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ORIGINAL ARTICLE

Antioxidant, anticancer and electrochemical redox properties of new bis(2,3-dihydroquinazolin-4(1*H*)-one) derivatives

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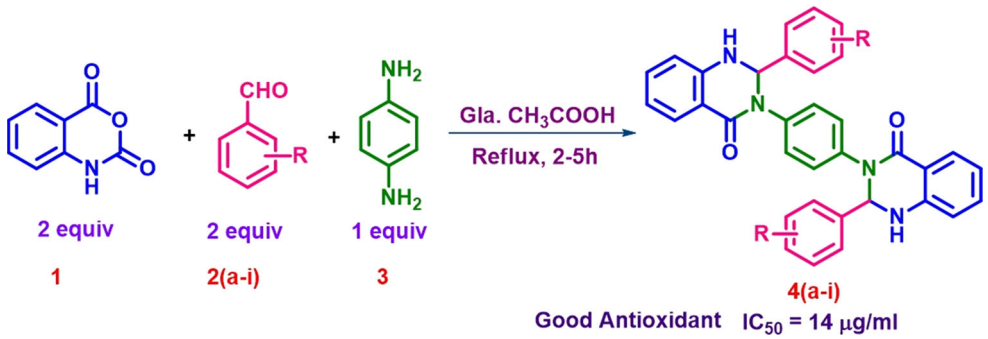
Abstract In this paper, a series of bis(2,3-dihydroquinazolin-4(1*H*)-one) derivatives (**4a–i**, **10a–k**) were synthesized by the one-pot pseudo-five-component reaction of isatoic anhydride with aromatic aldehydes and aromatic amines under reflux in glacial acetic acid. The synthesized compounds were screened for their antioxidant properties using the DPPH radical scavenging method. Compounds **4i** and **10h** showed potent radical scavenging activities at 20 μg/mL compared to BHA and ascorbic acid. The anticancer activity of compound **4f** was evaluated against human breast cancer cell line (MCF 7), and the observed GI_{50} was found to be 11.4 μm. The redox behaviour of some analogues was evaluated by cyclic voltammetric methods, and it is found that compound **7d** possesses the maximum redox potential.

Graphical Abstract



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Keywords Bis(2, 3-dihydroquinazolin-4(1*H*)-one) · Antioxidant · DPPH radical scavenging activity · Anticancer · Redox potential

Introduction

In recent years, the exploration of novel synthetic compounds with antioxidant properties has become an active area of research. Free radicals and oxygen derivatives are constantly generated *in vivo* by specific metabolic processes [1]. These radicals can easily react with most biological molecules including proteins, lipids, lipoproteins, DNA and damage them. The damage of cells caused by free radicals might be responsible for the production of a wide range of human diseases such as arthritis, haemorrhagic shock, coronary artery diseases, cataract, cancer, AIDS as well as age-related degenerative brain diseases [2]. The production of these free radicals could be prevented by the addition of free radical scavengers like antioxidants. In this regard, there are some natural antioxidants such as beta-carotene, lycopene, vitamins A, C and E that are used to capture free radicals and neutralize them. Due to the expensive and lengthy isolation processes of the natural antioxidants from the various natural sources and their unprecise activity against many diseases, synthetic antioxidants play an important role in the treatment and prevention of major diseases that are associated with oxidative stress. Initially, various polyphenolic and thiol compounds were used as free radical scavengers [3,4]. Recently, a variety of heterocyclic compounds such as quinazolinone, oxadiazole, thiadiazole, coumarin, pyrazole and pyrimidines also serve as antioxidants [5–9]. Thus, there is a constant need for identifying new and effective therapeutic agents.

2,3-Dihydroquinazolinone and its derivatives are a class of nitrogen containing heterocyclic compounds that exhibit a variety of pharmacological properties such as antimicrobial, antitumor, antibiotic, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant and vasodilating activities [10–16]. In addition to that, they comprise potent tubulin inhibitors with remarkable anti-proliferative activity against a variety of human cancer cells [17] and act as antimitotic agents [18]. Moreover, these 2,3-dihydroquinazolinone derivatives could be easily oxidized to produce quinazolin-4(3*H*)-one analogues [19] which are promising bioactive heterocyclic compounds [20–22] and are present in some natural products [23]. There are numerous reports available in the literature for the synthesis of mono 2,3-dihydroquinazolinone derivatives. Structurally complex quinazolinone-based natural product precursors have also been constructed indirectly *via* thioamide formation [24], oxidation of dehydroquinazolinone [25], aza-Wittig condensations [26] or from benzoxazinones [27]. However, only a few reports are available for the synthesis of bisquinazolinone [28–32] derivatives and, to the best of our knowledge, this is the first report for the biological and electrochemical properties of these compounds. Considering this limited background, we planned the synthesis of new 3,3′-bis(dihydroquinazolin-4(1*H*)-one) and 2,2′-bis(dihydroquinazolin-4(1*H*)-one) derivatives to investigate their DPPH radical scavenging and electrochemical redox properties.

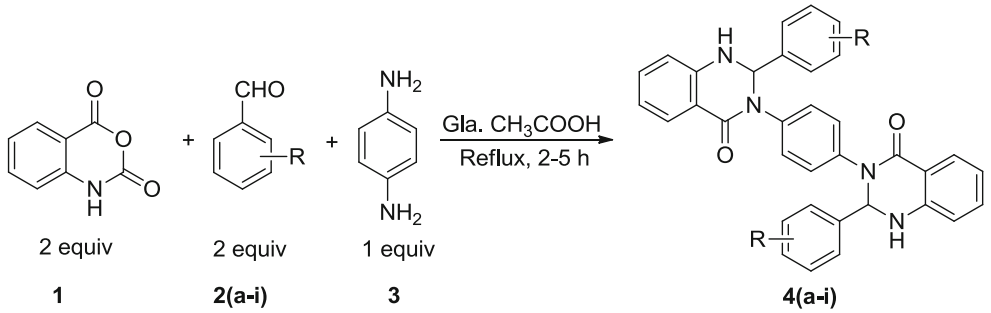
Results and discussion

Chemistry

In continuation of our effort to develop novel heterocyclic compounds [33–35], herein we present a simple and efficient synthesis of novel bis(2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) derivatives from the one-pot five-component reaction of isatoic anhydride with aromatic aldehydes and *p*-phenylenediamine under refluxing conditions in glacial acetic acid (Scheme 1).

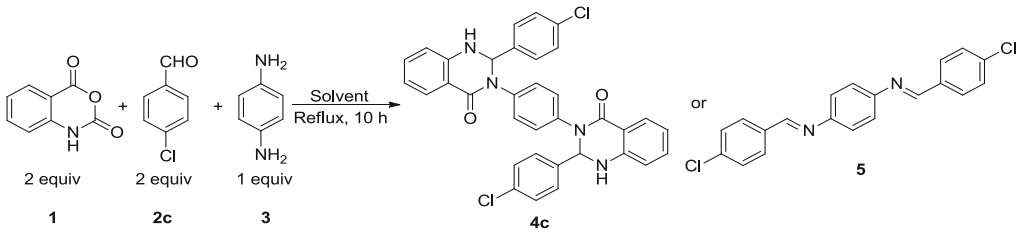
In order to optimize the reaction conditions, initially this cyclocondensation reaction was conducted in different solvents including ethanol, methanol, PEG-300, ethylene glycol, diethylene glycol, acetonitrile, DMF and dioxane in the presence of 30 mol% *p*-TSA as a catalyst (Table 1). When the reaction was refluxed in polar protic solvents such as ethanol and methanol, the expected compound **4c** was not formed even after 10h (Table 1, Entry 1 and 2) and only imine **5** were observed. For the other solvents, moderate yields of compound **4c** was observed (Table 1, Entry 3-5) except when using acetonitrile and 1,4-dioxane (Table 1, Entry 6 and 8). When glacial acetic acid was used, **4c** was formed in excellent yields (Table 1, Entry 9). Furthermore, we have performed a control experiment by using glacial acetic acid as the reaction medium without the use of *p*-TSA as catalyst where **4c** was also obtained in excellent yield (Table 1, Entry 10). This prompted us to use acetic acid as reaction medium for further reactions.

Next, we explored the scope and generality of the reaction with respect to aromatic aldehydes **2(a–i)** using the first reaction conditions (without *p*-TSA in glacial acetic acid). Aromatic aldehydes having both electron-donating and electron-withdrawing substituents are well tolerated, affording the corresponding compounds **4(a–i)** in good to excellent yields (Table 2). From the Table 2, we observed that aldehydes having electron-withdrawing groups produced the corresponding products in higher yields than those aldehydes containing electron-donating groups. When an electron-withdrawing group was at the *ortho*-position of the aromatic aldehydes, longer reaction times were required to obtain the desired products; however, these were obtained in



Scheme 1 Synthesis of bis(2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) analogues

Table 1 Optimization of reaction conditions



Entry	Solvent	Temperature (°C)	Reaction time (h)	Product	Yield (%)[b]
1	Ethanol	Reflux	10	**5**	95
2	Methanol	Reflux	10	**5**	92
3	PEG-300	120	6	**4c**	65
4	Ethylene glycol	120	7	**4c**	52
5	Diethylene glycol	120	7	**4c**	55
6	Acetonitrile	Reflux	10	**4c**	–
7	DMF	Reflux	5	**4c**	73
8	1,4-Dioxane	Reflux	10	**4c**	–
9	Glacial acetic acid	Reflux	3	**4c**	88
10	Glacial acetic acid[a]	Reflux	3	**4c**	88

Cyclocondensation reaction of isatoic anhydride (2 equiv) with *p*-phenylenediamine (1 equiv) and *p*-chlorobenzaldehyde (2 equiv) in the presence of 30 mol% of *p*-TSA

[a] Absence of *p*-TSA

[b] Isolated yield

Table 2 Synthesis of 3,3′-(1,4-phenylene)bis(2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) derivatives

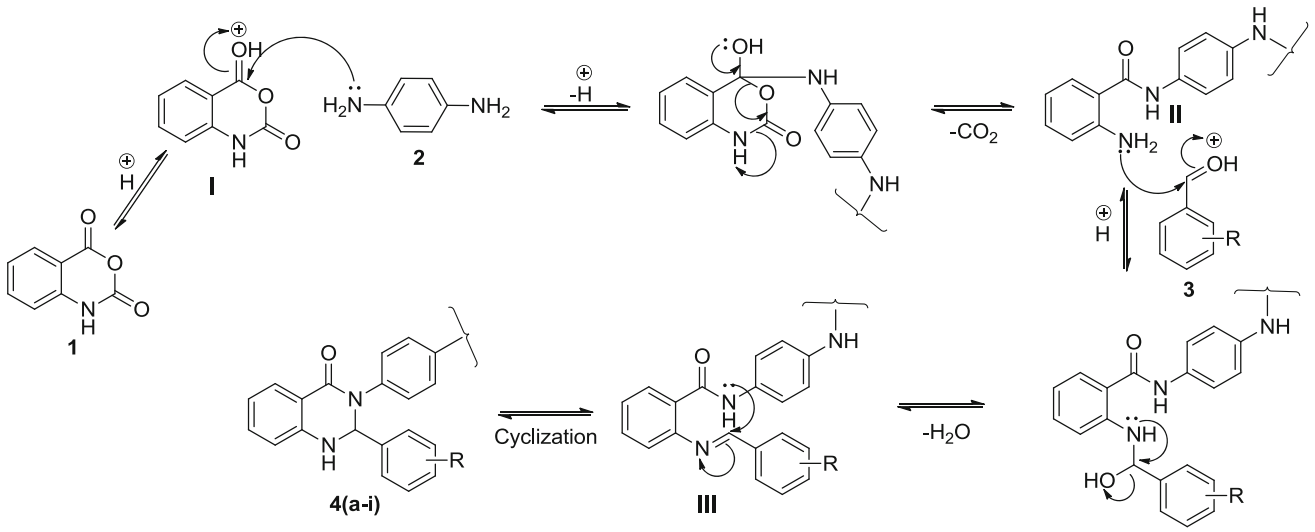
Entry	R	Product **4 (a–i)**	Time (h)	Yield (%)[a]	mp (°C)
1	H	**4a**	3.5	83	>300
2	2-Cl	**4b**	3.5	79	290–292[b]
3	4-Cl	**4c**	3.0	88	258–260
4	4-Br	**4d**	3.0	87	272–274[b]
5	4-F	**4e**	2.5	90	228–230[b]
6	2-NO_2	**4f**	2.5	80	>300[b]
7	3-NO_2	**4g**	2.5	82	270–272[b]
8	4-NO_2	**4h**	2	92	292–294
9	4-OMe	**4i**	4.5	75	236–238

R refers to Scheme 1

Cyclocondensation reaction of isatoic anhydride (2 equiv) with *p*-phenylenediamine (1 equiv) and different aromatic aldehydes (2 equiv) at reflux in glacial acetic acid

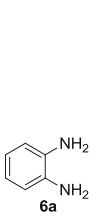
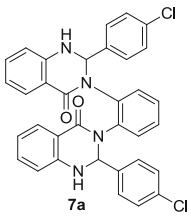
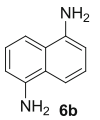
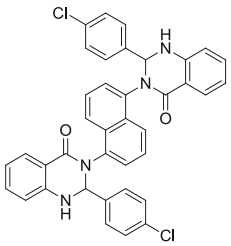
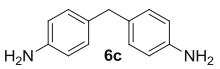
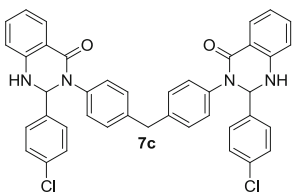
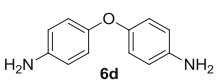
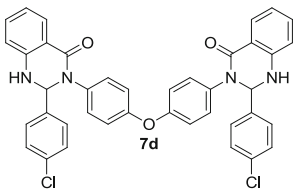
[a] Isolated yield

[b] Novel compounds



Scheme 2 Proposed mechanism for the formation of products **4(a–i)**

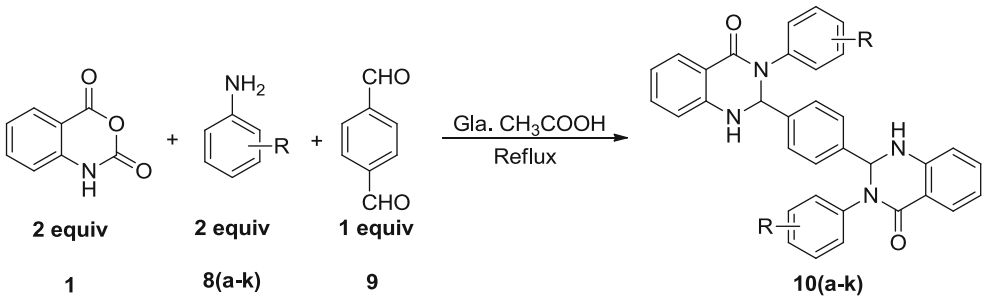
Table 3 Synthesis of 3,3′-bisquinazolinone derivatives

Entry	Amine 6(a–d)	Product **7(a–d)**	Time (h)	Yield (%)[a]
1	 **6a**	 **7a**	4	85[b]
2	 **6b**	 **7b**	3.5	89[b]
3	 **6c**	 **7c**	4	88[b]
4	 **6d**	 **7d**	4	82[b]

Cyclocondensation reaction of isatoic anhydride (2 equiv) with different aromatic diamines (1 equiv) and *p*-chlorobenzaldehyde (2 equiv) at reflux in glacial acetic acid

[a] Isolated yield

[b] Novel compounds



Scheme 3 Synthesis of 2,2′-bisquinazolinone derivatives

Table 4 Synthesis of 2,2′-(1,4-phenylene)bis(3-phenyl-2,3-dihydroquinazolin-4(1*H*)-ones)

Entry	R	Product **10(a–k)**	Reaction time (h)	Yield (%)[a]	mp (°C)
1	H	**10a**	3.0	76	266–268
2	2-Cl	**10b**	3.5	73	120–122[b]
3	3-Cl	**10c**	4.0	70	180–182[b]
4	4-Cl	**10d**	3.0	80	288–290
5	4-Br	**10e**	3.5	79	256–258[b]
6	3-$COCH_3$	**10f**	4.0	72	114–116[b]
7	4-$COCH_3$	**10g**	3.5	75	178–180[b]
8	4-OH	**10h**	2.5	83	>300[b]
9	1-Naphthyl	**10i**	4.0	72	>300[b]
10	4-Isopropyl	**10j**	2.0	85	>300[b]
11	4-COOH	**10k**	3.5	73	>300[b]

R refers to Scheme 3

Cyclocondensation reaction of isatoic anhydride (2 equiv) with terephthalaldehyde (1 equiv) and different aromatic amines (2 equiv) by refluxing in glacial acetic acid

[a] Isolated yield

[b] Novel compounds

lower yields than those with groups present in either *m*- or *p*-positions. The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR and LC-MS spectroscopic techniques.

The formation of compounds **4(a–i)** can be explained by the proposed mechanism shown in Scheme 2. The carbonyl group of isatoic anhydride (**1**) could be protonated to give the intermediate (**I**), which might facilitate the nucleophilic attack of *p*-phenylenediamine (**3**) on the carbonyl group. Nucleophilic addition of *p*-phenylenediamine (**3**) to the intermediate (**I**) followed by decarboxylation produces 2-aminobenzamide (**II**). Condensation of **II** with protonated aldehyde (**2**) gives imine (**III**), which undergoes intramolecular cyclization to afford the final product **4(a–i)**.

In addition, we have also applied the same protocol for the synthesis of 3,3′-bisquinazolinone derivatives (Table 3, Entries 1-4) using *o*-phenylenediamine, 1,5-diaminonaphthalene, 4,4’-diaminodiphenyl ether and 4,4’-diaminodiphenyl methane with isatoic anhydride and *p*-chlorobenzaldehyde and their results are shown in Table 3.

We have also tried to synthesize new 2,2′-(1,4-phenylene) bis(3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) derivatives from the one-pot five-component reaction of isatoic anhydride and aromatic amine with terephthalaldehyde by refluxing the mixture in glacial acetic acid. It was observed that aromatic amines having electron-donating groups afforded products in higher yields faster than the electron-withdrawing counterparts (Scheme 3, Table 4).

Antioxidant study

We studied the antioxidant potential of the synthesized bis(2,3-dihydroquinazolin-4(1*H*)-one) compounds **4(a–i)** and **8(a–k)** by using the DPPH radical scavenging assay (RSA) [36,37]. The radical scavenging activities of the test compounds were assessed by how the tested compounds are capable of stabilizing the DPPH radical, and the percentage of inhibition and 50% inhibitory concentration values are presented in Tables 5 and 6 and compared with those of the standards BHA and ascorbic acid. A stock solution of DPPH free radical in methanol (7.1 mg/300 mL) was prepared, and the absorbance was recorded at 517 nm. Then, a stock solution of the sample was prepared by dilution method to get solutions with 20, 40, 60, 80 100 μg/mL. The test solu-

Table 5 Antioxidant activities of synthesized compounds **4(a–i)**

Entry	Compounds	DPPH RSA[a] (20 μg/mL)	
		(%)	IC_{50} value (μg)
1	**4a**	56.90 ± 0.31	17.5
2	**4b**	59.36 ± 0.54	16.8
3	**4c**	59.72 ± 0.78	16.7
4	**4d**	58.76 ± 0.54	16.9
5	**4e**	59.92 ± 0.53	16.6
6	**4f**	60.83 ± 0.68	16.4
7	**4g**	57.55 ± 0.40	17.2
8	**4h**	58.66 ± 0.17	16.9
9	**4i**	70.75 ± 0.38	14.0
10	BHA	88.12 ± 1.66	11.2
11	Ascorbic acid	81.62 ± 0.49	12.3

[a] Antioxidant activities were expressed in percentage compared with standard BHA and ascorbic acid. The data represent mean value (SEM) of triplicates

Table 6 Antioxidant activities of synthesized compounds **10(a–k)**

Entry	Compounds	DPPH RSA[a] (20 μg/mL)	
		(%)	IC_{50} value (μg)
1	**10a**	60.12 ± 0.40	16.5
2	**10b**	62.19 ± 1.45	16.0
3	**10c**	62.34 ± 0.63	15.9
4	**10d**	61.48 ± 0.69	16.2
5	**10e**	62.13 ± 0.31	16.0
6	**10f**	62.24 ± 1.06	16.0
7	**10g**	62.13 ± 1.11	16.0
8	**10h**	64.15 ± 0.83	15.5
9	**10i**	56.75 ± 0.83	17.5
10	**10j**	59.92 ± 2.99	16.6
11	**10k**	62.03 ± 1.30	16.0

[a] Antioxidant activities were expressed in percentage. The data represent mean value (SEM) of triplicates

tions at different concentrations (1 mL) were mixed with the DPPH stock solution (2 mL) and were incubated in the dark for 30 min. After 30 min, the absorbance was measured at 517 nm. From these absorbance values, the percentage antioxidant activities were calculated according to the following equation,

$$\text{Radical scavenging activity}\ (\%) = [(A_c - A_s)/A_c] \times 100$$

where A_c = absorbance of DPPH , A_s = absorbance of test sample.

The DPPH radical scavenging activity of the test compounds was found to be good to moderate when compared with the standards BHA and ascorbic acid. Initially, we chose compound **4a** as our baseline for antioxidant activity and observed that the antioxidant activity remained within the range of 57–60% with increasing concentration. So, the antioxidant activities of the remaining compounds were evaluated at 20 μg/mL, and the results are presented in Table 5.

It was observed that all the compounds reduced the concentration of DPPH free radical and exhibited their antioxidant activities in the range of 57–71%. Compounds having electron-withdrawing groups showed 58–61% activities (Table 5, Entries 5, 6, 7 and 8), whereas compound possessing electron-donating groups showed a maximum (71%) antioxidant ability (Table 5, Entry 9). It is clear from Table 5 that compound **4i** is the best antioxidant out of the analogues made.

The dihydroquinazolinone derivatives derived from terephthalaldehyde **10(a–k)** also showed good antioxidant activities (Table 6). As evidenced from the data presented in Table 6, compound **10h** was found to be the best antioxidant among the analogues studied (Table 6, Entry 8) which may be attributed to the –OH groups on the phenyl ring as they are known to scavenge DPPH.

Table 7 Cytotoxicity of compound **4f**

Entry	Concentration in μM	% Viability[a]	
		Vero cells	MCF-7
1	0	100	90.21 ± 0.40
2	6.25	96.45 ± 0.75	65.73 ± 2.51
3	12.5	87.94 ± 1.28	56.65 ± 1.11
4	25	79.40 ± 0.48	45.54 ± 1.11
5	50	65.44 ± 2.79	34.60 ± 0.64
6	100	45.68 ± 1.79	22.99 ± 1.64
7	200	17.33 ± 2.18	
GI_{50} value		84 μM	11.4 μM

[a] Data presented are the means ± SD of results from three independent experiments

Anticancer activity

The *in vitro* anticancer activity of **4f** was determined against both normal Vero cell line as well as human breast cancer cell line (MCF-7). The cell viability in the presence of test sample was measured by using the MTT assay and is presented in Table 7. The basic principle of this colorimetric assay is the reduction of water soluble yellow 3-(4,5-dimethylthiazol2-yl)-2,5-diphenyl tetrazolium bromide (MTT) to the water insoluble purple-coloured formazan by mitochondrial succinate dehydrogenase. The resulting intracellular purple formazan could be solubilized and measured by spectrophotometric means [38]. The treatment of MCF-7 cells with **4f** at different concentrations (0–200 μM) for 24 h resulted in the decrease in number of MCF-7 cells cor-

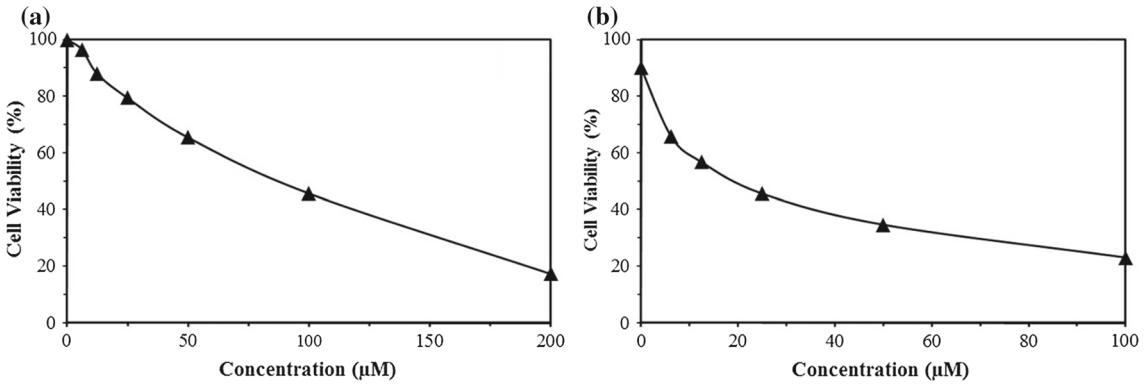


Fig. 1 **a** Cytotoxicity on Vero cell lines, **b** cytotoxicity on MCF-7 cell lines

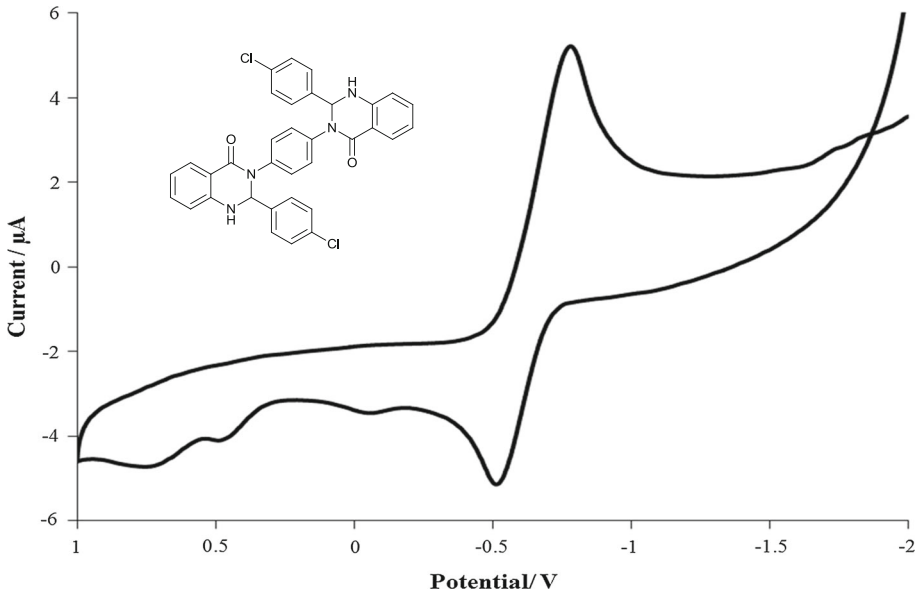


Fig. 2 Cyclic voltammogram of compound **4c**

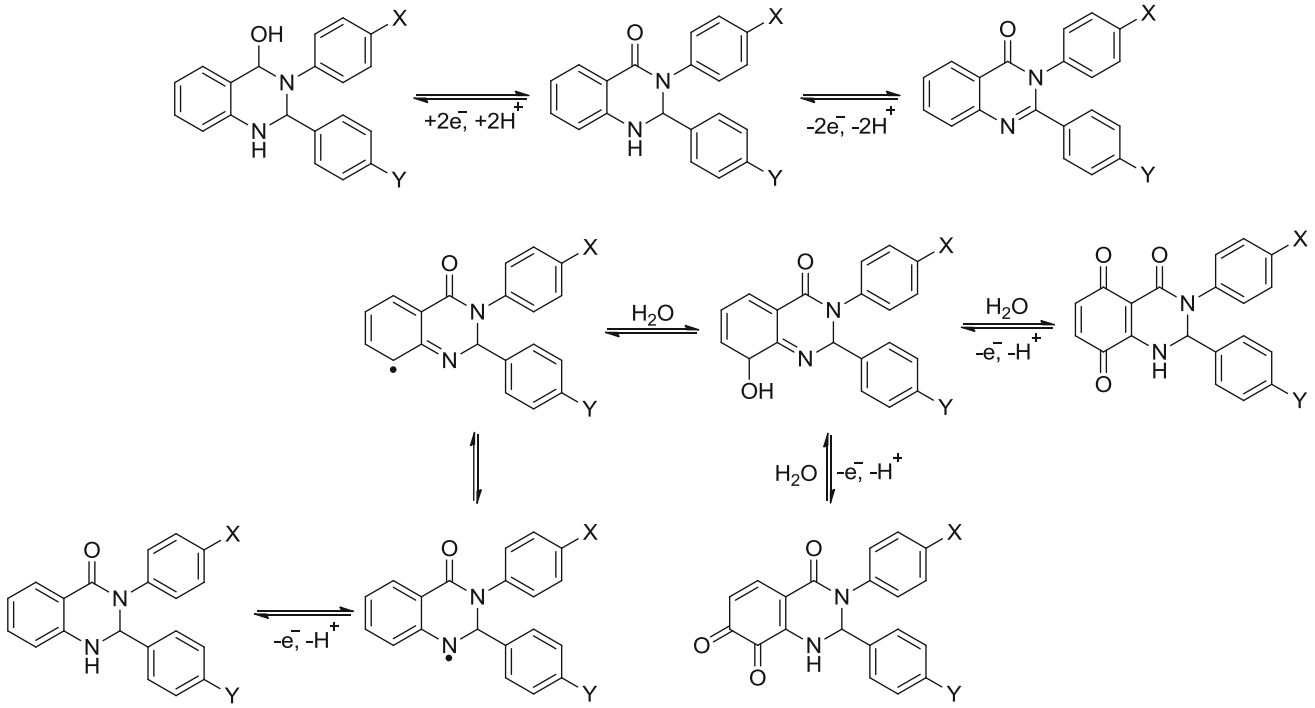
Table 8 Formal redox potential of compounds **4c**, **7(a–d)**, **10d** and **11**

Entry	Compound	Oxidation potential (V)			Reduction potential (V)
		E_{pa1}	E_{pa2}	E_{pa3}	E_{pc1}(V)
1	**4c**	−0.512	−0.063	0.492	−0.782
2	**7a**	−0.317	–	0.651	−0.834
3	**7b**	−0.498	0.019	0.538	−0.718
4	**7c**	−0.398	0.028	–	−0.684
5	**7d**	−0.556	−0.087	0.453	−0.792
6	**10d**	−0.501	−0.011	0.524	−0.693
7	**11**	−0.226	0.150	0.661	−0.854

Electrolyte: tetrabutylammonium perchlorate in DMSO; scan rate: 50 mV/s

responding to the concentration of the tested compound **4f** (Fig. 1b). In contrast, cytotoxic effect of normal Vero cell was poorly affected by **4f** (Fig. 1a). The cell viability of this compound was calculated from the percentage of viable **4f**-treated cells and with untreated cells. Then we obtained the 50% of growth inhibition values (GI_{50}).

These results show that compound **4f** possesses good growth inhibition towards human breast cancer cell (MCF-7). However, in the case of normal Vero cells, exposure to **4f** at 200 μM for 24 h only led to 17% of viable cells with maximum GI_{50} value (84 μM), which indicated that compound **4f** is toxic only to cancer cells and not to normal cells.



Scheme 4 Proposed electrochemical redox mechanism of compounds **4c, 7(a–d), 10d** and**11**

The GI_{50} value for compound **4f** was found to be 11.4 μM, whereas in normal Vero cell it was 84 μM, indicating that compound **4f** has anticancer activity.

Cyclic voltammetric studies

Finally, the synthesized bisquinazolinones **4c**, **7(a–d)** and **10d** were screened for their redox behaviour using the cyclic voltammetric technique and their results are compared to 2,3-bis(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one **11**. The representative cyclic voltammogram of compound **4c** is shown in Fig. 2 and the major oxidation and reduction potential of the studied compounds are presented in Table 8.

It is clear from Fig. 2, the cyclic voltammogram of the studied compounds show three irreversible anodic signals and one cathodic signal during the reverse scan. In the cyclic voltammogram of compound **4c**, the first anodic signal at −0.512 V may be due to the oxidation of secondary -NH group of quinazolinone ring. In addition, two more signals observed at more positive potentials (−0.063 V and +0.492 V) may be attributed to the oxidation of aromatic ring of quinazoline. In the reverse scan, we obtained a signal at −0.782 V that could be accounted for the reduction of the carbonyl group of the quinazolinone ring. Among the studied compounds, compound **7d** was easily electrochemically oxidized (Table 8, Entry 5). However, all the compounds showed higher oxidation potential than that of monoquinazolinone **11** (Table 8, Entry 7). The relative ease of oxidation was expressed based on their first oxidation potential and the order is **7d** > **4c** > **10d** > **7b** > **7c** > **7a** > **11**.

Based on these results, we propose a possible electrochemical mechanism as shown in Scheme 4.

Conclusions

In conclusion, bis(2,3-dihydroquinazolin-4(1*H*)-one derivatives have been successfully synthesized and characterized by IR, NMR and mass spectroscopic techniques. The antioxidant properties of all the synthesized compounds were evaluated using the DPPH radical scavenging method. In the series **4(a–i)**, compound **4i** showed the highest (IC_{50} = 14 μg/mL) and compound **4a** showed the lowest (IC_{50} = 17.5 μg/mL) radical scavenging activities, whereas in the series **10(a–k)**, compound **10h** showed the highest (IC_{50} = 15.5 μg/mL) and compound **10i** showed the lowest (IC_{50} = 17.5 μg/mL) radical scavenging activities. In addition to that, we have studied the anticancer activity of the synthesized compound **4f** against human breast cancer cell line and the observed GI_{50} value was 11.4 μM.

Experimental

General remarks

All the reagents used for this study are commercially available and were freshly used after being purified by standard

procedures. Reactions were monitored by TLC using silica gel-coated plates and chloroform/methanol (9:1) mixture as the mobile phase. Melting points are uncorrected and were measured using an electrothermal apparatus. The IR spectra (neat) were recorded on a Nicolet 6700 FT-IR spectrometer. NMR spectra were obtained on an FT-NMR Bruker Spectro Spin DRX-500 and 400 MHz instrument as DMSO solution, and the chemical shifts are expressed as δ units with Me4Si as the internal standard. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m) and doublet of doublet (dd). The mass spectra were recorded on an LC-MS-Agilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min duration.

General procedure for the synthesis of 3,3′-bis(2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) derivatives 4(a–i)

A mixture of *p*-phenylenediamine (1 equiv), aromatic aldehydes (2 equiv) and isatoic anhydride (2 equiv) was refluxed in glacial acetic acid until the completion of the reaction as indicated by TLC. After completion, the reaction mixture was cooled to room temperature. Then, the solid was separated, washed with hot a methanol and chloroform mixture (1:1) and dried.

General procedure for the synthesis of 2,2′-bis(3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) derivatives 10(a–k)

A mixture of terephthalaldehyde (1 equiv), aromatic amine (2 equiv) and isatoic anhydride (2 equiv) was refluxed in glacial acetic acid until the completion of the reaction as indicated by TLC. After completion, the reaction mixture was cooled to room temperature, the solid separated, washed with 1:1 mixture of hot methanol and chloroform and dried.

Cyclic voltammetric studies

Cyclic voltammetric experiments were carried out using a CHI 760C electrochemical workstation with a three-electrode system (platinum counter electrode, glassy carbon working electrode and Ag/AgCl reference electrode) at a scan rate of 50 mVs^{-1} in the presence of tetrabutylammonium perchlorate as a supporting electrolyte in DMSO.

Supplementary data

Spectral data, copies of ^{1}H, ^{13}C NMR, mass spectra of novel compounds and cyclic voltammogram of tested compounds are given as a separate supplementary file.

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