An Efficient Synthesis of Thio- and Thiazoloquinazolinones by the Electrochemical Oxidation of Catechols in the Presence of 2-Mercapto-4(3*H*)-quinazolinone

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Abstract: Thio- and thiazoloquinazolinones were synthesized efficiently by the anodic oxidation of catechols in the presence of 2-mercapto-4(3*H*)-quinazolinone in aqueous solution. 4-Methylcatechol and 3-methoxycatechol convert into thioquinazolinones via an EC (E: electron transfer, C: chemical reaction) pathway. Catechol, 3-methylcatechol, and 3,4-dihydroxybenzoic acid convert into thiazoloquinazolinones via an ECEC pathway.

Key words: electrochemical synthesis, phenols, thiols, heterocycles, decarboxylation

Quinazolinone **A** and its derivatives (Figure 1) are known to have a broad range of pharmaceutical properties, such as anticancer, anti-inflammatory, anticonvulsant, and antidiuretic activities.[1–7] The presence of the thiazole ring in many natural and synthetic quinazolinones has generated interesting biological properties.[8,9] Moreover, thiazolo[2,3-*b*]quinazolinones **B** (Figure 1) are potentially interesting from a biological and synthetic point of view. A number of classic methods for the preparation of thiazoloquinazolinones have been developed. These include the reaction of heteroaromatic 2-aminoesters with 2-(methylthio)-2-thiazoline,[10] solid-phase methods,[11] condensation of *o*-aminobenzoic acid hydrochloride with the appropriate α- or ω-thiocyanato ketone,[12] condensation of substituted anthranilic acids or esters with methyl 2-chlorothiazole-5-carboxylate,[13] reaction of anthranilic acid with 2-chlorobenzothiazole, and the reaction of ethylanthranilate with 2-chlorobenzothiazole.[14,15]

In this paper, we report a simple electrochemical method for the synthesis of several novel thio- and thiazoloquinazolinone derivatives from catechols **1a–e** and 2-mercapto-4(3*H*)-quinazolinone (**3**) (Table 1).

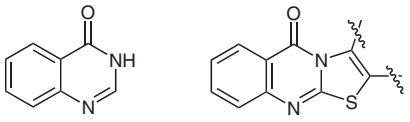
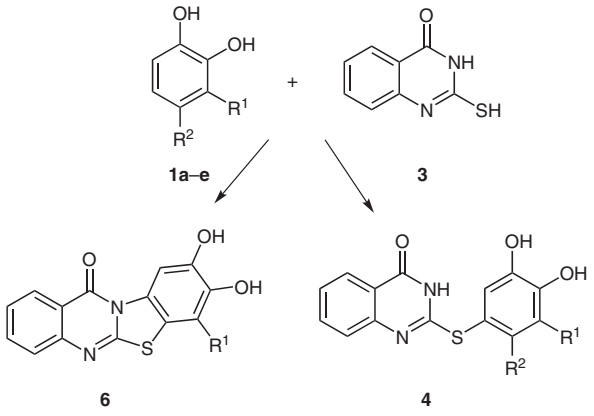


Figure 1 Quinazolinone **A** and thiazolo[2,3-*b*]quinazolinones **B**

Table 1 Electrochemical Synthesis of **4** and **6**



Product	R^1	R^2	Yield[a] (%)	Applied potential (V)
4a	H	Me	92	0.20
4b	OMe	H	87	0.15
6c	H	H	79	0.25
6c[b]	H	CO_2H	68	0.35
6e	Me	H	90	0.20

[a] Isolated yield.
[b] Decarboxylated product.

The electrochemical oxidation of catechols **1a–e** in the presence of 2-mercapto-4(3*H*)-quinazolinone (**3**) results in a smooth 1:1 addition reaction in water at ambient temperature to produce thioquinazolinones **4** and thiazoloquinazolinones **6** (Table 1). Cyclic voltammetry of a 1 mM solution of catechol **1c** in water–acetonitrile (90:10) containing 0.15 M phosphate buffer (pH 7.4) results in one anodic (A_1) and corresponding cathodic peak (C_1) (Figure 2, curve a), which is related to the transformation of catechol **1c** into the corresponding *o*-benzoquinone **2c** and vice versa through a quasi-reversible two-electron process (Scheme 1).

A peak current ratio (I_P^{C1}/I_P^{A1}) of nearly one, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-benzoquinone produced at the surface of the electrode under the

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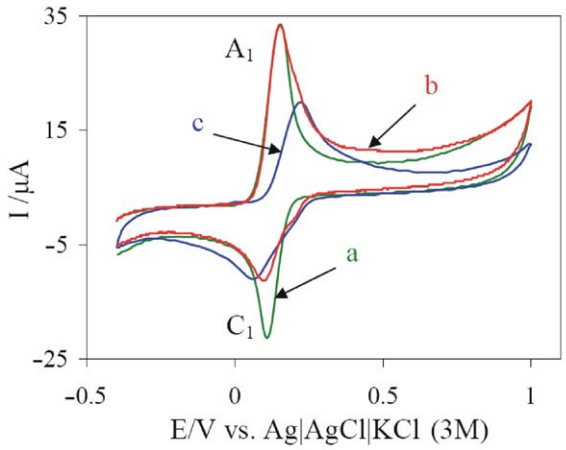
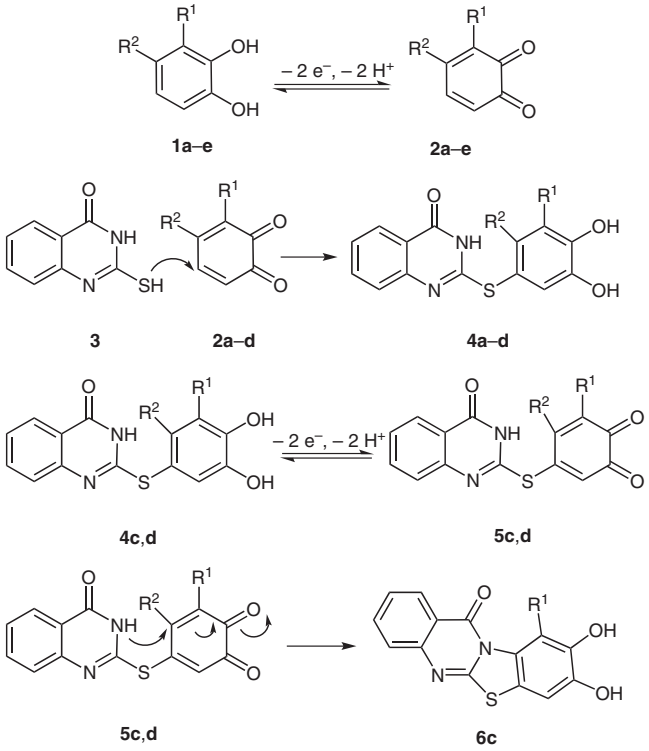


Figure 2 Cyclic voltammograms (scan rate = 100 mV·s^{-1}, r.t.): (a) 1 mM of **1c**, (b) 1 mM of **1c** in the presence of 1 mM of **3**; (c) 1 mM of **3** at a glassy carbon electrode (1.8 mm diameter) in 0.15 M phosphate buffer (pH 7.4).



Scheme 1 Proposed mechanism for the electrooxidation of catechols in the presence of 2-mercapto-4(3*H*)-quinazolinone

experimental conditions. In other words, chemical reactions such as hydroxylation[16] and dimerization[17] are too slow to be observed on the time scale of the cyclic voltammetry. The electrochemical oxidation of catechols **1a–e** was also studied in the presence of 2-mercapto-4(3*H*)-quinazolinone (**3**) as a nucleophile. Figure 2 (curve b) shows the cyclic voltammogram obtained for 1mM catechol **1c** in the presence of 1 mM 2-mercapto-4(3*H*)-quinazolinone (**3**). Decrease of cathodic peak height is related to the coupling reaction between the *o*-quinone derived from catechol **2c** and 2-mercapto-4(3*H*)-quinazolinone (**3**). The cyclic voltammogram of 1 mM 2-mercapto-4(3*H*)-quinazolinone (**3**) is also shown in Figure 2 (curve c), for comparison.

Because the oxidation potential peaks of **1c** and **3** (Figure 2) are close together, and we wanted to minimize the oxidation of **3** to achieve higher selectivity, we applied 0.25 V potential versus Ag/AgCl/KCl(3 M) in the preparative synthesis processes (Table 1). Multicyclic voltammetry of **1c** in the presence of **3** shows a new peak A_0 appearing in the second cycle, parallel to the shift of the A_1 peak in a positive potential direction (Figure 3). This new peak is related to the electrochemical oxidation of intermediate **4c** (Scheme 1). The positive shift of the A_1 peak in the presence of **3** is due to the formation of a thin film of product on the surface of the electrode, which decreases the performance of the electrochemical process.

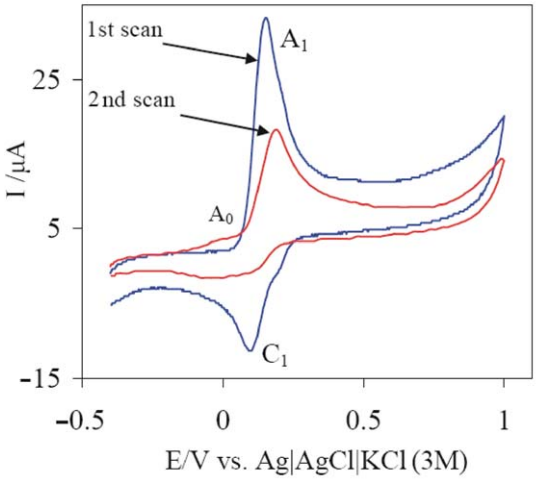


Figure 3 Multicyclic voltammograms. *Conditions*: 1 mM catechol **1c**, 2-mercapto-4(3*H*)-quinazolinone (**3**), glassy carbon electrode (1.8 mm diameter), H_2O–MeCN (90:10), 0.15 M phosphate buffer/supporting electrolyte (KH_2PO_4/K_2HPO_4, pH 7.4), scan rate 100 mV·s^{-1}, r.t.

As shown in Table 1, we have obtained various derivatives of thio- and thiazoloquinazolinones from the reaction of catechols **1a–e** and 2-mercapto-4(3*H*)-quinazolinone (**3**). The possible mechanism for the formation of products **4** and **6** is shown in Scheme 1. The initial event is the nucleophilic attack of 2-mercapto-4(3*H*)-quinazolinone (**3**) on *o*-quinone **2** (Scheme 1). For 4-methyl- and 3-methoxycatechol (**1a** and **1b**), the reaction was stopped at this step to give products **4a** and **4b** (Schemes 1 and 2, Table 1). But in the case of catechols **1c–e**, the reaction was continued to give cyclic compounds **6c** and **6e** (Schemes 1 and 2). For 3,4-dihydroxybenzoic acid (**1d**) electro-decarboxylation occurred to give product **6c** (Scheme 1 and Table 1, entry 4). It should be mentioned that for each of 3-methoxy- and 3-methyl-

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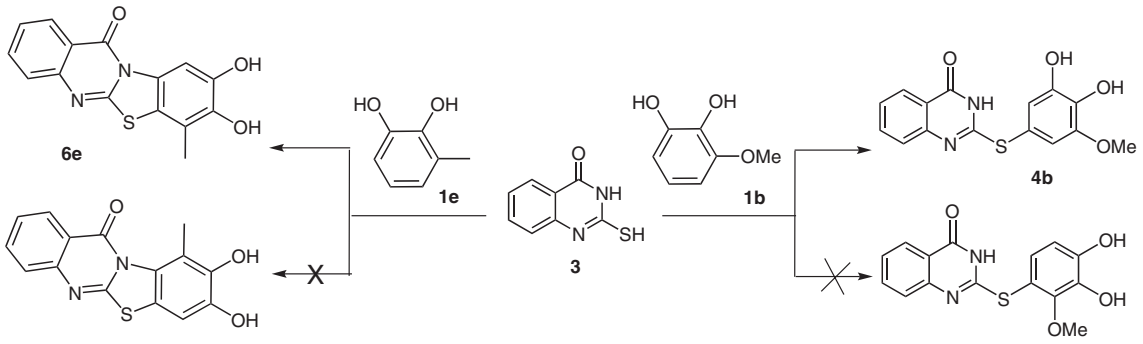

Scheme 2 Possible products for the electrooxidation of 3-methoxy- and 3-methylcatechol (**1b** and **1e**) in the presence of 2-mercapto-4(3*H*)-quinazolinone

catechol (**1b** and **1e**) two possible products can be predicted (Scheme 2), but we obtained selectively **4b** from 3-methoxycatechol (**1b**) and **6e** from 3-methylcatechol (**1e**).

Chemicals were purchased from Merck, Aldrich, and Fluka, and were used without further purification. All experiments were carried out at r.t. Cyclic voltammetry (CV) was performed on a μAutolab potentiostat/galvanostat type III and preparative analysis was carried out on an EG&G PAR A Model 174 A potentiostat/galvanostat. The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter) and platinum wire was used as the counter electrode (CE). The WE used in controlled-potential coulometry and macroscale electrolysis was an assembly of three carbon rods (8 mm diameter, 4 cm long) and a large platinum gauze (3 cm × 3 cm) constituted the CE. The WE potentials were measured versus Ag/AgCl/KCl (3 M) as a reference electrode. All electrodes were obtained from Azar Electrode, Urmia, I. R., Iran. NMR spectra were recorded on a Bruker DRx-300 Avance instrument. IR spectra were recorded on a Bruker IFS-66 FT-IR spectrophotometer. Mass spectra were obtained on a QP-1100EX Shimadzu GC-MS (EI, 70 eV). Melting points of the products were obtained on an electrothermal melting point model 9200.

Electro-organic Synthesis of 4 and 6; General Procedure

A mixture (100 mL) of H_2O–MeCN (90:10) containing 0.15 M phosphate buffer/supporting electrolyte (KH_2PO_4/K_2HPO_4, pH 7.4) was pre-electrolyzed at the applied potential (Table 1) in an undivided cell. Subsequently, catechol **1** (2 mmol) and **3** (2 mmol) were added to the cell. Finally, the electrolysis was performed at the same potential (Table 1). The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted several times during the electrolysis and the carbon anode was washed in acetone to reactivate it. At the end of the electrolysis, the cell was placed in a refrigerator and left overnight. The precipitated solid was collected by filtration and was then washed several times with distilled H_2O. Then the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and MS.

2-[(4,5-Dihydroxy-2-methylphenyl)thio]quinazolin-4(3*H*)-one (4a)

Pale brown solid; mp 227–228 °C (dec).

IR (KBr): 3415 (OH), 2899 (CH_3), 1657 (C=O), 1578 and 1514 (Ar) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.18 (s, 3 H, CH_3), 6.77 (s, 1 H, CH of Ar), 6.94 (s, 1 H, CH of Ar), 7.28 (d, $^3J_{HH}$ = 7.71 Hz, 1 H, CH of Ar), 7.37 (t, $^3J_{HH}$ = 7.71 Hz, 1 H, CH of Ar), 7.66 (t, $^3J_{HH}$ = 7.71 Hz, 1 H, CH of Ar), 8.00 (d, $^3J_{HH}$ = 7.71 Hz, 1 H, CH of Ar), 9.39 (br, 2 H, 2 OH), 12.46 (br, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.20 (CH_3), 114.22 (CH of Ar), 118.29 (CH of Ar), 120.44 (C_{ipso}–CO), 124.18 (CH of Ar), 126.06 (CH of Ar), 126.42 (CH of Ar and C_{ipso}–S), 134.63 (CH of Ar), 134.92 (C_{ipso}–CH_3), 144.00 (C_{ipso}–OH), 148.17 (C_{ipso}–OH), 148.92 (C_{ipso}–N), 156.24 (C=O), 161.98 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 300 (50) [M$^+$], 267 (100), 249 (20), 178 (60), 124 (20), 90 (60), 63 (20), 39 (40).

2-[(3,4-Dihydroxy-5-methoxyphenyl)thio]quinazolin-4(3*H*)-one (4b)

White solid; mp 223–224 °C (dec).

IR (KBr): 3329 (OH), 1652 (C=O), 1576 and 1554 (Ar) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H, OCH_3), 6.70 (s, 1 H, CH of Ar), 6.74 (s, 1 H, CH of Ar), 7.34 (d, $^3J_{HH}$ = 7.64 Hz, 1 H, CH of Ar), 7.39 (t, $^3J_{HH}$ = 7.64 Hz, 1 H, CH of Ar), 7.68 (t, $^3J_{HH}$ = 7.64 Hz, 1 H, CH of Ar), 8.01 (d, $^3J_{HH}$ = 7.64 Hz, 1 H, CH of Ar), 9.16 (br, 2 H, 2 OH), 12.42 (br, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.53 (OCH_3), 111.64 (CH of Ar), 114.65 (CH of Ar), 117.16 (C_{ipso}–CO), 120.53 (CH of Ar), 126.14 (CH of Ar), 126.44 (CH of Ar and C_{ipso}–S), 134.92 (CH of Ar), 136.84 (C_{ipso}–OCH_3), 146.50 (C_{ipso}–OH), 148.92 (C_{ipso}–N), 148.96 (C_{ipso}–OH), 156.9 (C=O), 162.1 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 316 (10) [M$^+$], 284 (6), 178 (100), 140 (75), 119 (70), 92 (52), 51 (30).

8,9-Dihydroxy-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (6c)

Pale green solid; mp 217–218 °C (dec).

IR (KBr): 3412 (OH), 1705 (C=O), 1627 and 1569 (Ar) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.29 (s, 1 H, CH of Ar), 7.49 (t, $^3J_{HH}$ = 6.18 Hz, 1 H, CH of Ar), 7.62 (d, $^3J_{HH}$ = 6.18 Hz, 1 H, CH of Ar), 7.83 (d, $^3J_{HH}$ = 6.18 Hz, 1 H, CH of Ar), 8.28 (t, $^3J_{HH}$ = 6.18 Hz, 1 H, CH of Ar), 8.46 (s, 1 H, CH of Ar), 9.63 (br, 2 H, 2 OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 106.86 (CH of Ar), 109.05 (CH of Ar), 112.87 (C_{ipso}–S), 118.47 (C_{ipso}–CO), 125.77 (CH of Ar), 126.01 (CH of Ar), 126.90 (CH of Ar), 128.44 (C_{ipso}–N), 135.02 (CH of Ar), 145.12 (C_{ipso}–N), 145.70 (C_{ipso}–OH), 147.22 (C_{ipso}–OH), 158.26 (C=O), 160.06 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 284 (5) [M$^+$], 178 (100), 119 (35), 92 (31), 64 (17), 43 (12).

8,9-Dihydroxy-7-methyl-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (6e)

Pale brown solid; mp 242–243 °C (dec).

IR (KBr): 3517 (OH), 2965 (CH_3), 1715 (C=O), 1580 and 1553 (Ar) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.26 (s, 3 H, CH_3), 3.6 (br, 2 H, 2 OH), 7.14 (s, 1 H, CH of Ar), 7.47 (t, $^3J_{HH}$ = 7.97 Hz, 1 H, CH

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of Ar), 7.57 (d, $^3J_{HH}$ = 7.97 Hz, 1 H, CH of Ar), 7.81 (t, $^3J_{HH}$ = 7.97 Hz, 1 H, CH of Ar), 8.18 (d, $^3J_{HH}$ = 7.97 Hz, 1 H, CH of Ar).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.87 (CH_3), 106.02 (CH of Ar), 113.90 (C_{ipso}–CO), 118.21 (C_{ipso}–CH_3), 119.28 (C_{ipso}–S), 125.35 (CH of Ar), 125.62 (CH of Ar), 127.13 (CH of Ar), 127.19 (C_{ipso}–N), 134.85 (CH of Ar), 144.21 (C_{ipso}–N), 145.69 (C_{ipso}–OH), 147.10 (C_{ipso}–OH), 159.24 (CO), 160.2 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 298 (100) [M^+], 283 (25), 269 (25), 178 (5), 149 (15).

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