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A regioselective approach toward the synthesis of pharmacologically important quinone-containing heterocyclic systems

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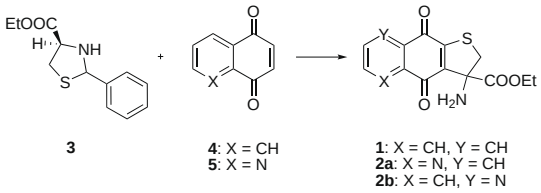
ABSTRACT

An inexpensive and regioselective approach to dihydrothieno[3,2-*g*]quinoline-4,9-dione is reported. A combination of a mild version of Skraup reaction with a sequential substitution/Michael addition allowed the selective preparation in acceptable yield of a pharmacologically important quinone derivative, previously obtained only in trace and together with the other regioisomer.

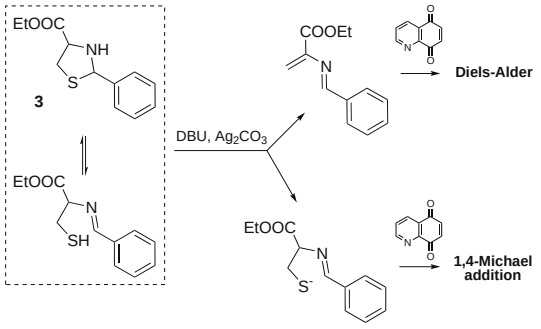
Quinone moiety is a key structural feature of antitumoral anthracyclines (as doxorubicin and actinomycin D) and anthracenediones (mitoxantrone), two of the most effective classes of anticancer agents clinically used to treat a wide range of cancers, including leukemias, lymphomas, and breast, uterine, ovarian, and lung cancers. As a consequence, in the search for novel agents endowed with improved pharmacokinetic properties, potency or activity spectrum and lower side effects, a number of quinone and heterocyclic quinone derivatives were prepared and several of them have shown promise in clinical studies.

Following our research program on antitumor agents, we lately focussed our interest on dihydrothieno[2,3-*b*]naphtho-4,9-dione (DTNQ) derivative **1** and its aza analogues dihydrothieno[2,3-*g* and 3,2-*g*]quinoline-4,9-diones (DTQQ) **2a** and **2b** (Scheme 1) prepared, by some of us[1–7] by reacting a thiazolidine derivative **3** with naphthoquinone (**4**) or quinoline-5,8-dione (**5**) in the presence of silver carbonate and DBU as bases (Scheme 1).[2] However, this method suffered from a few drawbacks, such as poor reproducibility, the use of expensive reagents, and the difficult separation of the DTQQ cores **2a** and **2b**.

Moreover, as the quinoline-5,8-dione **5** could react with both the thiolate and the azadiene resulting from the cleavage of thiazolidine **3** in the aforementioned basic medium (Scheme 2), derivatives **2a** and **2b**, resulting from 1,4-Michael addition pathway, were obtained in very low yield (18% and 4%, respectively) together



Scheme 1. Synthesis of DTNQ and DTQQ involving double Michael addition.



Scheme 2. Thiazolidine cleavage in basic medium and possible reaction pathways with quinoline-5,8-dione.

with the derivatives resulting from the Diels–Alder pathway.[2] To overcome these problems, we have recently described a practical, cheap and environment-friendly method to selectively obtain **2a**

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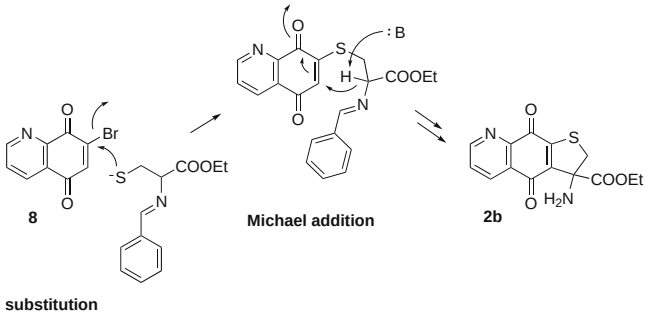
by using alumina as a catalyst in the double Michael addition to quinone system.[8]

With the intention to further explore the structure–activity relationships (SARs) of this class of compounds, we were also interested in the other isomer **2b**, previously obtained only as a minor product.[2,3,7–9] Therefore, we herein report a selective approach to the DTQQ derivative **2b**.

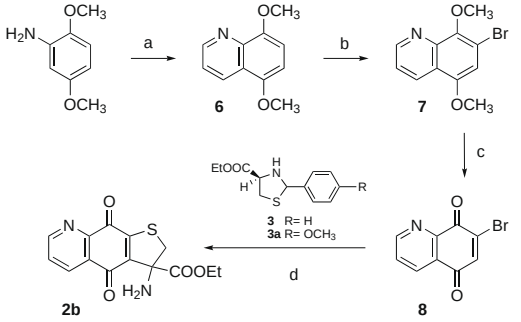
We assumed that the regioselective preparation of this derivative could be conveniently achieved by replacing quinoline-5,8-dione **5** with 7-bromoquinoline-5,8-dione **8** in the reaction with thiazolidine **3**. With the latter substrate, the substitution of the bromine (actually through a Michael addition followed by elimination of bromide) and Michael addition can advantageously replace the previously reported double Michael addition (Scheme 3). In this way the nucleophilic attack of the sulfur atom should occur preferentially at the C-7 position of the quinoline ring.

Thus, the first step was the synthesis of the key intermediate 7-bromo-5,8-dimethoxyquinoline **8** (Scheme 4). We started from the inexpensive 2,5-dimethoxyaniline to prepare 5,8-dimethoxyquinoline **6** in 45% yield by our modification[10] of a mild variant of the Skraup reaction.[11] Then, the regioselective bromination of 5,8-dimethoxyquinoline **6** with *N*-bromosuccinimide[12] furnished derivative **7** which was oxidized with ceric ammonium nitrate to compound **8**.[13]

Afterwards, we focussed on the reaction of 7-bromoquinoline-5,8-dione **8** with thiazolidine **3**. We applied conditions similar to those previously reported by some of us to obtain DTQQ derivative **2a** in 18% yield and the desired compound **2b** only as a minor product (4%).[2,3] In order to avoid the possibility of a competition between the substitution at the C-7 position and the Michael addition at the C-6 position of the thiolate resulting from the opening of thiazolidine ring,[2,3] we used sodium carbonate instead of silver carbonate. In fact, the coordination bond with a Lewis acid such as silver or aluminum[8] ion increases the electron-withdrawing effect of the heterocyclic nitrogen atom thus strongly enhancing the reactivity of the 6-position.[14]



Scheme 3. Synthesis of DTQQ **2b** via sequential substitution/Michael addition. B = base.



Scheme 4. Regioselective synthesis of DTQQ **2b**. Reagents and conditions: (a) glycerol (2.5 equiv), $FeSO_4{\cdot}7H_2O$ (0.03 equiv), sodium *m*-nitrobenzenesulfonate (0.6 equiv), $MeSO_3H$, 125 °C, 45%; (b) NBS (2 equiv), THF, K_2CO_3 (0.5 equiv), rt, 2 h; (c) CAN (3 equiv), acetic acid/water, rt, 10 min; and (d) base (Table 1), CH_3CN, rt, 1 h.

As a matter of fact, a solution of thiazolidine **3** (1 mmol) and Na_2CO_3 (1 mmol) in anhydrous acetonitrile was treated with a solution of 7-bromoquinoline-5,8-dione **8** (1 mmol) in the same solvent and then with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1 mmol) to obtain DTQQ derivative **2b** in modest yield (10%) but, as expected, as a single regioisomer (Table 1, entry 1), as confirmed by 2D NMR experiments (HMQC and HMBC, not shown) which gave results identical to the previously reported ones.[2] This confirmed the potential of this approach in terms of regioselectivity.

In order to optimize the reaction parameters, we then decided to set up a series of experiments to study the effect of the nature of the base, the reactant ratio, the order of addition and also of (eventual) substituents on thiazolidine ring.

The experimental results reported in Table 1 seem to suggest that the reaction yield is greatly influenced by the strength of the base employed.

In fact, when only DBU (pK_a in CH_3CN = 24.3[15,16]) was used as a base, the yield raised to 34% (Table 1, entry 3) while the use of sodium carbonate alone gave no desired product (Table 1, entry 2). The replacement of DBU with Hünig's base (*N*,*N*-diisopropylethylamine, pK_a in CH_3CN = 18.8[15,16]) or triethylamine (pK_a in CH_3CN = 18.8;[15,16] Table 1, entries 6 and 7, respectively) had a negative effect on the yield. The lower reactivity of Hünig's base relative to triethylamine may be due to the highest sterical hindrance of the former. However, changes in the amount of DBU (Table 1, entries 4 and 5) as well as the order of addition of the reagents were also crucial to the success of reaction (compare entries 3, 8, and 9 in Table 1). In fact, when either DBU was added in excess of the stoichiometric amount or it was not allowed to react with thiazolidine **3** before the addition of quinolinedione **8**, the resulting yield was significantly decreased.

Finally, the substitution of thiazolidine **3** with the methoxy-analogue **3a**[17] in the reaction with quinolinedione **8** further improved the yield to 37%,[18] particularly noteworthy if considering that derivative **2b** was previously obtained only as a minor product (maximum yield 8%).[3]

In conclusion, we have developed an inexpensive and regioselective approach to obtain in acceptable yield the pharmacologically important quinone derivative **2b**, previously obtained only in trace and together with its regioisomer **2a**.

Table 1
Reaction of 7-bromoquinoline-5,8-dione **8** with thiazolidines **3** and various catalysts, solvents, and different reaction conditions

Entry	Base (equiv)	R	Method[a]	Yield[b]
1	Na_2CO_3 (1) and then DBU (1)	**3**	A	10
2	Na_2CO_3	**3**	B	—
3	DBU (1)	**3**	B	34
4	DBU (0.5)	**3**	B	10
5	DBU (2)	**3**	B	5
6	DIPEA(1)	**3**	B	8
7	TEA (1)	**3**	B	15
8	DBU (1)	**3**	C	—
9	DBU (1)	**3**	D	5
10	DBU (1)	**3a**	E	37

[a] Reaction conditions: (A) a solution of **8** was added to a solution of **3** and Na_2CO_3, then DBU was added; (B) a solution of **8** in acetonitrile was added to a solution of **3** and base; (C) the base was added to a solution of **3** and **8** in acetonitrile; (D) a solution of **3** and base in acetonitrile was added to a solution of **8**; and (E) the same as B, thiazolidine **3a** was used as reactant.
[b] Isolated yield.

The key step was a sequential substitution/Michael addition reaction between 7-bromoquinoline-5,8-dione **8** and thiazolidine **3**.

This method together with the one we recently reported for the selective obtainment of isomer **2a**, provide a valuable tool to a rapid access to DTQQ derivatives, thus allowing a thorough exploration of structure–activity relationships (SARs) of this class of antiproliferative agents.

Acknowledgments

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10. *Experimental procedure for the Skraup synthesis of 5,8-dimethoxyquinoline* **6**: Sodium *m*-nitrobenzenesulfonate (9.11 g; 40.47 mmol) was added to methanesulfonic acid (34.00 mL) at 20 °C followed by iron sulfate heptahydrate (0.54 g, 1.96 mmol). This addition is slightly exothermic and raised the temperature to 27 °C. To the resulting mixture 2,5-dimethoxylaniline (10.00 g, 65.28 mmol) was added through an addition funnel over 30 min while stirring, then the funnel was flushed with methanesulfonic acid (2.5 mL), and the mixture was kept stirring until the solid dissolved (≈15 min). The addition is exothermic, and the temperature reached ≈60 °C after the addition. The reaction mixture was heated to 125 °C, and glycerol (12 mL, 163.2 mmol) was added dropwise over 5 h. After stirring at 125 °C for 24 h, the mixture was left cooling to room temperature, treated with cold aqueous NaOH (6 M, 75 mL) up to pH ≈ 3 and then with $NaHCO_3$ (3.38 g) up to pH ≈ 5. The resulting mixture was then extracted with DCM for 120 h by means of a continuous extractor. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (gradient, petroleum ether/ethyl acetate, 50:50 to 20:80) to obtain derivative **8** as a white solid (yield 45%).
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18. *Experimental procedure for the reaction of 7-bromoquinoline-5,8-dione* **8** *and thiazolidine derivative* **3a**. To a solution of thiazolidine **3a** (1.0 equiv, 2.93 mmol, 0.783 g) in dry acetonitrile (10 mL) 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU, 1.0 equiv, 2.93 mmol, 0.438 mL) was added. A solution of 7-bromoquinoline-5,8-dione **8** (1.0 equiv, 2.93 mmol, 0.697 g) in dry acetonitrile (40 mL) was then added to the resulting mixture by means of a cannula. The yellow solution turned dark immediately and was kept stirring at room temperature for 1 h. After solvent removal under vacuum, the brown oily residue was taken up with DCM (4 mL) and HCl 1 M (30 mL). The mixture was kept stirring for additional 30 min, then the two phases were separated and the aqueous one was washed with diethyl ether (3 × 25 mL), basified with 10% $NaHCO_3$ solution up to pH 7–8, and extracted with chloroform (3 × 25 mL). The combined organic phases were washed with brine (3 × 25 mL) and dried over anhydrous sodium sulfate. After filtration and solvent removal under vacuum a brown oil was obtained which was purified by flash column chromatography on silica gel (DCM/ethyl acetate, 7:3) to obtain dihydrothieno[3,2-*g*]quinoline-4,9-dione **2b** as a yellow solid (yield 37%).