

## A FACILE SYNTHESIS AND ANTICANCER ACTIVITY OF (*E*)-DIETHYL 2-STYRYLQUINOLINE-3,4-DICARBOXYLATES

Shuling Liu,<sup>1</sup> Jing Wang,<sup>1</sup> Yang Li,<sup>1\*</sup> and Yu Chen<sup>2\*</sup>

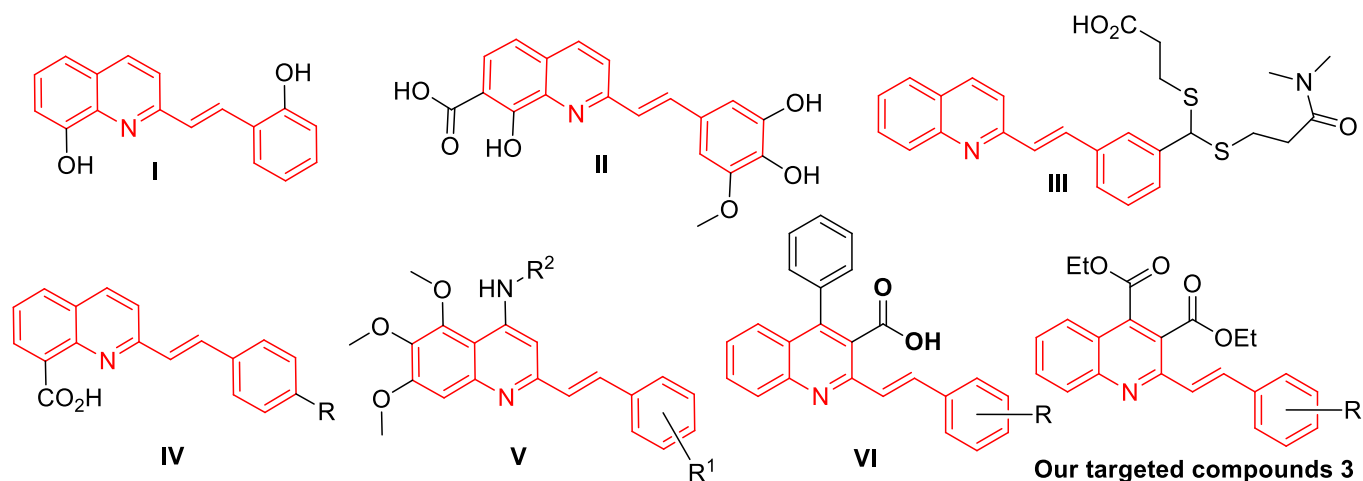
<sup>1</sup> College of Chemistry and Chemical Engineering, Bohai University, Jinzhou 121013, China. <sup>2</sup> School of Life Science and Biopharmaceutics, Shenyang Pharmaceutical University, Shenyang, 110016, China; E-mail: bhuzh@163.com; 569180398@qq.com

**Abstract** – In the present investigation, a simple and flexible synthesis of a series of novel (*E*)-diethyl 2-styrylquinoline-3,4-dicarboxylates **3a-q** has been achieved for the first time in good yields, involving one-pot sequential Arbuzov/Horner–Emmons reaction sequence using the newly-synthesized diethyl 2-(bromomethyl)quinoline-3,4-dicarboxylate as the substrate. The latter was obtained by NBS-mediated radical bromination reaction of the readily available diethyl 2-methylquinoline-3,4-dicarboxylate. A primary *in vitro* evaluation for their antiproliferative activity against human cancer cell lines (A549, HT29 and T24) revealed that the compound **3k** with 3,4,5-trimethoxystyryl moiety represented the most active molecule against the tested A549 cell lines in this round of effort with the IC<sub>50</sub> value of 2.38 μmol•L<sup>-1</sup>, being higher than the reference cisplatin.

### INTRODUCTION

Among a great variety of quinoline derivatives, 2-styrylquinolines (SQLs) form an important type of structural motifs in medicinal chemistry,<sup>1</sup> and many members of this family such as WK14 (**I**),<sup>2</sup> FZ-41 (**II**),<sup>3</sup> and MK-571 (**III**)<sup>4</sup> as shown in Figure 1 have been widely applied as antiproliferative, antiviral, anti-HIV, and antimicrobial agents. Recently, Dhanawat *et al.* have revealed that the 2-styrylquinoline structure template could be considered as an elite scaffold and a wonderful pharmacophore in anticancer drug discovery.<sup>5</sup> For example, (*E*)-8-carboxyl-2-styrylquinoline (**IV**, Figure 1) was reported to demonstrate a marked antiproliferative activity against the P388 leukemia cell line.<sup>6</sup> Similarly, (*E*)-5,6,7-trimethoxy-N-aryl-2-styrylquinolin-4-amines (**V**, Figure 1) were reported to exhibit potent anticancer activity against human cancer cell lines A-2780 and MCF-7.<sup>7</sup> Recent studies from Mittal and

coworker on the antiproliferative activity evaluation of 2-styrylquinoline-3-carboxylate derivatives against tumor cell lines have also validated the importance of this class of compounds as a new hope in developing novel anticancer drugs.<sup>8</sup> Thereafter, they reported that (*E*)-4-phenyl-2-styrylquinoline-3-carboxylic acids (**VI**, Figure 1) could be used as effective antiproliferative agents with excellent selectivity toward cancer tissue, the selectivity of which will enhance concentration in the cancer cells and will reduce the absorption in the non-cancerous cells, enabling these molecules much less toxic.<sup>9</sup> Owing to their striking biological activities and in order to have structurally diversified molecules for bio-screening, considerable synthetic efforts have been made surrounding the 2-styrylquinoline structure template for further functionalization and modification by organic and medicinal chemists with the aim of enhancing the potency of this privileged class of quinolines.<sup>10-12</sup>

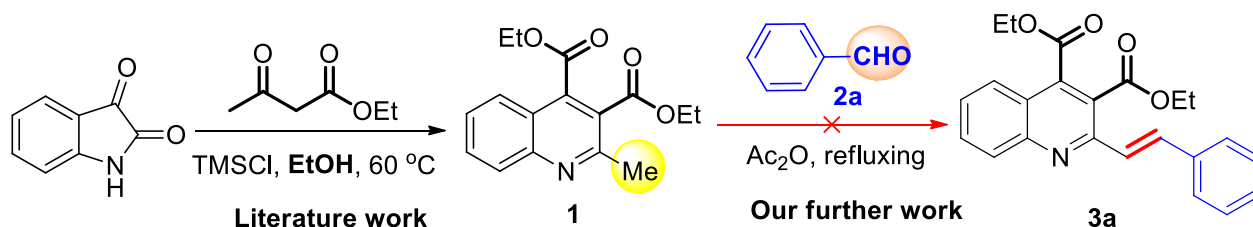


**Figure 1.** Structures of some biologically active 2-styrylquinolines **I-VI** and our targeted compounds **3**

In light of the above findings, and in view of (*E*)-2-styrylquinoline-3-carboxylate representing an elite scaffold towards new drug discovery, we envisioned that it might be a worthwhile effort to design and synthesize a new class of carboxylate functionalized 2-styrylquinoline derivatives, which might lead to a new dimension of structural diversity as potential candidates for biological evaluations or provide more opportunities for further synthetic manipulations. Accordingly, in the context of our continuing interest in the construction of interesting types of quinoline-based compounds,<sup>13-16</sup> we would like to report herein a simple and convenient two-step one-pot synthesis of a series of structurally new and intriguing (*E*)-diethyl 2-arylvinylquinoline-3,4-dicarboxylates as shown in Figure 1. To the best of our knowledge, the synthesis and anticancer activity evaluation of such quinoline derivatives has not been reported so far, which might be an attractive template for further study from both a biological as well as a building block perspective.

## RESULTS AND DISCUSSION

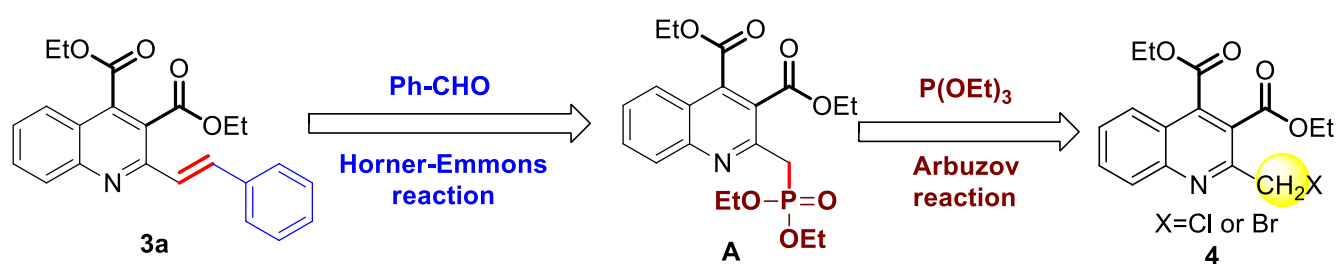
Recently, Lu *et al.* reported a TMSCl-mediated Pfitzinger reaction of isatin with ethyl acetoacetate for the synthesis of diethyl 2-methylquinoline-3,4-dicarboxylate as shown in Scheme 1.<sup>17</sup> Considering the presence of dicarboxylate functional groups at 3- and 4-positions of quinoline ring, we devised that if its 2-methyl group could be further transformed into styrene moiety, the synthesis of the desired diethyl 2-styrylquinoline-3,4-dicarboxylate derivatives might be achieved. Thus, in our initial experimental we attempted such synthesis by subjecting 2-methylquinoline-3,4-dicarboxylate to the condensation reaction with benzaldehyde under the classical reaction conditions as described in literature,<sup>18</sup> using boiling acetic anhydride as reaction media followed by hydrolysis in pyridine-water mixture (Scheme 1). However, the reaction proceeded very poorly in our case, giving an intractable complex mixture, from which the desired product could not be isolated in any appreciable yield.



**Scheme 1.** An unsuccessful synthesis of diethyl 2-styrylquinoline-3,4-dicarboxylate (**3a**)

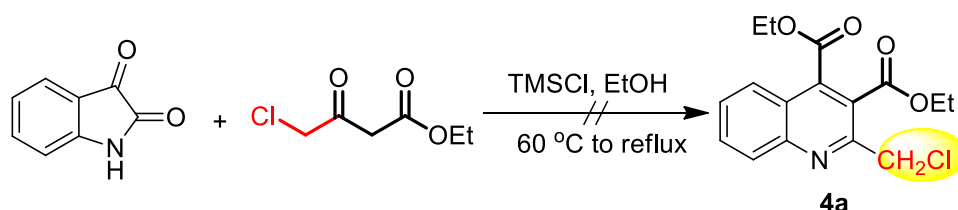
Attempts to use other reaction conditions such as NaOAc in H<sub>2</sub>O/AcOH (v: v = 1 : 1),<sup>19</sup> Aliquat 336 as a phase-transfer in boiling aqueous 5 M NaOH,<sup>20</sup> or the use of In(OTf)<sub>3</sub><sup>21</sup> as catalyst were also unfruitful and the starting materials were recovered unchanged. In addition, although there are some elegant syntheses of (*E*)-2-styrylquinoline-3-carboxylates using 1-methylimidazolium trifluoroacetate ([Hmim]TFA)<sup>22</sup> or Brønsted acidic imidazolium ionic liquids as reaction medium,<sup>23</sup> following these purported approaches was found to be not suitable for our transformation as well, giving poor yields of highly impure products. Moreover, the high cost and environmental toxicity of these ionic liquids have limited their practical application. After these failed trials, we decided to circumvent the problem by designing an alternative approach. As we know that halomethyl-functionalized aromatic heterocycles have been widely served as versatile building blocks for wide-ranging applications in many chemical transformations in accessing various intriguing and complex small molecules. For example, they can proceed to Arbuzov reaction with phosphites to furnish the corresponding phosphonates.<sup>24</sup> On the other hand, the Horner-Emmons olefination reaction of phosphonates with aldehydes has served as a powerful method for the construction of carbon-carbon double bonds.<sup>25,26</sup> Thus, we envisioned that if the 2-methyl group **1** could be converted into halomethyl moiety, the resulting 2-halomethylquinoline derivative might

open opportunity for the synthesis of our targeted compounds through combination of the two name reactions (Scheme 2).



**Scheme 2.** Designed two-step one-pot reaction for diethyl 2-styrylquinoline-3,4-dicarboxylate (**3a**)

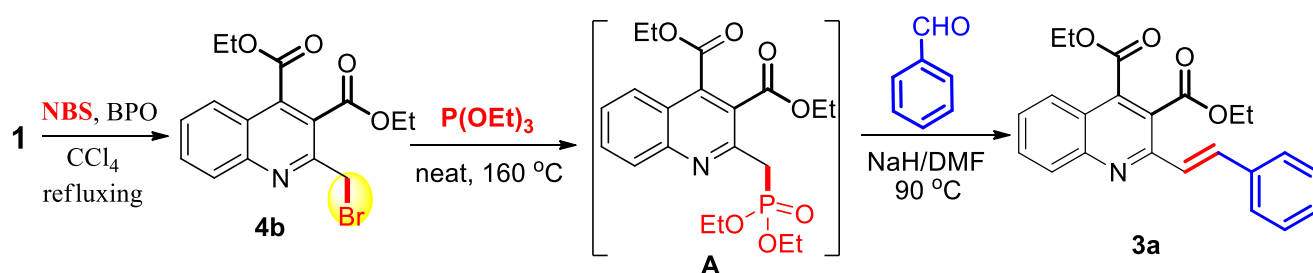
To this end, the first stage to implement our strategy was the realization of the requisite diethyl 2-halomethylquinoline-3,4-dicarboxylate. It occurred to us that the required 2-halomethylquinoline might be readily synthesized using the aforementioned method of literature<sup>17</sup> via Pfitzinger reaction of isatin with ethyl 4-chloro-3-oxobutanoate as shown in Scheme 3. Disappointingly, contrary to our expectation, this was not the case in our hands and the reaction was found to be very complex and we could not obtain any of the desired product in any appreciable yields.



**Scheme 3.** An unsuccessful synthesis of diethyl 2-chloromethylquinoline-3,4-dicarboxylate

With the unsuccessful attempt, we decided to conduct the classical radical bromination reaction of **1** with NBS in refluxing  $\text{CCl}_4$  with the presence of catalytic amount of benzoyl peroxide (BPO) as initiator as shown in Scheme 4. In this bromination reaction the desired monobromo product **4b** could be produced but was always accompanied by the excess byproducts together with small amount of unreacted substrate **1**, leading to a unsatisfactory yield of 41%. Moreover, due to their very close polarities the product isolation became quite tedious and cumbersome. In order to improve the product yield, we further modified the bromination manipulation and found that if the slightly excessive NBS was added in batches in the amount of 1/3 portions of 1.2 equiv. every 3 h to the gently refluxing  $\text{CCl}_4$  solution, a 25% increase in the product yield to 66% was achieved with only a slight amount of byproduct after the reaction was complete. Presumably, the resulting  $\text{Br}_2$  derived from NBS remained in a lower concentration throughout the bromination reaction course, thereby restraining the side reaction and leading to the formation of the desired product in a higher yield. Subsequently, our attention was focused on its Arbuzov reaction with

triethyl phosphite. Initially, we used ZnBr<sub>2</sub> as catalyst in dichloromethane solution according to the method as described in the literature.<sup>24</sup> However, the approach was not suitable for our transformation and the product was obtained in a poor yield together with some undefined byproducts. Interestingly, we found that upon heating **4b** in neat triethyl phosphite media (35.0 equiv.) at 160 °C without added any solvent or catalyst, the Arbuzov reaction proceeded very smoothly with nearly quantitative conversion to the corresponding 2-((diethoxyphosphoryl)methyl)quinoline **A** within 3 h as monitored by TLC. Considering that the reaction proceeded very cleanly and did not involve any additional solvents or catalysts, we speculated at this stage that the followed Horner-Emmons olefination reaction might proceed in one-pot sequential procedure without isolation of the intermediate **A** as shown in Scheme 4.



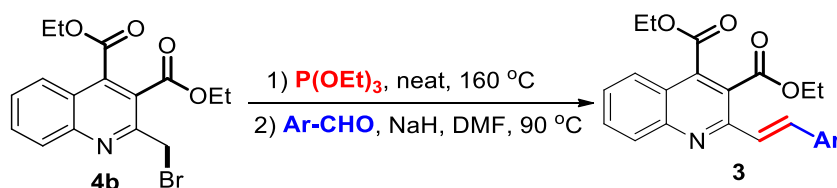
**Scheme 4.** Synthetic route for diethyl 2-styrylquinoline-3,4-dicarboxylate (**3a**)

Accordingly, after completion of the Arbuzov reaction as monitored by TLC, the excessive triethyl phosphite was evaporated to dryness under reduced pressure, and then to the resulting residue was added directly 1.2 equiv. benzaldehyde solution in THF with the presence of <sup>t</sup>BuOK as base to conduct the olefination reaction according to the protocol of literature.<sup>27</sup> However, the reaction did not proceed satisfactorily, producing intractable complex mixtures, in which we could not isolate any of the desired product. We further investigated the reaction using NaOMe as base in DMF solution as described in literature.<sup>28</sup> But this attempt was also less satisfactory, and the expected product **3a** was obtained in a modest yield of 32%. After these attempts, we were delighted to observe that the utilization of NaH as base was very suitable to prompt the reaction proceeding efficiently, giving the expected product **3a** in a good yield of 74% within 3.5 h.

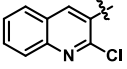
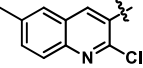
Subsequently, we investigated the viability of the one-pot reaction sequence by extending to a variety of aromatic aldehydes available in our laboratory in a similar fashion for building differently substituted analogs. Satisfactorily, all these substituted aromatic aldehydes were equally amenable to the reaction process without any experimental difficulties, successfully delivering the corresponding **3b-3o** in satisfactory yields of 51%-76%. These experimental results as listed in Table 1 demonstrated that the electronic nature of the substituent present in the aromatic aldehydes appeared to hardly affect the transformation, neither in product yield nor in reaction rate. For example, the compound **3c** with electron-donating methyl group and **3o** bearing electron-withdrawing nitro group were obtained in

comparable yields of 76% and 72%, respectively, showing little distinction (Entries 3 and 15). Conversely, the site of substituent present in the aromatic aldehydes appeared to have an steric hindrance effect on the product yields. Generally, in comparison with *meta*- and *para*-substituted benzaldehydes the reaction with those with *ortho*-substituted ones gave the corresponding products in relatively lower yields with longer reaction time (Entries 4, 6, 8, 9 and 14). In particular, the reactions with some di-*ortho*-substituted benzaldehydes such as 2,6-dimethyl-, 2,6-dimethoxy and 2,6-dichlorobenzaldehydes scarcely proceeded, and the corresponding products were detected only in negligible amount that did not warrant isolation. With the aim of further diversifying our synthetic work, we became interested in seeing whether quinoline aldehydes would exhibit a similar reactivity, considering potent biological activities exhibited by many bisquinoline derivatives.<sup>29</sup> To our delight, the 2-chloroquinoline-3-carbaldehydes were viable substrates for this one-pot transformation as well, invariably furnishing the expected vinyl-bridged bisquinolines **3p** and **3q** products though in slightly low yields (Entries 16 and 17). Currently, our work is ongoing and more studies toward extending the reaction scope will be part of our future efforts.

**Table 1.** Yields of products **3a-q** and their anti-proliferative activity (inhibition/%)



Entry	Ar	<b>3a-j</b>	Yield /% <sup>a</sup>	IC <sub>50</sub> /(μmol•L <sup>-1</sup> )		
				A549	HT29	T24
1	Ph	<b>3a</b>	74	18.47	24.86	> 40
2	3-MeC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	72	20.58	30.94	> 40
3	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	76	18.61	28.15	> 40
4	2,5-(Me) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3d</b>	55	18.15	25.92	30.88
5	3,4-(Me) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3e</b>	70	23.49	> 40	35.89
6	2-MeOC <sub>6</sub> H <sub>4</sub>	<b>3f</b>	51	16.85	34.12	> 40
7	3-MeOC <sub>6</sub> H <sub>4</sub>	<b>3g</b>	66	8.27	33.51	> 40
8	2,3-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3h</b>	60	9.27	25.76	> 40
9	2,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3i</b>	57	12.84	19.56	37.69
10	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3j</b>	71	5.24	20.32	25.16
11	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	<b>3k</b>	69	2.38	14.52	29.86
12	2-ClC <sub>6</sub> H <sub>4</sub>	<b>3l</b>	65	19.45	23.08	> 40

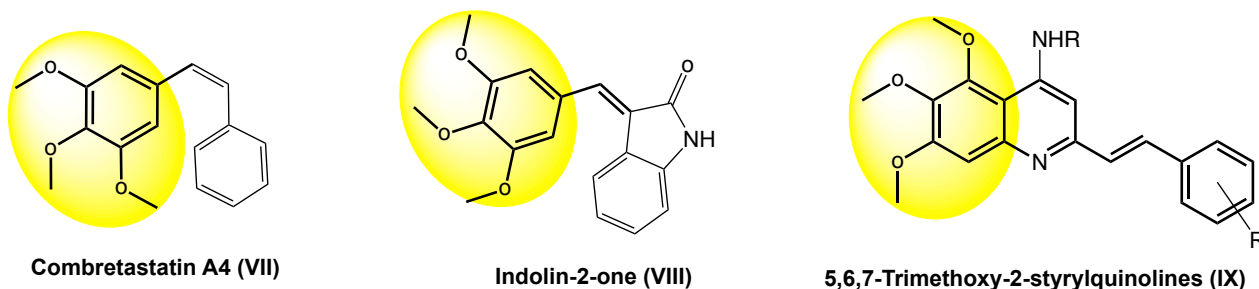
13	3-BrC <sub>6</sub> H <sub>4</sub>	<b>3m</b>	73	25.40	21.34	30.61
14	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3n</b>	59	> 40	> 40	> 40
15	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3o</b>	72	> 40	> 40	> 40
16		<b>3p</b>	53	16.79	10.33	26.55
17		<b>3q</b>	51	20.41	8.04	31.18
18	cisplatin	—	—	2.73	6.82	7.69

<sup>a</sup>Isolated yield.

To the best of our knowledge, the products **3a-q** have never been reported, and their structures were explicitly characterized based on the spectral and analytical data. As an example, the <sup>1</sup>H NMR spectrum of **3h** was devoid of the singlet signal of bromomethyl protons and instead displayed the appearance of two new sharp methoxy proton singlets at 3.61 ppm and 3.64 ppm along with the signals for 3 benzene protons (6.61, 6.78, and 6.99 ppm) and 2 vinyl protons (7.38 and 7.98 ppm), which is consistent with the introduction of the nascent 2,3-dimethoxystyryl moiety to the quinoline ring. It is worthy to note that the newly arising two vinylic proton CH=CH doublets bear large spin-spin coupling constants  $J_{ab} = 16.0$  Hz and 15.6 Hz, respectively, which are indicative of the *E*-configuration for the exocyclic vinyl double bond. Further, its <sup>13</sup>C NMR spectrum was also in good agreement with the assigned structure which revealed the presence of two nascent methoxy carbons at 55.6 ppm and 60.9 ppm, together with 17 aromatic carbons in the aromatic range of 112.34-152.85 ppm, which exactly matching its structure. Finally, the structure assigned to **3h** was fully supported by its elemental analysis, which established its molecular formula in accordance with the suggested molecular structure. Similarly, the other synthesized compounds exhibited the same spectral characteristics except the substituents, which exhibited characteristic signals with appropriate chemical shifts.

With the newly-synthesized diethyl 2-styrylquinoline-3,4-dicarboxylate derivatives in hand, we became interested in evaluating their antitumor activity. Thus, a preliminary screening for their *in vitro* antitumor activities against human cancer cell lines A549, HT29 and T24 was conducted by the (dimethylthiazolyl)diphenyltetrazolium bromide (MTT) conversion assay using cisplatin as a reference. As listed in Table 1, it is found that diethyl 2-styrylquinoline-3,4-dicarboxylate (**3a**) showed poor antiproliferative activities against the three tested cell lines. Furthermore, the activity was not further potentiated with the introduction of methyl, chloro, bromo or nitro group (Entries 2-5 and 12-15, Table 1). Interestingly, compounds **3f-k** with the presence of methoxyl group were observed to exhibit superior antiproliferative activity against A549 cell lines in comparison with unsubstituted **3a**. These results

suggested that the introduction of methoxy substituent appeared to be beneficial in terms of the antitumor activity. Especially, compound **3k** with the 3,4,5-trimethoxystyryl fragment showed the best antiproliferative activity with the  $IC_{50}$  value of  $2.38 \mu\text{mol}\cdot\text{L}^{-1}$ , being higher than the reference cisplatin. It is worthy to mention that some significant antitumor agents such as combretastatin A4 (**VII**)<sup>30</sup> and indolin-2-one (**VIII**)<sup>31</sup> also contain the 3,4,5-trimethoxystyryl fragment as the key pharmacophore for their anticancer activity as shown in Figure 2. Recently, Mirzaei *et al.*<sup>7</sup> reported the synthesis of the structurally similar 2-styrylquinolines, *viz.* (*E*)-5,6,7-trimethoxy-N-phenyl-2-styrylquinolin-4-amines (**IX**, Figure 2), which also showed potent anticancer activity (Figure 2). Thus, the compound **3k** has the significant potential to further exploitation in new drug discovery. In addition, the vinylene-linked bisquinolines **3p** and **3q** also exhibit the satisfactory inhibition property against the tested HT29 cell lines growth (Entries 16 and 17, Table 1), being comparable to cisplatin. In general, these insights from the *in vitro* antitumor activity might provide valuable information for further optimization of the series of derivatives, and hopefully, contribute to the development of new and effective antitumor candidates. Now, the investigations concerning the possible improvements in their activities are underway and the further structural modification and optimization will be part of our future efforts.



**Figure 2.** 3,4,5-Trimethoxyphenyl-containing antitumor compounds **VII-IX**

In summary, a convenient and facile synthesis of a series of structurally intriguing (*E*)-diethyl 2-arylvinylquinoline-3,4-dicarboxylates has been achieved involving the radical bromination reaction of diethyl 2-methylquinoline-3,4-dicarboxylate followed by the one-pot sequential Arbuzov/Horner-Emmons reaction procedure. The merits of the synthetic protocol described herein include experimental simplicity, inexpensive reagents, easy work-up procedure and satisfactory yields, which would contribute to the usefulness of this method. A preliminary evaluation for their *in vitro* antitumor activity bioassay revealed that 3,4,5-trimethoxy substituted compound **3k** showed the best antiproliferative activity. Our work is currently ongoing, mainly focusing on the antitumor activity mechanism, structural optimization, and exploration of the potential of these compounds, which will be communicated in due course.

## EXPERIMENTAL

The chemicals used in this report were obtained from Energy Chemical and were used without further purification. Melting points were determined using a WRS-1B melting point apparatus. The  $^1\text{H}$  (400 MHz) and  $^{13}\text{C}$  (100 MHz) NMR spectra were recorded on an Agilent 400-MR spectrometer using  $\text{DMSO-}d_6$  as the solvent. The reported chemical shifts ( $\delta$  values) are given in parts per million downfield from tetramethylsilane (TMS) as the internal standard (NMR abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, J = coupling constant). Elemental analyses were carried out on an EA 2400II elemental analyzer (PerkinElmer, Waltham, MA). The progress of reactions was monitored by TLC on silica gel GF254 using EtOAc/petroleum ether (1:10) as eluent.

**Procedure for the synthesis of diethyl 2-(bromomethyl)quinoline-3,4-dicarboxylate (4b).** Diethyl 2-methylquinoline-3,4-dicarboxylate (**1**) (14.4 g, 50 mmol) was added to  $\text{CCl}_4$  (600 mL) and heated with stirring until refluxed gently. A catalytic amount of benzoyl peroxide (BPO) as initiator was then added to the reaction mixture. After that, a slightly excessive amount of NBS (10.678 g, 60 mmol) was added carefully in three batches to the gently refluxing  $\text{CCl}_4$  solution, i.e., 3.56 g (20 mmol) portions of 10.678 g (60 mmol) NBS were added every 3 h. After the addition was complete, the mixture continued to reflux gently till the disappearance of **1** (as monitored by TLC). The reaction mixture was cooled to room temperature and the precipitated succinimide was filtered off. The obtained filtrate was washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent under reduced pressure afforded a crude solid product, which was subjected to column chromatography over silica gel (200-400 mesh) using petroleum ether/EtOAc mixture (10:1, v/v) as eluent to give 12.1 g of product **4b** in 66% yield. White solid, 141.2-143.4 °C.  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz): 1.34 (t,  $J = 7.2$  Hz, 6H,  $2 \times \text{CH}_3\text{CH}_2$ ), 4.39 (q,  $J = 7.2$  Hz, 2H,  $\text{CH}_3\text{CH}_2$ ), 4.47 (q,  $J = 7.2$  Hz, 2H,  $\text{CH}_3\text{CH}_2$ ), 5.01 (s, 2H,  $\text{CH}_2$ ), 7.78 (t,  $J = 8.0$  Hz, 1H, Quin-H), 7.95 (t,  $J = 7.6$  Hz, 1H, Quin-H), 7.99 (d,  $J = 8.4$  Hz, 1H, Quin-H), 8.11 (d,  $J = 8.4$  Hz, 1H, Quin-H);  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz): 13.97, 14.11, 32.81, 62.50, 62.59, 122.89, 123.00, 125.48, 128.80, 129.71, 131.79, 141.12, 147.78, 154.38, 165.91, 166.02. Anal. Calcd for  $\text{C}_{16}\text{H}_{16}\text{BrNO}_4$ : C, 52.48; H, 4.40; N, 3.82%. Found: C, 52.69; H, 4.14; N, 3.66%.

### **General procedure for the synthesis of (*E*)-diethyl 2-arylvinylquinoline-3,4-dicarboxylates (3a-q).**

Diethyl 2-(bromomethyl)quinoline-3,4-dicarboxylate (**4b**) (0.366 g, 1 mmol) was added in triethyl phosphite (6 mL). The resulting reaction mixture was stirred at 160 °C for 3 h. The conversion was monitored by TLC. After the reaction was complete, the excessive triethyl phosphite was removed in vacuo, and a solution of respective aromatic aldehydes, and 2-chloroquinoline-3-carbaldehydes (1.2 mmol) in DMF (15 mL) and NaH (0.036 g, 1.5 mmol) were added to the residue. The resulting mixture was stirred for about 0.5 h at room temperature and then stirred at 90 °C for about 3-6 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature, poured slowly into icy water

and left to stand for 30 min, and then extracted with EtOAc (3 × 10 mL). The organic layers were washed with water, saturated brine solution and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography using EtOAc/petroleum ether (1:10) as eluent to give the pure compounds **3a-q**. The yields, physical properties, and spectral and analytical data are given below.

**(E)-Diethyl 2-styrylquinoline-3,4-dicarboxylate (3a)**: White solid, yield 74%, mp 92.4-93.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.36 (d, *J* = 8.4 Hz, 1H, ArH), 8.28 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.23 (d, *J* = 8.8 Hz, 1H, ArH), 8.02 (t, *J* = 7.6 Hz, 1H, ArH), 7.85 (d, *J* = 8.0 Hz, 2H, ArH), 7.80 (t, *J* = 7.2 Hz, 1H, ArH), 7.77 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.62 (t, *J* = 7.6 Hz, 2H, ArH), 7.55 (t, *J* = 7.2 Hz, 1H, ArH), 4.75 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.71 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 1.67 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.66 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.64, 165.99, 151.73, 148.26, 138.94, 136.61, 136.25, 131.08, 129.46, 128.56, 128.44, 127.41, 127.34, 125.13, 123.86, 123.48, 122.08, 62.08, 61.95, 13.88, 13.85. Anal. Calcd for C<sub>23</sub>H<sub>21</sub>NO<sub>4</sub>: C, 73.58; H, 5.64; N, 3.73%. Found: C, 73.74; H, 5.61; N, 3.91%.

**(E)-Diethyl 2-(3-methylstyryl)quinoline-3,4-dicarboxylate (3b)**: Yellow solid, yield 72%, mp 78.2-79.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.33 (d, *J* = 8.4 Hz, 1H, ArH), 8.24 (d, *J* = 16.0 Hz, 1H, ArH), 8.18 (d, *J* = 8.4 Hz, 1H, ArH), 7.98 (t, *J* = 8.0 Hz, 1H, ArH), 7.78 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.75 (t, *J* = 7.6 Hz, 1H, ArH), 7.63 (s, 1H, ArH), 7.61 (d, *J* = 7.2 Hz, 1H, ArH), 7.48 (t, *J* = 7.6 Hz, 1H, ArH), 7.34 (d, *J* = 7.2 Hz, 1H, ArH), 4.73-4.64 (m, 4H, CH<sub>2</sub>), 2.57 (s, 3H, CH<sub>3</sub>), 1.65 (t, *J* = 7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.85, 166.15, 151.97, 148.42, 139.07, 138.15, 136.98, 136.36, 131.23, 129.60, 128.50, 128.18, 127.53, 125.28, 124.72, 123.79, 123.66, 122.22, 62.24, 62.11, 21.31, 14.03. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>NO<sub>4</sub>: C, 74.02; H, 5.95; N, 3.60%. Found: C, 73.81; H, 6.06; N, 3.83%.

**(E)-Diethyl 2-(4-methylstyryl)quinoline-3,4-dicarboxylate (3c)**: Yellow solid, yield 76%, mp 89.3-90.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.36 (d, *J* = 8.4 Hz, 1H, ArH), 8.26 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.23 (d, *J* = 7.6 Hz, 1H, ArH), 8.01 (t, *J* = 7.6 Hz, 1H, ArH), 7.79 (t, *J* = 7.6 Hz, 1H, ArH), 7.77 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.75 (d, *J* = 8.0 Hz, 2H, ArH), 7.42 (d, *J* = 7.6 Hz, 2H, ArH), 4.75-4.67 (m, 4H, CH<sub>2</sub>), 2.59 (s, 3H, CH<sub>3</sub>), 1.68-1.64 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.94, 166.24, 152.14, 148.50, 139.07, 138.95, 136.85, 133.73, 131.26, 129.63, 129.40, 127.53, 127.51, 125.34, 123.71, 123.06, 122.23, 62.29, 62.15, 21.34, 14.11, 14.08. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>NO<sub>4</sub>: C, 74.02; H, 5.95; N, 3.60%. Found: C, 74.19; H, 5.78; N, 3.67%.

**(E)-Diethyl 2-(2,5-dimethylstyryl)quinoline-3,4-dicarboxylate (3d)**: Yellow oily liquid, yield 55%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.26 (d, *J* = 15.2 Hz, 1H, CH=CH), 8.13 (d, *J* = 8.4 Hz, 1H, ArH), 7.99 (d, *J* = 8.4 Hz, 1H, ArH), 7.77 (t, *J* = 8.4 Hz, 1H, ArH), 7.55 (t, *J* = 7.6 Hz, 1H, ArH), 7.45 (d, *J* = 15.2 Hz, 1H, CH=CH), 7.43 (s, 1H, ArH), 7.08 (d, *J* = 7.6 Hz, 1H, ArH), 7.02 (d, *J* = 7.6 Hz, 1H, ArH), 4.51-4.41 (m, 4H, CH<sub>2</sub>), 2.45 (s, 3H, CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 1.43-1.36 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ

167.00, 166.26, 152.20, 148.49, 139.02, 135.45, 135.30, 134.97, 134.13, 131.24, 130.47, 129.79, 129.51, 127.59, 126.63, 125.34, 124.97, 123.84, 122.29, 62.32, 62.19, 21.02, 19.53, 14.09, 14.08. Anal. Calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>4</sub>: C, 74.42; H, 6.25; N, 3.47%. Found: C, 74.24; H, 6.29; N, 3.31%.

**(E)-Diethyl 2-(3,4-dimethylstyryl)quinoline-3,4-dicarboxylate (3e)**: Yellow solid, yield 70%, mp 108.1-110.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23 (d, *J* = 8.4 Hz, 1H, ArH), 8.13 (d, *J* = 16.0 Hz, 1H, CH=CH), 8.09 (d, *J* = 7.6 Hz, 1H, ArH), 7.87 (t, *J* = 8.0 Hz, 1H, ArH), 7.64-7.60 (m, 2H, ArH), 7.49-7.45 (m, 2H, CH=CH, ArH), 7.23 (s, 1H, ArH), 4.62-4.55 (m, 4H, CH<sub>2</sub>), 2.37 (s, 6H, CH<sub>3</sub>), 1.54-1.52 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.99, 166.27, 152.20, 148.52, 139.04, 137.74, 137.08, 136.79, 134.16, 131.25, 129.99, 129.64, 128.82, 127.48, 125.35, 125.19, 123.75, 122.87, 122.22, 62.29, 62.15, 19.77, 19.68, 14.12, 14.10. Anal. Calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>4</sub>: C, 74.42; H, 6.25; N, 3.47%. Found: C, 74.61; H, 6.13; N, 3.18%.

**(E)-Diethyl 2-(2-methoxystyryl)quinoline-3,4-dicarboxylate (3f)**: Yellow solid, yield 51%, mp 98.0-100.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.32 (d, *J* = 16.0 Hz, 1H, CH=CH), 8.13 (d, *J* = 8.4 Hz, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.74 (t, *J* = 7.6 Hz, 1H, ArH), 7.64 (d, *J* = 16.0 Hz, 1H, CH=CH), 7.61 (d, *J* = 7.6 Hz, 1H, ArH), 7.53 (t, *J* = 7.6 Hz, 1H, ArH), 7.27 (t, *J* = 7.6 Hz, 1H, ArH), 6.95 (t, *J* = 7.2 Hz, 1H, ArH), 6.89 (d, *J* = 8.4 Hz, 1H, ArH), 4.49-4.40 (m, 4H, CH<sub>2</sub>), 3.87 (s, 3H, CH<sub>3</sub>), 1.42-1.36 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.07, 166.27, 157.92, 152.51, 148.53, 138.81, 132.21, 131.13, 129.94, 129.80, 128.07, 127.47, 125.56, 125.30, 124.82, 123.98, 122.20, 120.63, 111.00, 62.27, 62.10, 55.45, 14.08. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>NO<sub>5</sub>: C, 71.10; H, 5.72; N, 3.45%. Found: C, 71.31; H, 5.60; N, 3.62%.

**(E)-Diethyl 2-(3-methoxystyryl)quinoline-3,4-dicarboxylate (3g)**: Yellow oily liquid, yield 66%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (d, *J* = 8.4 Hz, 1H, ArH), 8.01 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.99 (d, 1H, *J* = 8.0 Hz, ArH), 7.78 (t, *J* = 7.6 Hz, 1H, ArH), 7.56 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.54 (t, 1H, *J* = 8.0 Hz, ArH), 7.30 (t, *J* = 8.0 Hz, 1H, ArH), 7.22 (d, *J* = 7.6 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 6.87 (d, *J* = 8.0 Hz, 1H, ArH), 4.47 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.45 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 3.82 (s, 3H, CH<sub>3</sub>), 1.41 (t, *J* = 7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.79, 166.14, 159.73, 151.82, 148.42, 139.12, 137.85, 136.70, 131.26, 129.63, 129.56, 127.61, 125.30, 124.37, 123.67, 122.28, 120.10, 114.47, 112.77, 62.25, 62.12, 55.17, 14.05, 14.03. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>NO<sub>5</sub>: C, 71.10; H, 5.72; N, 3.45%. Found: C, 71.21; H, 5.87; N, 3.57%.

**(E)-Diethyl 2-(2,3-dimethoxystyryl)quinoline-3,4-dicarboxylate (3h)**: Yellow solid, yield 60%, mp 71.7-72.6 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.90 (d, *J* = 8.4 Hz, 1H, ArH), 7.75 (d, *J* = 8.8 Hz, 1H, ArH), 7.52 (t, *J* = 7.6 Hz, 1H, ArH), 7.42 (d, *J* = 16.0 Hz, 1H, CH=CH), 7.31 (t, *J* = 7.6 Hz, 1H, ArH), 7.00 (d, *J* = 7.6 Hz, 1H, ArH), 6.81 (t, *J* = 8.0 Hz, 1H, ArH), 6.63 (d, *J* = 8.0 Hz, 1H, ArH), 4.26-4.16 (m, 4H, CH<sub>2</sub>), 3.64 (s, 3H, CH<sub>3</sub>), 3.61 (s, 3H, CH<sub>3</sub>), 1.18-1.13 (m, 6H, CH<sub>3</sub>).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.76, 165.98, 152.85, 152.01, 148.26, 147.82, 138.63, 131.57, 130.94, 130.45, 129.63, 127.38, 125.62, 125.06, 123.78, 123.71, 122.03, 119.27, 112.34, 62.05, 61.93, 60.86, 55.58, 13.84. Anal. Calcd for  $\text{C}_{25}\text{H}_{25}\text{NO}_6$ : C, 68.95; H, 5.79; N, 3.22%. Found: C, 69.17; H, 5.83; N, 3.07%.

**(E)-Diethyl 2-(2,5-dimethoxystyryl)quinoline-3,4-dicarboxylate (3i)**: Yellow oily liquid, yield 57%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 (d,  $J = 16.0$  Hz, 1H, CH=CH), 8.01 (d,  $J = 8.4$  Hz, 1H, ArH), 7.86 (d,  $J = 8.4$  Hz, 1H, ArH), 7.63 (t,  $J = 7.6$  Hz, 1H, ArH), 7.49 (d,  $J = 15.6$  Hz, 1H, CH=CH), 7.42 (t,  $J = 7.6$  Hz, 1H, ArH), 7.03 (s, 1H, ArH), 6.72 (d,  $J = 7.2$  Hz, 1H, ArH), 6.70 (d,  $J = 7.2$  Hz, 1H, ArH), 4.37-4.28 (m, 4H,  $\text{CH}_2$ ), 3.72 (s, 3H,  $\text{CH}_3$ ), 3.65 (s, 3H,  $\text{CH}_3$ ), 1.30-1.25 (m, 6H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.93, 166.15, 153.42, 152.42, 152.29, 148.42, 138.73, 131.96, 131.04, 129.72, 127.42, 126.19, 125.20, 125.08, 123.88, 122.13, 115.06, 113.05, 112.18, 62.18, 62.00, 56.02, 55.65, 13.99, 13.98. Anal. Calcd for  $\text{C}_{25}\text{H}_{25}\text{NO}_6$ : C, 68.95; H, 5.79; N, 3.22%. Found: C, 68.73; H, 5.64; N, 3.26%.

**(E)-Diethyl 2-(3,4-dimethoxystyryl)quinoline-3,4-dicarboxylate (3j)**: Brown oily liquid, yield 71%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J = 8.4$  Hz, 1H, ArH), 8.03 (d,  $J = 15.2$  Hz, 1H, CH=CH), 8.01 (d,  $J = 8.8$  Hz, 1H, ArH), 7.80 (t,  $J = 7.6$  Hz, 1H, ArH), 7.58 (t,  $J = 7.6$  Hz, 1H, ArH), 7.47 (d,  $J = 15.2$  Hz, 1H, CH=CH), 7.23 (d,  $J = 8.4$  Hz, 1H, ArH), 7.16 (s, 1H, ArH), 6.90 (d,  $J = 8.4$  Hz, 1H, ArH), 4.54-4.45 (m, 4H,  $\text{CH}_2$ ), 3.95 (s, 3H,  $\text{CH}_3$ ), 3.92 (s, 3H,  $\text{CH}_3$ ), 1.47 (t,  $J = 7.2$  Hz, 6H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.99, 166.25, 152.14, 149.93, 149.02, 148.52, 139.08, 136.77, 131.28, 129.60, 129.56, 127.45, 125.36, 123.62, 122.18, 122.10, 121.29, 111.12, 109.88, 62.30, 62.11, 55.89, 55.83, 14.13, 14.08. Anal. Calcd for  $\text{C}_{25}\text{H}_{25}\text{NO}_6$ : C, 68.95; H, 5.79; N, 3.22%. Found: C, 68.69; H, 5.86; N, 3.14%.

**(E)-Diethyl 2-(3,4,5-trimethoxystyryl)quinoline-3,4-dicarboxylate (3k)**: Yellow oily liquid, yield 69%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 (d,  $J = 8.4$  Hz, 1H, ArH), 8.01 (d,  $J = 8.0$  Hz, 1H, ArH), 7.96 (d,  $J = 15.6$  Hz, 1H, CH=CH), 7.79 (t,  $J = 7.6$  Hz, 1H, ArH), 7.58 (t,  $J = 7.6$  Hz, 1H, ArH), 7.49 (d,  $J = 16.0$  Hz, 1H, CH=CH), 6.84 (s, 2H, ArH), 4.53-4.44 (m, 4H,  $\text{CH}_2$ ), 3.91 (s, 6H,  $\text{CH}_3$ ), 3.88 (s, 3H,  $\text{CH}_3$ ), 1.45 (t,  $J = 7.2$  Hz, 6H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.96, 166.25, 153.32, 151.85, 148.51, 139.26, 138.92, 136.90, 132.18, 131.43, 129.62, 127.69, 125.42, 123.62, 123.49, 122.31, 104.67, 62.40, 62.20, 60.98, 56.10, 14.18, 14.12. Anal. Calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}_7$ : C, 67.09; H, 5.85; N, 3.01%. Found: C, 66.91; H, 6.04; N, 3.17%.

**(E)-Diethyl 2-(2-chlorostyryl)quinoline-3,4-dicarboxylate (3l)**: Yellow oily liquid, yield 65%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (d,  $J = 15.6$  Hz, 1H, CH=CH), 8.14 (d,  $J = 8.4$  Hz, 1H, ArH), 7.98 (d,  $J = 8.4$  Hz, 1H, ArH), 7.77 (t,  $J = 8.4$  Hz, 1H, ArH), 7.70 (d,  $J = 7.2$  Hz, 1H, ArH), 7.58 (d,  $J = 15.6$  Hz, 1H, CH=CH), 7.54 (t,  $J = 8.4$  Hz, 1H, ArH), 7.38 (d,  $J = 7.6$  Hz, 1H, ArH), 7.24 (t,  $J = 7.6$  Hz, 1H, ArH), 7.20 (t,  $J = 7.6$  Hz, 1H, ArH), 4.50 (q,  $J = 7.6$  Hz, 2H,  $\text{CH}_2$ ), 4.43 (q,  $J = 7.6$  Hz, 2H,  $\text{CH}_2$ ), 1.42 (t,  $J = 7.6$  Hz, 3H,  $\text{CH}_3$ ), 1.38 (t,  $J = 7.6$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.78, 166.19, 151.67,

148.50, 139.31, 134.76, 134.47, 132.88, 131.36, 129.99, 129.95, 129.58, 127.88, 127.29, 126.87, 126.84, 125.31, 123.59, 122.43, 62.33, 62.23, 14.09, 14.06. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>ClNO<sub>4</sub>: C, 67.40; H, 4.92; N, 3.42%. Found: C, 67.23; H, 4.79; N, 3.33%.

**(E)-Diethyl 2-(3-bromostyryl)quinoline-3,4-dicarboxylate (3m)**: Yellow solid, yield 73%, mp 68.9-70.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.11 (d, *J* = 8.4 Hz, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.96 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.79 (t, *J* = 8.0 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 7.58 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.54 (d, *J* = 7.6 Hz, 1H, ArH), 7.51 (d, *J* = 8.0 Hz, 1H, ArH), 7.43 (d, *J* = 8.0 Hz, 1H, ArH), 7.24 (t, *J* = 7.2 Hz, 1H, ArH), 4.52-4.43 (m, 4H, CH<sub>2</sub>), 1.44 (t, *J* = 7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.43, 165.92, 151.24, 148.21, 139.20, 138.40, 134.92, 131.29, 131.20, 129.97, 129.92, 129.49, 127.62, 125.96, 125.24, 125.13, 123.28, 122.59, 122.20, 62.10, 62.03, 13.91, 13.84. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>BrNO<sub>4</sub>: C, 60.81; H, 4.44; N, 3.08%. Found: C, 60.69; H, 4.25; N, 3.16%.

**(E)-Diethyl 2-(2-nitrostyryl)quinoline-3,4-dicarboxylate (3n)**: Yellow solid, yield 59%, mp 118.7-119.6 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.43 (d, *J* = 16.0 Hz, 1H, CH=CH), 8.14 (d, *J* = 8.4 Hz, 1H, ArH), 7.97 (d, *J* = 8.4 Hz, 1H, ArH), 7.94 (d, *J* = 8.0 Hz, 1H, ArH), 7.79 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.77 (t, *J* = 7.6 Hz, 1H, ArH), 7.61-7.55 (m, 3H, CH=CH, ArH), 7.45 (t, *J* = 7.6 Hz, 1H, ArH), 4.50 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.44 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 1.41 (t, *J* = 7.6 Hz, 3H, CH<sub>3</sub>), 1.37 (t, *J* = 7.6 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.30, 165.87, 150.78, 148.25, 148.20, 139.35, 132.80, 132.10, 131.44, 131.25, 129.83, 128.81, 128.63, 128.51, 127.88, 125.02, 124.41, 123.02, 122.29, 62.06, 62.00, 13.81, 13.73. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 65.71; H, 4.79; N, 6.66%. Found: C, 65.48; H, 4.84; N, 6.52%.

**(E)-Diethyl 2-(4-nitrostyryl)quinoline-3,4-dicarboxylate (3o)**: Yellow solid, yield 72%, mp 161.5-162.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.4 Hz, 2H, ArH), 8.12 (d, *J* = 8.4 Hz, 1H, ArH), 8.06 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (t, *J* = 8.4 Hz, 1H, ArH), 7.78 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.70 (d, *J* = 8.4 Hz, 2H, ArH), 7.60 (t, *J* = 8.0 Hz, 1H, ArH), 4.52-4.42 (m, 4H, CH<sub>2</sub>), 1.44-1.38 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.48, 166.07, 151.00, 148.47, 147.48, 142.85, 139.84, 134.05, 131.69, 129.83, 128.42, 128.28, 127.98, 125.46, 124.06, 123.43, 122.68, 62.43, 62.39, 14.09. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 65.71; H, 4.79; N, 6.66%. Found: C, 65.64; H, 4.82; N, 6.81%.

**(E)-Diethyl 2-(2-(2-chloroquinolin-3-yl)vinyl)quinoline-3,4-dicarboxylate (3p)**: Yellow solid, yield 53.4%, mp 143.8-144.2 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.46 (s, 1H, ArH), 8.43 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.22 (d, *J* = 8.8 Hz, 1H, ArH), 8.03 (d, *J* = 8.4 Hz, 2H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.85 (t, *J* = 8.0 Hz, 1H, ArH), 7.78 (d, *J* = 16.0 Hz, 1H, CH=CH), 7.75 (t, *J* = 8.0 Hz, 1H, ArH), 7.64 (t, *J* = 8.0 Hz, 1H, ArH), 7.59 (t, *J* = 8.0 Hz, 1H, ArH), 4.56 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.51 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 1.48 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.45 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.64,

166.14, 151.16, 150.46, 148.51, 147.23, 139.66, 135.04, 131.68, 131.58, 130.69, 130.04, 129.65, 128.61, 128.29, 128.16, 127.77, 127.30, 127.26, 125.36, 123.29, 122.58, 62.37, 62.34, 14.10, 14.03. Anal. Calcd for C<sub>26</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 67.75; H, 4.59; N, 6.08%. Found: C, 67.86; H, 4.62; N, 5.88%.

**(E)-Diethyl 2-(2-(2-chloro-6-methylquinolin-3-yl)vinyl)quinoline-3,4-dicarboxylate (3q):** Yellow solid, yield 51.1%, mp 158.6-161.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.46 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.38 (s, 1H, ArH), 8.23 (d, *J* = 8.4 Hz, 1H, ArH), 8.04 (d, *J* = 8.0 Hz, 1H, ArH), 7.92 (d, *J* = 8.4 Hz, 1H, ArH), 7.86 (t, *J* = 8.0 Hz, 1H, ArH), 7.76 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.64 (s, 1H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 7.58 (d, *J* = 8.4 Hz, 1H, ArH), 4.57-4.46 (m, 4H, CH<sub>2</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 1.49-1.42 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.51, 161.02, 146.10, 144.44, 143.32, 140.74, 134.53, 132.22, 129.34, 127.91, 126.81, 126.48, 124.86, 124.35, 123.19, 123.03, 122.81, 122.17, 121.47, 120.23, 118.18, 117.43, 57.27, 57.22, 16.44, 8.98, 8.93. Anal. Calcd for C<sub>27</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 68.28; H, 4.88; N, 5.90%. Found: C, 68.47; H, 4.63; N, 5.93%.

**Experimental procedure for cancer cell growth inhibition assay (MTT assay).** The antiproliferative activity of the target compounds on the human non-small cell lung cancer cell (A549), human colon cancer cell (HT29) and human bladder carcinoma cells (T24) was tested using the MTT assay, in comparison to cisplatin. A549, HT29 and T24 cell lines were obtained from the Cell Resource Center (Shanghai Institutes for Biological Sciences, China Academy of Sciences). Briefly, the three cell types were seeded in 96-well culture platet at the cell density of 5×10<sup>4</sup> cells per well in 100 μL of culture medium at 37 °C in 5% CO<sub>2</sub> incubator for 24 h seeding. The stock solutions of test compounds **3a-q** were prepared in DMSO. After incubation, the target compounds were added into the culture medium at a five times concentration gradient. The final concentration of DMSO in the medium was less than 0.5%. Triplicates of each concentration were used. After 48 h incubation, the supernatant was removed and 5 mg/mL of a freshly prepared solution of MTT was added to each well. The plates were then incubated with the cells at 37 °C for another 4 h. The medium was then removed and 100 μL DMSO was added to each well to dissolve the formazan. The OD values were measured using SPECTRA max 190 Cell microplate reader under 490 nm (for absorbance of MTT formazan) and 630 nm (for the reference wave length). Cell growth inhibition rate formula is (AC-AT)/AC × 100%. AC, the absorbance value of the blank control group; AT, the absorbance value of the experimental group. The average 50% inhibitory concentration (IC<sub>50</sub>) was calculated using GraphPadPrism version 6.00 software from the non-linear curve.

## ACKNOWLEDGEMENTS

We appreciate financial support of Scientific Research Foundation of the Education Department of Liaoning Province (Grant no. LQ201902006) and Doctoral Start-up Foundation of Liaoning Province (Grant no. 2019-BS-004).

## REFERENCES

1. M. Dhanawat, D. K. Mehta, and R. Das, *Mini-Rew. Med. Chem.*, 2021, **21**, 1849.
2. J. Szczepaniak, W. Cieslik, A. Romanowicz, R. Musioł, and A. Krasowska, *Int. J. Antimicrob. Agents*, 2017, **50**, 171.
3. R. Musiol, *Curr. Pharm. Des.*, 2013, **19**, 1835.
4. W. S. F. Wong, H. Zhu, and W. Liao, *Eur. J. Pharmacol.*, 2007, **575**, 134.
5. M. Dhanawat, D. K. Mehta, and R. Das, *Mini-Rew. Med. Chem.*, 2021, **21**, 1849.
6. B. Podeszwa, H. Niedbala, J. Polanski, R. Musiol, D. Tabak, J. Finster, K. Serafin, M. Milczarek, J. Wietrzyk, S. Boryczka, W. Mol, J. Jampilek, J. Dohnal, D. S. Kalinowskif, and D. R. Richardsonf, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6138.
7. S. Mirzaei, F. Eisvand, F. Hadizadeh, F. Mosaffa, A. Ghasemi, and R. Ghodsi, *Bioorg. Chem.*, 2020, **98**, 103711.
8. R. K. Mittal and P. Purohit, *Anti-Cancer Agent Med.*, 2020, **20**, 1981.
9. R. K. Mittal and P. Purohit, *Anti-Cancer Agent Med.*, 2021, **21**, 1708.
10. S. Prameela and F. N. Khan, *Eur. J. Org. Chem.*, 2020, 5394.
11. N. Satyanarayana, K. Sathish, S. Nagaraju, R. Pawar, M. Faizan, M. Arumugavel, T. Shirisha, and D. Kashinath, *New J. Chem.*, 2022, **46**, 1637.
12. G. Balamurugan and R. Ramesh, *ChemCatChem*, 2022, **14**, e202101455.
13. Y. Li, B. Tang, S. Dong, W. Gao, W. Jiang, and Y. Chen, *ChemistrySelect*, 2020, **5**, 2746.
14. Y. Li, Q. Xu, Z. Li, W. Gao, and Y. Chen, *Mol. Divers.*, 2020, **24**, 167.
15. W. Gao, Z. Li, Q. Xu, and Y. Li, *RSC Adv.*, 2018, **8**, 38844.
16. H. Zhang and Y. Li, *Heterocycles*, 2015, **91**, 2180.
17. L. Lu, P. Zhou, B. Hu, X. Li, R. Huang, and F. Yu, *Tetrahedron Lett.*, 2017, **58**, 3658.
18. F. S. Chang, W. Chen, C. Wang, C. C. Tzeng, and Y. L. Chen, *Bioorg. Med. Chem.*, 2010, **18**, 124.
19. A. Kamal, A. Rahim, S. Riyaz, Y. Poornachandra, M. Balakrishna, C. G. Kumar, S. M. A. Hussaini, B. Sridhar, and P. K. Machiraju, *Org. Biomol. Chem.*, 2015, **13**, 1347.
20. S. Achelle, A. Barsella, C. Baudequin, B. Caro, and F. R. Guen, *J. Org. Chem.*, 2012, **77**, 4087.
21. D. Kumar, A. Kumar, M. M. Qadri, M. I. Ansari, A. Gautam, and A. K. Chakraborti, *RSC Adv.*, 2015, **5**, 2920.

22. M. Dabiri, P. Salehi, M. Baghbanzadeh, and M. S. Nikcheh, *Tetrahedron Lett.*, 2008, **49**, 5366.
23. P. Sarma, S. Saikia, and R. Borah, *Synth. Commun.*, 2016, **46**, 1187.
24. G. G. Rajeshwaran, M. Nandakumar, R. Sureshbabu, and A. K. Mohanakrishnan, *Org. Lett.*, 2011, **13**, 1270.
25. K. Kobayashi, K. Tanaka, and H. Kogen, *Tetrahedron Lett.*, 2018, **59**, 568.
26. D. Roman, M. Sauer, and C. Beemelmans, *Synthesis*, 2021, **53**, 2713.
27. E. Diez-Barra, J. C. Garcia-Martinez, and J. Rodríguez-López, *Tetrahedron Lett.*, 1999, **40**, 8181.
28. D. P. Flaherty, S. M. Walsh, T. Kiyota, Y. Dong, T. Ikezu, and J. L. Vennerstrom, *J. Med. Chem.*, 2007, **50**, 4986.
29. S. Li, Q. Huang, Y. Liu, X. Zhang, S. Liu, C. He, and P. Gong, *Eur. J. Med. Chem.*, 2013, **64**, 62.
30. C. Borrel, S. Thoret, X. Cachet, D. Guénard, F. Tillequin, M. Kocha, and S. Michel, *Bioorg. Med. Chem.*, 2005, **13**, 3853.
31. A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, and M. W. Kunkel, *J. Med. Chem.*, 2006, **49**, 6922.