conditions: *O*-phenylenediamine (1.0 mmol), 5-(4-chlorophenyl) furan-2-carbaldehyde (1.0 mmol), in the presence of CAN in EtOH under reflux and Ultrasound conditions.
[b] Isolated yield.

sures the lipophilicity of compounds, which can influence their absorption rates in the body. In some cases, designing more lipophilic compounds is desirable to enhance their absorption efficiency. Kinetics provides insights into how drugs behave within the body. Additional kinetic parameters include the "rule of five," which evaluates factors such as the octanol/water partition coefficient, molecular weight (in Daltons), and the number of hydrogen bond donors and acceptors in the compound's structure.[42,43]

2.2.1. Binding Affinity

Molecular docking is a computational technique that predicts the binding affinity of ligands to receptor proteins. Binding affinity is usually measured and reported by the equilibrium dissociation constant (KD), which is used to evaluate and rank the order strengths of bimolecular interactions. The smaller the KD value, the higher the binding affinity of the ligand to its target.[44]

2.2.2. Molecular Mass

Under this guideline, the molecular mass of a drug should not exceed 500 g/mol, as a heavier molecule tends to have reduced absorption and permeability. Thankfully, all of the synthesized compounds conform to this rule.

2.2.3. Ligand Dissociation Factor

This aims to achieve a balance between the hydrophilicity and lipophilicity of the drug molecule. Ideally, the octanol/water partition coefficient should not surpass 5. However, this benchmark is not met by several ligands—specifically 3f, 3b, 3e, 3m, 3l, 3a, 3h, 3k, 3j, 3o, and 3n—with ligand dissociation factors of 5.036, 5.133, 5.295, 5.214, 5.217, 5.140, 5.661, 5.148, 5.292, 5.114, and 5.294, respectively.

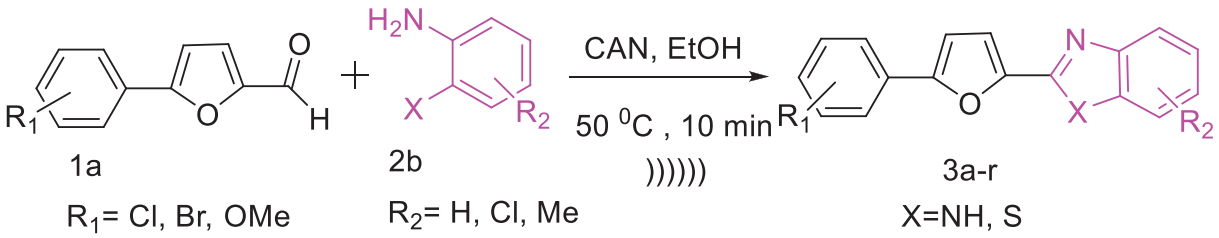
2.2.4. Edible Potential

Compounds 3c, 3i, 3k, 3g, 3p, and 3q exhibit the highest edible potential. The other compounds have very low edible potential, resulting in minimal absorption potential. The absorption percentage of other ligands in the body is high, and 100% of the drug is absorbed (Figure 2).

2.2.5. Number of Hydrogens Donating Groups

This measure pertains to the quantity of hydrogen-donating groups (such as NH and OH) present in the drug molecule. The

Table 5. CAN catalyzed the synthesis of 2-(5-(4-chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole derivatives.[a)]



					Reflux		Ultrasound			
Entry	Name	R_1	X	R_2	Time (min)	Yield (%)	Time (min)	Yield[b)] (%)	m.p. (°C)	Lit. m.p. (°C)
1	3a	4-Cl	NH	H	60	88	10	90	224–228	225–227[9]
2	3b	4-Br	NH	H	65	82	13	89	245–247	243–245[9]
3	3c	4-OMe	NH	H	75	75	15	82	264–266	262–263[9]
4	3d	2-Cl	NH	H	70	80	14	87	250–252	251–253[9]
5	3e	3-Cl	NH	H	80	70	20	75	234–236	232–234[9]
6	3f	4-Cl	NH	Me	80	76	15	83	218–220	215–217[9]
7	3g	4-Br	NH	Me	90	68	20	71	265–270	270–271[9]
8	3h	4-Br	NH	Cl	80	70	15	78	169–170	167–168[9]
9	3i	2-Cl	NH	Cl	60	86	12	90	226–229	224–226[9]
10	3j	3-Cl	NH	Cl	95	68	20	75	230–231	231–233[9]
11	3k	4-Cl	NH	Cl	60	87	12	90	211–214	210–212[9]
12	3l	2-Cl	NH	Me	80	77	15	85	224–228	240–241[9]
13	3m	4-Cl	S	H	80	78	18	78	183–185	182–183[9]
14	3n	4-Br	S	H	70	80	20	84	190–191	189–190[9]
15	3o	2-Cl	S	H	85	76	22	78	209–210	208–210[9]
16	3p	3-Cl	S	H	82	77	20	77	203–204	204–206[9]
17	3q	2-Cl, 4-Cl	S	H	90	72	15	80	225–226	–

[a)] Reaction conditions: *o*-phenylenediamine (1.0 mmol), 5-(4-chlorophenyl) furan-2-carbaldehyde (1.0 mmol), solvent (5.0 mL).
[b)] Isolated yield.

limit for these groups is set at no more than five, a threshold that, according to the findings, all compounds meet.

2.2.6. Investigating How Protein 5WS1 Binds to its Natural Ligand in the Anticancer

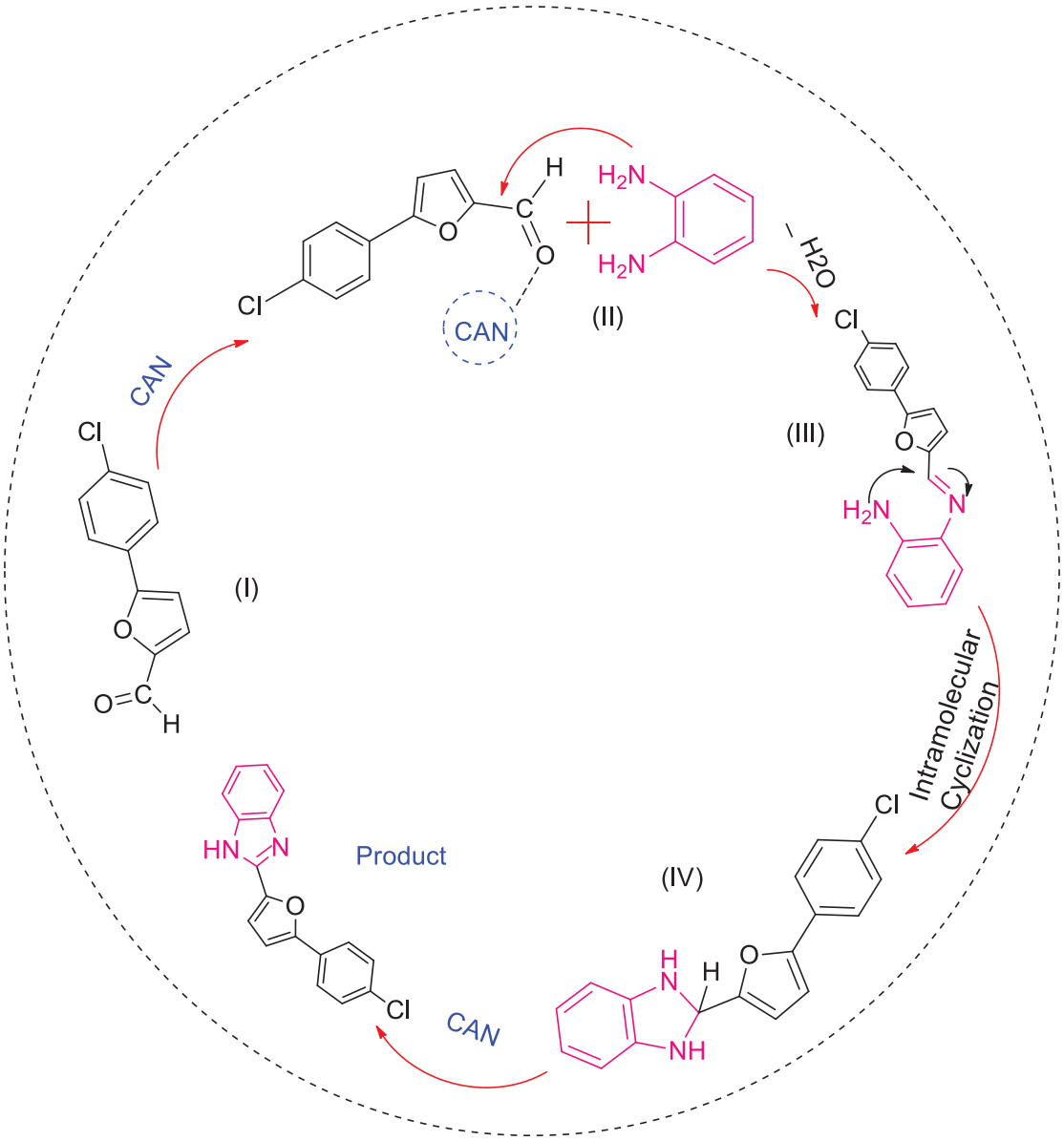
This protein, known as PARP-1 (poly (ADP-ribose) polymerase-1), is influenced by cancer, as depicted in Figures 3 and 4, where the ligand's interactions with the protein are shown in 2D. The diagrams illustrate that one of the ligands forms hydrogen bonds with the Glycine 863 residues through its nitrogen and also establishes π bonds with Tyrosine 907 and Histidine 862. These connections are critical and play an essential role in both biological sciences and pharmaceutical development (Figure 5). As shown in Figure 3, all synthesized compounds act as agonists at the active site of the 5WS1 protein, leading to its inactivation and contributing beneficial effects in cancer treatment (Figure 4).

2.3. Cytotoxicity Analyzes

The MTT, or 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide, was used in the experiment to assess the toxic impact of the tested on 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole the growth of MCF-7 cells. The percentage of viable MCF-7 cells for all the tested compounds at the different doses (3.9–500 µg/mL) for 24 h of incubation is displayed in Figure 6. At 500 µg/mL, approximately 10% of the cells were alive. This result suggests that 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole, with an IC50 concentration (44.5 µg/mL), may have potential anticancer properties (Figure 6).

2.4. Mammalian Cytotoxicity

The cytotoxicity impact of 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole on MCF-7 cell line was evaluated by performing an MTT assay and the inhibitory concentration (IC50) was assessed. Briefly, 10,000 cells were seeded in each well of 96-well plate media. After 24 h, the media was replaced with fresh media supplemented with varying concentrations of synthesized 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole. DMSO-treated cells were considered as vehicle control for evaluation. After 24 h, the media was replaced with fresh media supplemented with varying concentrations



Scheme 2. Synthesis of 2-(5-(4-chlorophenyl) furan-2-yl)-1*H*-benzo[d]imidazole in the presence of CAN.

of the synthesized 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole were also evaluated. Then the media from each well was replaced with 100 µL of DMSO to dissolve the formed formazan crystal in each well. The samples were absorbed at 570 nm and with a reference filter of 630 nm by the Elizarider device. Cell viability percentage is calculated as follows:

$$A_T = A_{570} - A_{630}$$

$$\text{Cell viability \%} = [A_T \text{ sample}/A_T \text{ control}] \times 100$$

3. Experimental Section

3.1. General

All solvents and reagents were procured from Aldrich and Merck chemical companies and were used without any further purification. Fourier transform infrared (FT-IR) spectroscopy was performed using a Nicolet Magna-400 spectrometer with KBr pellets. Proton NMR (^{1}H NMR) spectra were recorded in DMSO-d_6 and $CDCl_3$ solvents on a Bruker DRX-400 spectrometer, using tetramethyl silane (TMS) as the internal reference. Chemical shifts are reported in delta (δ) values in parts per million (ppm). Melting points were determined using capillary tubes in a Scientific Thermo apparatus (model 9300, England).

3.2. The Typical Procedure for the Synthesis of 5-Phenylfuran-2-carbaldehydes, 2-(5-arylfuran-2-yl)-1*H*-benzo[d]imidazole, and 2-(5-Aryl furan-2-yl) benzothiazole

4-Substituted aniline (7.0 mmol) was dissolved in a mixture of water (1.2 mL) and concentrated hydrochloric acid (1.7 mL). The solution was then cooled to 0 °C and diazotized using sodium nitrite ($NaNO_2$, 7.0 mmol) dissolved in water (1.3 mL), maintaining the temperature between 0 and 5 °C. After stirring for 15 min, the mixture was fil-

Table 6. Results of molecular docking calculations for 3a–q compounds as ligands of protein 5WS1.

Entry	Molecular Weight	Octanol/Water Ratio	Number of Acceptor Hydrogen Bonds	Number of Donor Hydrogen Bonds	Cell Permeability	Edibility Percentage	Edible Potential	Binding Affinity
3f	308.76	5.036	2.000	1.000	4282.823	100	1	−72.271
3e	294.74	5.295	2.000	0.000	7153.344	100	1	−69.816
3c	290.32	4.340	2.750	1.000	4268.664	100	3	−69.693
3g	339.19	5.133	2.000	1.000	4678.560	100	1	−73.400
3l	308.76	5.217	2.000	1.000	4280.656	100	1	−65.856
3a	294.74	5.140	2.000	1.000	4670.763	100	1	−68.307
3h	373.63	5.661	2.000	0.000	7147.733	100	1	−71.571
3b	339.15	4.612	2.000	1.000	4613.015	100	3	−67.600
3d	294.74	4.956	2.000	1.000	4687.204	100	1	−65.466
3k	329.18	5.148	2.000	0.000	7147.570	100	3	−66.835
3i	329.18	4.698	2.000	1.000	4268.555	100	3	−66.585
3j	329.18	5.292	2.000	0.000	7153.444	100	1	−70.643
3o	311.79	4.795	2.000	1.000	4269.393	100	3	−49.508
3n	356.24	5.114	2.000	1.000	4282.769	100	1	−63.273
3q	346.23	5.294	2.000	1.000	4280.709	100	1	−49.454
3m	311.79	5.374	2.000	0.000	7153.314	100	1	−50.730
3p	311.79	4.695	2.000	1.000	4269.440	100	3	−59.503

Table 7. Docking scores of the compounds 3a–p and standard drugs.

Entry	Docking score
3f	−8.825
3e	−8.813
3c	−8.641
3g	−8.499
3l	−8.458
3a	−8.351
3h	−8.342
3b	−8.331
3d	−8.331
3k	−8.299
3i	−8.281
3j	−8.278
3o	−6.352
3n	−6.293
3q	−6.125
3m	−5.713
3p	−5.591
Veliparib	−7.060
Olaparib	−4.300

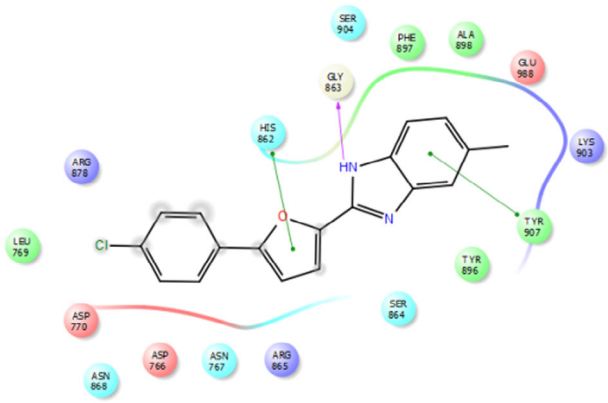


Figure 1. Bonds and interactions between ligand 3f and protein 5WS1.

tered, and furan-2-carboxaldehyde (8.5 mmol) in water (2.5 mL) was added, along with a cerium(IV) ammonium nitrate (0.05 mol%) solution in water (1.3 mL). The reaction mixture was slowly warmed to 50 °C, where it was stirred for an additional 4 h. The precipitate was then filtered, washed with water and a 5.0% sodium bicarbonate ($NaHCO_3$) solution, and dried at 25 °C. Following this, a solution containing o-phenylenediamines or 2-aminothiophenol (1.0 mmol), 5-phenylfuran-2-carbaldehydes (1.0 mmol), and CAN (0.05 mol%) in ethanol (5.0 mL) was sonicated at 50 °C. The reaction progress was monitored using thin-layer chromatography (TLC) with a n-hexane/ethyl acetate (7:3) solvent system. Once the reaction was complete, the precipitate was filtered and purified through recrystallization using ethyl acetate and petroleum ether. The products were characterized based on ^{1}H-NMR, ^{13}C-NMR, FT-IR, and elemental analysis. The data is given below.

3.2.1. Spectra Data (Compound 3a–3q)

3.2.1.1. 2-(5-(4-Chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole (3a): Isolated yield: 90%. IR (KBR): 3440 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.20 (s, 1H), 7.99–7.92 (m, 2H), 7.61 (dd, J = 5.9, 3.4 Hz, 2H), 7.59–7.54 (m, 2H), 7.32 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.23 (dd, J = 6.0, 3.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 152.9, 145.3, 132.5, 128.9, 128.4, 125.5, 122.4, 122.3, 112.5, 108.9; MS (m/z): 295 (M^{+}).

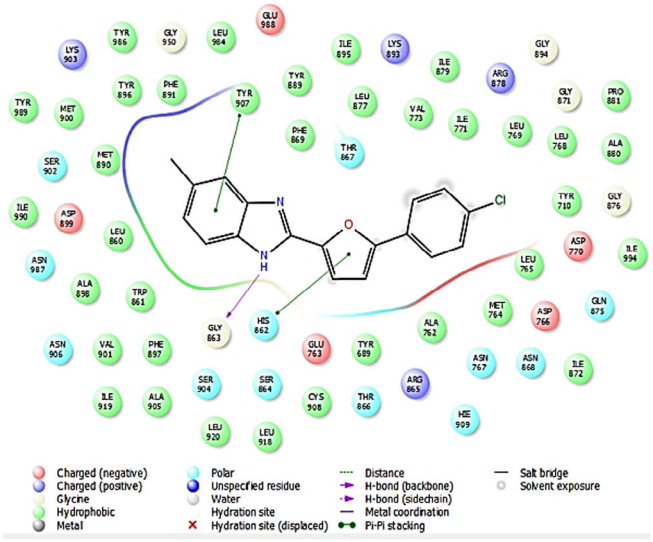


Figure 2. Links and connections of 3f and extended protein 5WS1.

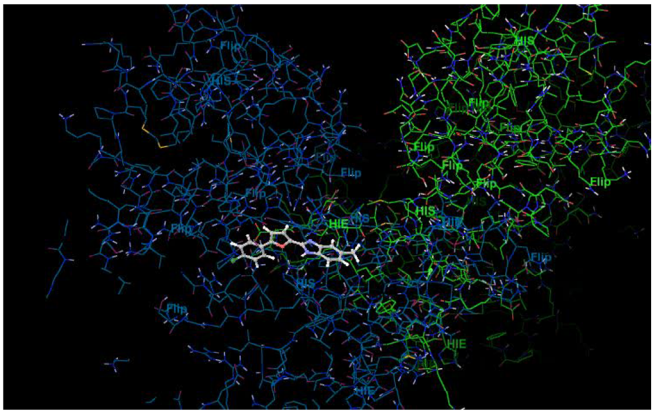


Figure 3. The interaction of ligand 3f and protein.

3.2.1.2. 2-(5-(4-Bromophenyl) furan-2-yl)-1H-benzo[d]imidazole (3b): Isolated yield: 89%. IR (KBR): 3438 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.13 (s, 1H), 7.93–7.85 (m, 2H), 7.75–7.68 (m, 2H), 7.67–7.55 (m, 2H), 7.32 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.23 (dt, J = 6.9, 3.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 153.0, 145.1, 143.7, 143.3, 134.2, 131.8, 128.7, 125.8, 122.8, 121.9, 121.1, 118.7, 112.6, 111.3, 109.0 MS (*m/z*): 339 (M^+).

3.2.1.3. 2-(5-(4-Methoxyphenyl) furan-2-yl)-1H-benzo[d]imidazole (3c): Isolated yield: 82%. IR (KBR): 3435 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.86 (d, J = 8.4 Hz, 2H), 7.64–7.55 (m, 2H), 7.30 (d, J = 6.6 Hz, 1H), 7.21 (dt, J = 5.9, 3.5 Hz, 2H), 7.12–6.97 (m, 3H), 3.81 (s, 3H).; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 159.7, 154.8, 144.5, 126.0, 122.8, 122.6, 114.9113.2, 106.8, 55.7; MS (*m/z*): 291 (M^+).

3.2.1.4. 2-(5-(2-Chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole (3d): Isolated yield: 87%. IR (KBR): 3437 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.17 (s, 1H), 8.20 (dd, J = 8.0, 1.7 Hz, 1H), 7.62 (ddd, J = 11.8, 7.0, 2.1 Hz, 3H), 7.53 (td, J = 7.6, 1.3 Hz, 1H), 7.41 (dd, J = 7.7, 1.8 Hz, 1H), 7.40–7.36 (m, 2H), 7.28–7.20 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 150.2, 145.0, 143.1, 130.7, 129.4, 129.2, 128.2, 127.6, 127.5, 122.4, 113.3, 112.4; MS (*m/z*): 295 (M^+).

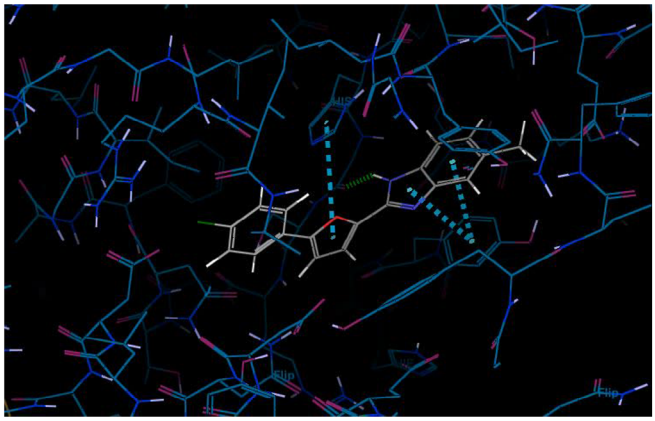


Figure 4. Molecular docking of derivatives on ligand 3f of protein 5WS1.

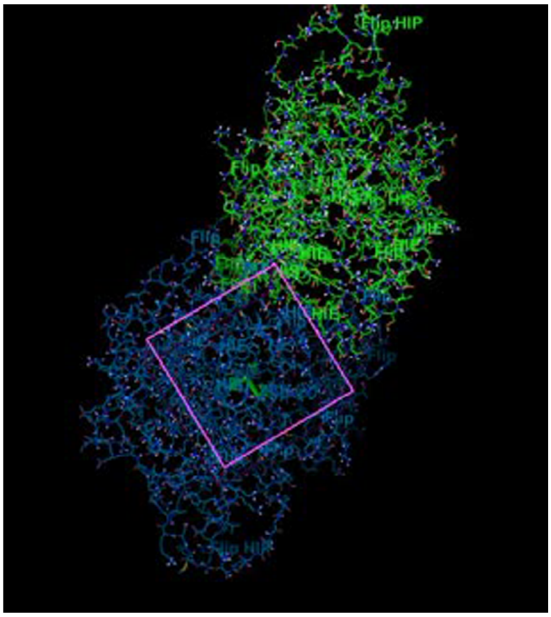


Figure 5. Active site of protein 5WS1.

3.2.1.5. 2-(5-(3-Chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole (3e): Isolated yield: 75%. IR (KBR): 3412 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.16 (s, 1H), 8.05 (t, J = 1.9 Hz, 1H), 7.92–7.87 (m, 1H), 7.66–7.58 (m, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.45–7.42 (m, 1H), 7.33 (d, J = 3.6 Hz, 2H), 7.27–7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 152.4, 145.4, 143.2, 133.9, 131.5, 130.8, 127.7, 123.3, 122.4, 112.5, 109.6; MS (*m/z*): 295 (M^+).

3.2.1.6. 2-(5-(4-Chlorophenyl) furan-2yl)-5-methyl-1H-benzo[d]imidazole (3f): Isolated yield: 83%. IR (KBR): 3442 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60–7.52 (m, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.34 (s, 1H), 7.30–7.25 (m, 2H), 7.17 (d, J = 3.8 Hz, 1H), 7.03 (dd, J = 8.5, 1.5 Hz, 1H), 6.70 (d, J = 3.7 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.3, 154.3, 153.3, 147.6, 133.7, 132.1, 128.2, 126.8, 126.0, 125.4, 122.6, 122.3, 121.7, 114.5, 109.7, 21.4; MS (*m/z*): 309 (M^+).

3.2.1.7. 2-(5-(4-Bromophenyl) furan-2yl)-5-methyl-1H-benzo[d]imidazole (3g): Isolated yield: 71%. IR (KBR): 3455 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.91 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 9.0 Hz,

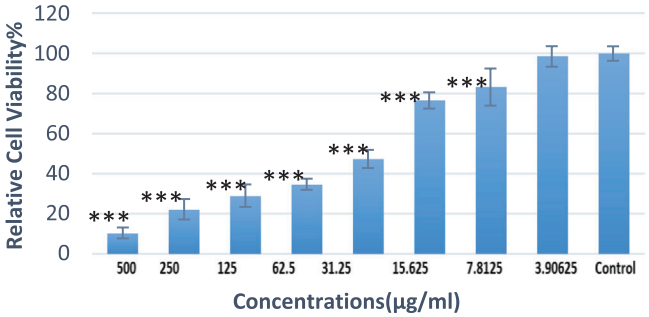


Figure 6. The effect of 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d] imidazole.

Table 8. Docking scores of the compound 3a–3f and previously reported compounds.

Compound	Docking Score	Ref.
3a–3f	−4.300 to −8.825	This work
2-(4-[4-Acetylpiperazine-1-carbonyl]) phenyl)-1*H*-benzo[d]imidazole-4-carboxamide	−3.07 to −6.81	[45]
Quinazolin-4(3*H*)-one-morpholine hybrids	−0.978 to −6.205	[46]
NU1025	−7.6	[47]

1H), 7.24 (d, J = 20.3 Hz, 1H), 7.20 (d, J = 3.2 Hz, 1H), 6.98 (dd, J = 13.9, 8.1 Hz, 1H), 2.[38] (s, 3H).; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 152.8, 145.3, 131.8, 128.7, 125.7, 124.2123.5, 121.0, 118.3, 112.2, 111.0, 108.9, 21.3; MS (*m/z*): 353 (M^+).

3.2.1.8. 2-(5-(4-Bromophenyl) furan-2yl)-5-chloro-1H-benzo[d]imidazole (3h): Isolated yield: 78%. IR (KBR): 3451 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.26 (s, 1H), 7.91–7.85 (m, 2H), 7.74–7.70 (m, 2H), 7.57 (d, J = 10.0 Hz, 2H), 7.34 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.27–7.21 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 153.3, 144.6, 131.9, 128.6, 125.8, 122.8, 122.3, 121.3, 119.9, 118.0, 113.3, 112.6, 111.0109.0; MS (*m/z*): 375 (M^+).

3.2.1.9. 5-Chloro-2-(5-(2-chlorophenyl) furan-2-yl)-1H-benzo[d]imidazole (3i): Isolated yield: 90%. IR (KBR): 3432 (NH); ^{1}H NMR (400 MHz, DMSO) δ 13.16 (s, 1H), 8.05 (t, J = 1.9 Hz, 1H), 7.67–7.59 (m, 2H), 7.53 (t, J = 7.9 Hz, 2H), 7.43 (dd, J = 7.9, 2.2 Hz, 2H), 7.21–725 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 150.5, 144.6, 130.8, 129.5, 129.3, 128.2, 127.6, 127.5, 127.5, 126.9, 122.9, 120.0, 118.1, 116.0, 113.3, 112.9; MS (*m/z*): 329 (M^+).

3.2.1.10. 2-[5-(3-Chlorophenyl)-2-furanyl]-5-chlor-1H-benzimidazole (3j): Isolated yield: 75%. IR (KBR): 3431 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (t, J = 2.0 Hz, 2H), 7.45 (d, J = 8.7 Hz, 1H), 7.37–7.39 (m, 1H), 7.21–7.11 (m, 5H), 6.68 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.6, 145.2, 144.8, 137.0, 134.8, 131.5, 130.0, 129.3, 127.9, 126.6, 124.0, 123.5, 123.2, 122.3, 112.9108.5; MS (*m/z*): 329 (M^+).

3.2.1.11. 2-[5-(4-Chlorophenyl)-2-furanyl]-5-chlor-1H-benzimidazole (3K): Isolated yield: 90%. IR (KBR): 3434 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.28 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.74–7.61 (m, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 3.7 Hz, 1H), 7.28 (d, J = 3.7 Hz, 1H), 7.27–7.11 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 153.2, 144.6, 136.2, 132.7, 129.0, 128.3, 125.6, 122.5, 119.9, 113.2, 110.7109.0; MS (*m/z*): 329 (M^+).

3.2.1.12. 2-(5-(2-Chlorophenyl) furan-2yl)-5-methyl-1H-benzo[d]imidazole (3l): Isolated yield: 85%. IR (KBR): 3440 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.57 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 7.9, 1.7 Hz, 1H), 7.30–7.27 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.15–7.09 (m, 2H), 6.98 (t, J = 7.7 Hz, 1H), 6.66 (t, J = 8.3 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 151.5, 144.5, 143.9143.8, 138.7, 138.5, 130.5, 130.0, 128.4, 127.9, 127.6, 126.5, 125.7, 123.8, 123.3, 113.2, 112.6,17.6; MS (*m/z*): 309 (M^+).

3.2.1.13. 2-(5-(4-Chlorophenyl) furan-2-yl) benzo[d]thiazole (3m): Isolated yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.19–8.15 (m, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.94–7.87 (m, 2H), 7.63–7.58 (m, 2H), 7.58–7.54 (m, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.48 (td, J = 7.6, 1.2 Hz, 1H), 7.36 (d, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 153.4, 147.6, 140.2, 133.1, 129.2, 127.9, 126.8, 125.8, 125.5, 122.6, 122.4, 114.5109.7; MS (*m/z*): 312 (M^+).

3.2.1.14. 2-(5-(4-Bromophenyl) furan-2-yl) benzo[d]thiazole (3n): Isolated yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.16 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.61–7.54 (m, 1H), 7.50 (t, J = 3.1 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 156.3154.3, 153.3, 147.6, 133.7, 132.1, 128.2, 126.8, 126,0, 125.4, 122.6, 122.3, 121.7, 114.5, 109.7; MS (*m/z*): 358 (M^+).

3.2.1.15. 2-(5-(2-Chlorophenyl) furan-2-yl) benzo[d]thiazole (3o): Isolated yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.18 (dd, J = 8.1, 1.3 Hz, 1H), 8.10–8.05 (m, 1H), 7.98 (dd, J = 7.9, 1.7 Hz, 1H), 7.64 (dd, J = 8.0, 1.3 Hz, 1H), 7.60–7.56 (m, 1H), 7.55 (dq, J = 5.9, 1.7 Hz, 2H), 7.51–7.44 (m, 2H), 7.40 (d, J = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 156.3, 153.3, 151.6, 147.5, 133.8, 130.9, 130.0, 129.6, 128.4, 127.8, 127.3, 126.8, 125.5122.7, 122.4, 113.8113.7; MS (*m/z*): 312 (M^+).

3.2.1.16. 2-(5-(3-Chlorophenyl) furan-2yl) benzo[d]thiazole (3p): Isolated yield: 77%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.00 (dt, J = 8.3, 0.9 Hz, 1H), 7.83–7.86 (m, 1H), 7.72 (t, J = 1.8 Hz, 1H), 7.62–7.58 (m, 1H), 7.42–7.46 (m, 1H), 7.37–7.27 (m, 3H), 7.26–7.21 (m, 2H), 6.80 (d, J = 3.6 Hz, 1H).; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 154,5, 154.0, 134.9, 131,3, 130.1, 128.4, 126.5, 125.2, 124.4, 123.9, 123.1, 122.4, 121.6, 113.4, 108.8; MS (*m/z*): 312 (M^+).

3.2.1.17. 2-(5-(2,4-Dichlorophenyl) furan-2-yl) benzo[d]thiazole (3q): Isolated yield: 80%. ^{1}H NMR (250 MHz, DMSO) δ 8.18–7.85 (m, 3H), 7.74 (s, 1H), 7.65–7.31 (m, 5H).^{13}C NMR (63 MHz, DMSO-d_6): δ(ppm) 111.49, 119.99, 120.35, 123.21, 124.45, 125.69, 127.12, 127.97, 131.17, 135.26, 137.35, 138.51, 145.74, 148.37, 149.01, 150.90; MS (*m/z*): 346 (M+); Anal. Calcd for $C_{17}H_9Cl_2NOS$: N, 4.05; H, 2.62; C, 58.98; S, 9.26. Found: N, 4.11; H, 2.53; C, 59.04. S, 9.19

3.3. The Comparison of Docking Scores of Synthesized Compounds with Previously Reported Compounds

According to Table 8, it can be seen that the docking score results of the compounds of this study are higher than the previously reported compounds with the names 2-(4-[4-acetylpiperazine-1-carbonyl]) phenyl)-1*H*-benzo[d]imidazole-4-carboxamide, quinazolin-4 (3*H*)-one-morpholine hybrids and NU1025. A more negative docking score than the docking score of the reference compounds

indicates higher inhibitory and better placement in the active site of the protein PARP-1.

4. Conclusion

In summary, in this research, an efficient protocol for the synthesis of di-heteroaryl molecules, including benzimidazole and benzothiazole derivatives, has been described using cerium(IV) ammonium nitrate as a homogeneous catalyst. Docking results showed that all the synthesized compounds in this study act as agonists at the active site of the 5WS1 protein, leading to its inactivation and delivering beneficial effects in breast cancer therapy. The lead compound interacts with histidine 862 via furan ring π-π stacking, with a binding distance of 4.85632 Å and an angle of 65.7491°. It also forms a π–π bond with tyrosine 907 from the benzene ring, with a binding distance of 3.79124 Å and an angle of 9.67512°. Additionally, the imidazole ring of the lead compound forms a hydrogen bond with glycine 863, with a binding distance of 1.99393 Å, an acceptor angle of 148.219°, and a donor angle of 154.318°. Therefore, the research revealed that compounds with a benzimidazole ring show more promise as anticancer agents than those with a benzothiazole ring. The MTT assay was conducted on the 2-(5-(4-chlorophenyl) furan-2-yl)-5-methyl-1*H*-benzo[d]imidazole and it displayed anti-tumor activity against MCF7 with an *IC50* value = 44.5 µg/mL (Supporting Information).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Anticancer · Benzimidazole · Benzothiazole · Cerium(IV) ammonium nitrate · Molecular docking

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