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Green synthesis and antitumor activity of (*E*)-diethyl 2-styrylquinoline-3,4-dicarboxylates†

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In this work, a green, efficient and catalyst-free synthesis of a series of structurally novel (*E*)-diethyl 2-styrylquinoline-3,4-dicarboxylates *via* a direct olefination reaction between diethyl 2-methylquinoline-3,4-dicarboxylate and various aromatic aldehydes was successfully accomplished by employing eco-friendly 1,3-dimethylurea/L-(+)-tartaric acid (DMU/LTA) as an inexpensive, non-toxic and reusable reaction medium. This methodology has the attractive advantages of mild reaction conditions, simple experimental operation, and the absence of any dangerous catalysts or unsafe volatile organic solvents, with satisfactory to good yields. Subsequently, a primary *in vitro* evaluation for their anti-proliferative activity against human cancer cell lines A549, HT29 and T24 revealed that the compound with the 3,4,5-trimethoxystyryl moiety exhibited potent anti-tumor activity with IC_{50} values of 2.38, 4.52 and 9.86 μmol L^{-1}, respectively, thereby being equipotent or even better than the reference cisplatin.

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Introduction

Among the quinoline derivatives, the 2-styrylquinoline (SQ) structure forms an important type of structural motif and represents an elite scaffold and a wonderful pharmacophore in drug discovery.[1] Many members of this family, such as FZ-41 (**I**), VUF5017 (**II**), WK14 (**III**), and L-660,771 (**IV**), have been widely applied as antiproliferative,[2] antiviral,[3] anti-HIV,[4] and antimicrobial[5] agents and antagonists,[6] as shown in Fig. 1. Recent anti-proliferative activity evaluation of 2-styrylquinoline derivatives against tumor cell lines has validated the importance of this class of compounds as a new hope in developing anti-cancer drugs.[7,8] For example, 8-hydroxyl-2-styrylquinoline (**V**, Fig. 1) was reported to demonstrate a marked anti-cancer activity against the human neuroblastoma cell line SK-N-MC,[9] and the newly-synthesized 5,6,7-trimethoxy-*N*-aryl-2-styrylquinolin-4-amines (**VI**, Fig. 1) were reported to exhibit potent anti-cancer activity against human cancer cell lines A-2780 and MCF-7.[10] Owing to their striking biological activities and in order to have structurally diversified molecules for bio-screening, considerable synthetic efforts have been directed toward developing synthetic approaches for the construction of 2-styrylquinoline derivatives. Considering the fact that 2-methylquinoline derivatives could be readily converted into an enamine tautomeric form *via* C(sp^3)–H activation by the nitrogen atom under various catalytic conditions,[11] the direct olefination of 2-methylquinolines *via* the Knoevenagel condensation reaction with aromatic aldehydes appears to be the most simple and straightforward approach in comparison with other possible methods such as Wittig reactions using expensive 2-quinolinecarboxaldehydes[12] and reductive olefinations of quinoline *N*-oxides.[13]

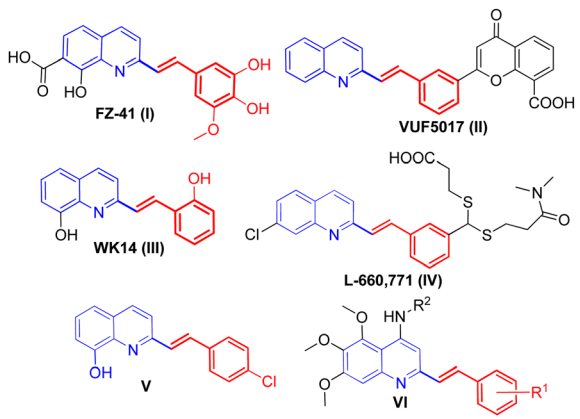

Fig. 1 Structures of some bioactive 2-styrylquinolines **I**–**VI**.

The conventional approach for the direct olefination of 2-methylquinolines with aldehydes involves the use of acetic anhydride as the reaction medium,[14] but the protocol is plagued by constraints such as high reaction temperature, the use of a large excess of aldehydes and low product yields. Owing to the great significance of direct olefination in organic synthesis, great efforts have been devoted during the past decades to develop more convenient and effective synthetic methods,

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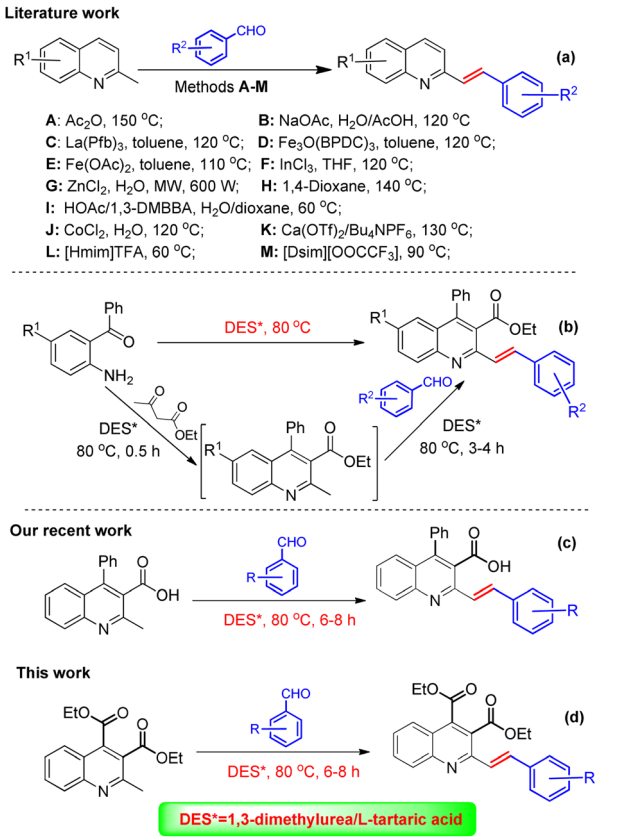
including (1) the utilization of NaOAc as a base in water-acetic acid binary solvents;[5] (2) the use of metal catalysts such as $La(Pfb)_3$,[15] $Fe_3O(BPDC)_3$,[16] or $Fe(OAc)_2$ [17] in toluene; $InCl_3$ in THF;[18] $CoCl_2$ in H_2O;[19] $Ca(OTf)_2/Bu_4NPF_6$ under solvent-free conditions;[20] and $ZnCl_2$ under microwave irradiation;[21] (3) solvent-free microwave irradiation under inert gas atmosphere (N_2) at high temperatures (170–175 °C);[22] (4) employment of 1,4-dioxane as the reaction medium under catalyst-free conditions at 140 °C;[23] and (5) the combination of 1,3-dimethylbarbituric acid and HOAc as synergistic catalysts,[24] as summarized in Scheme 1a. Although these elegant methods for the direct olefination of 2-methylquinolines have emerged, they were invariably associated with certain limitations such as harsh reaction conditions; toxic chemical reagents; expensive or unavailable catalysts; and volatile, flammable and harmful organic solvents. In addition, 2-styrylquinolines could also be facilely accessed using 1-methylimidazolium trifluoroacetate ([Hmim]TFA)[25] or Brønsted acidic imidazolium ionic liquids as the reaction medium,[26] which involved *in situ* generated 2-methylquinoine from *o*-aminoketone and β-ketoester, followed by its olefination reaction with aromatic aldehydes. However, the high cost and environmental toxicity have limited their practical application.

Nowadays, in light of the stringent environmental requirements and safety considerations in chemical production, increasing research efforts have been focused on the development of sustainable and environmentally benign reaction procedures to replace those efficient but somewhat outdated methods, particularly, to replace volatile, flammable and harmful organic solvents.[27] Deep eutectic solvents (DESs), as an emerging class of unconventional solvents derived from the combination of two or three safe and cheap components of Lewis or Brønsted acids and bases through hydrogen bond formation, have attracted enormous attention due to their unique properties, including a wide liquid range, negligible vapor pressure, low toxicity, non-flammability, high solvation capacity, high biodegradability, low cost of components and convenient preparation,[28] thereby rendering them acknowledged widely as an excellent alternative to volatile organic solvents in the development of environmentally friendly organic reactions.[29] For example, Zhang's group has developed the application of choline chloride (ChCl)/urea,[30] choline chloride/lactic acid (ChCl/LAC),[31] choline chloride/glycerol (ChCl/Gly),[32] choline chloride (ChCl)/malonic acid,[33] and ChCl/L-(+)-tartaric acid[34] as a biodegradable, recycled and reusable media in the green synthesis of heterocyclic compounds. Therefore, the synthesis of this class of 2-styrylquinoline derivative using deep eutectic solvents would be highly sought after. There was an impressive report from Kashinath group,[35] who described a green, metal-free, one-pot synthesis of 2-styrylquinolines using a combination of 1,3-dimethyl urea (1,3-DMU) and L-tartaric acid (LTA) (in a 3 : 1 ratio) as a deep eutectic solvent (DES) *via* Friedlander annulation, followed by Knoevenagel condensation, as shown in Scheme 1b. Inspired by the report, our group in this regard has recently achieved the green synthesis of (*E*)-2-styrylquinoline-3-carboxylic acid by using the non-toxic deep eutectic solvent (DES) of 1,3-dimethylurea (DMU)/L-tartaric acid (LTA) as medium (Scheme 1c).[36] In view of the structural diversity playing a prominent role in new drug discovery[37] and in the context of our ongoing studies concerning the green synthesis of quinoline derivatives, we envisioned that 2-methylquinoline-3,4-dicarboxylate as a very intriguing scaffold might be amenable to the green strategy to access a new class of 2-styrylquinoline compounds, which might exhibit interesting biological activities. Thus, we would like to report, herein, a new and environmentally benign synthesis and preliminary *in vitro* anti-tumor activity evaluation of a series of structurally novel diethyl 2-styrylquinoline-3,4-dicarboxylate derivatives by using the safe, eco-friendly and unconventional 1,3-DMU/LTA as a solvent (Scheme 1d). To the best of our knowledge, the green synthesis and biological activity evaluation of such quinoline derivatives has not been achieved so far and might be employed as potential candidates for future drug discovery.



Scheme 1 Synthesis of 2-styrylquinoline derivatives by using distinct methods (a)–(d).

Results and discussion

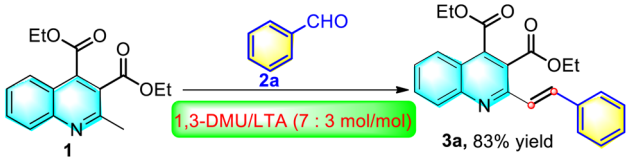
In the past decades, the synthesis of quinoline carboxylate derivatives has been a very attractive synthetic target due to their potent biological activities.[38–40] For example, Lu *et al.* recently reported a TMSCl-mediated Pfitzinger reaction of isatin with ethyl acetoacetate for the synthesis of diethyl 2-methylquinoline-3,4-dicarboxylate.[41] On the basis of the report, we devised that if its 2-methyl group could be further transformed

into styrene moiety, the resulting diethyl 2-styrylquinoline-3,4-dicarboxylate derivatives might lead to a new dimension of structural diversity as potential candidates for biological evaluations or provide more opportunities for further synthetic manipulations. On the other hand, our group has recently developed a green, efficient and catalyst-free strategy for the synthesis of (*E*)-2-styrylquinoline-3-carboxylic acid derivatives *via* direct olefination of 2-methylquinoline-3-carboxylic acid with aromatic aldehydes by using an environmentally benign and non-toxic deep eutectic solvent (DES) of 1,3-dimethylurea (DMU)/L-(+)-tartaric acid (LTA) as both catalyst and reaction medium.[36] Building on the evolving expertise, we were very keen to explore whether 2-methylquinoline-3,4-dicarboxylate could be converted into the desired diethyl 2-styrylquinoline-3,4-dicarboxylate derivatives under the same reaction conditions as well as the subsequent evaluation of their anti-tumor activity. Accordingly, following the line of green chemistry, we investigated the model reaction of diethyl 2-methylquinoline-3,4-dicarboxylate (**1**) with benzaldehyde (**2a**) by using the DES, namely DMU/LTA (7/3, mol mol^{-1}) as the reaction medium at 80 °C, as shown in Scheme 2. To our great delight, the application of DES was found to be very suitable to prompt the reaction proceeding efficiently, giving the corresponding product **3a** in a remarkably high yield of 83% within 6 h.

Due to the satisfactory yield obtained and in order to retain the simplicity of the procedure, no further optimization in reaction conditions was necessary. In order to highlight the advantages of the DES solvent, a control experiment was carried out, in which the model reaction was conducted employing the widely used Ac_2O as the medium based on the literature method.[2] However, from the experiment, product **3a** was obtained only in 38% yield. Thus, the use of DMU/LTA as the green reaction medium not only avoids the disadvantages of conventional organic solvents but also results in greatly enhanced reactivity. In addition, it is worth noting that we also carried out the model reaction in the presence of either L-(+)-tartaric acid or 1,3-dimethylurea in some common organic solvents at refluxing temperatures. However, we found that the product formed from these tests was only in a trace amount, as observed by TLC after 24 hours, which suggested that the reaction gave a good yield due to the interaction of DMU/L-(+)-tartaric acid system and not due to its individual component. The reason for the effectiveness of DMU/LTA might be its good solubility, high stability and positive synergic effect on the reaction through extensive hydrogen bonding. Finally, the recyclability of DMU/LTA for the model reaction was investigated by subjecting the fresh substrates **1** and **2a** to the recovered DMU/LTA obtained by evaporating the aqueous layer under vacuum after product removal to repeat the model reaction. We found that the recovered DMU/LTA could be re-used up to three consecutive runs, with the **3a** yields being 82%, 81% and 77%, respectively, demonstrating negligible changes in the synthetic efficiency, though a slight darkening of the eutectic mixture was observed after recycling. Thus, the DES could be successfully re-used over three cycles with a decrease of 6% in the final **3a** yield, and the corresponding *E*-factor value (total mass of waste/mass of product) from the three re-used cycles was calculated to be 93.68. However, starting from the fourth cycle, an obvious decrease in the product yield of 65% was noticed.

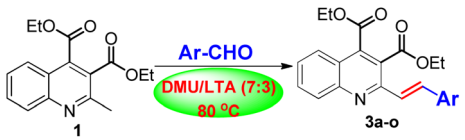
To demonstrate the synthetic potential by applying DMU/LTA as the privileged reaction medium in the Knoevenagel condensation reaction, we extended the reaction to other substituted aromatic aldehydes in a similar fashion. Satisfactorily, these aldehydes were equally amenable to the reaction process without any experimental difficulties, successfully delivering the corresponding **3b–o** in satisfactory yields of 61–86%, as listed in Table 1. It is worth noting that in all cases, the acid-sensitive ester and the newly formed olefin groups remain unaffected under the reaction conditions.

As shown in Table 1, the electronic nature of the substituent present in the aromatic aldehydes appeared not to affect the transformation, neither in product yield nor in reaction rate. For example, compound **3c** with an electron-donating methyl group and **3o** bearing an electron-withdrawing nitro group were obtained in comparable yields of 85% and 86%, respectively, showing little distinction (entries 3 *vs.* 15, Table 1). Conversely,



Scheme 2 Various methods for the synthesis of 2-styrylquinoline derivatives.

Table 1 Yields and physical properties of the newly-synthesized **3a–o**[a]



Entry	Compd	Ar	Yield[a]/%	Mp/°C
1	**3a**	Ph	83	92–94
2	**3b**	3-MeC_6H_4	82	78–79
3	**3c**	4-MeC_6H_4	85	89–90
4	**3d**	2,5-$(Me)_2C_6H_3$	72	Oily liquid
5	**3e**	3,4-$(Me)_2C_6H_3$	81	108–109
6	**3f**	2-MeOC_6H_4	70	98–100
7	**3g**	3-MeOC_6H_4	78	Oily liquid
8	**3h**	2,3-$(MeO)_2C_6H_3$	65	72–73
9	**3i**	2,5-$(MeO)_2C_6H_3$	67	Oily liquid
10	**3j**	3,4-(MeO)2C_6H_3	80	Oily liquid
11	**3k**	3,4,5-$(MeO)_3C_6H_3$	83	Oily liquid
12	**3l**	2-ClC_6H_4	69	Oily liquid
13	**3m**	3-BrC_6H_4	81	69–71
14	**3n**	2-$NO_2C_6H_4$	61	119–120
15	**3o**	4-$NO_2C_6H_4$	86	161–162

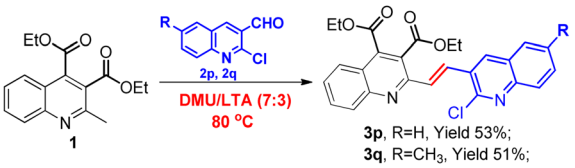
[a] Isolated yield.

the site of the substituent present in the aromatic aldehydes had a significant steric hindrance effect on the product yields. The reaction with *ortho*-substituted aromatic aldehydes generally gave the corresponding products **3d**, **3f**, **3h**, **3i**, **3l** and **3n** in relatively lower yields with longer reaction times compared with those of *meta*- and *para*-substituted ones (entries 4, 6, 8, 9, 12 and 14, Table 1). Particularly, we found that the reaction with di-*ortho* substituted aromatic aldehydes such as 2,6-dimethyl-, 2,6-dimethoxy and 2,6-dihalobenzaldehydes scarcely proceeded, from which the desired products were detected only in negligible amounts that did not warrant isolation. In addition, the reaction with aliphatic aldehydes such as butyraldehyde, isobutyraldehyde and cyclohexanecarboxaldehyde was also tested. However, the reaction was found to be fraught with difficulties associated with the combination of starting materials and numerous products, from which we could not separate the desired alkenylation products in any appreciable yield.

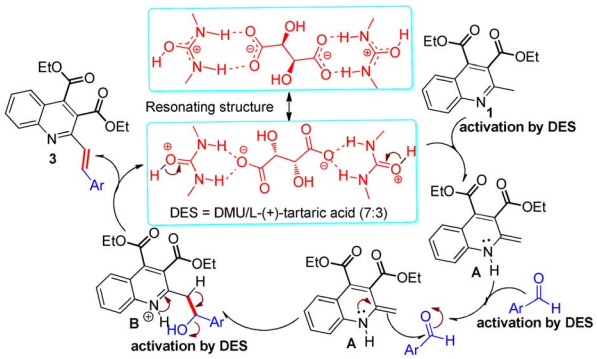
With the aim of further diversifying our synthetic work, we became interested in seeing whether quinoline aldehydes would exhibit a similar reactivity. To our delight, the two chosen 2-chloroquinoline-3-carbaldehydes were viable substrates for this transformation as well, invariably furnishing the corresponding vinyl-linked bisquinolines **3p** and **3q** though in low yields of 53% and 51%, respectively, with a longer reaction time of 8 hours, as shown in Scheme 3. Their structures would be very attractive as many bisquinoline derivatives usually exhibit potent biological activities.[42] Work is currently ongoing in this regard, and more studies on extending the reaction scope will be part of our future efforts.

To the best of our knowledge, all these newly synthesized products **3a–q** have never been reported, and their structures have been explicitly characterized based on their spectral and analytical data. Theoretically, these structures should exist as (*E*)- and/or (*Z*)-geometry due to the presence of the exocyclic vinyl double bond. The most diagnostic evidence for the geometry of vinyl moiety was the characteristic resonances of the arising two vinylic proton CH=CH doublets at δ 7.42–7.78 ppm and 8.01–8.38 ppm with large spin–spin coupling constants J_{ab} ~16.0 Hz in their ^{1}H NMR spectra, which clearly established the stereochemistry of the product as an *E*-stereoisomer.

Mechanistically, on the basis of the reports from Alvi *et al.*,[43] who recently described the resonance equation of the DES acting as a proton source, and Krishnakumar *et al.*,[44] who determined the structure, thermal stability and pH value of DMU/LTA (7 : 3), a proposed reaction mechanism for the synthesis of the title compounds is outlined in Scheme 4. First, the ability of the acidic DMU/LTA (7 : 3) (pH = 3.7) to *N*-



Scheme 3 Synthesis of vinyl-linked bisquinolines **3p** and **3q**.



Scheme 4 Proposed mechanistic pathway for the synthesis of **3**.

protonation might play an important role in the activation of 2-methylquinoline **1** to generate the enamine intermediate **A.** The formed intermediate **A** could behave as a nucleophile to attack the aromatic aldehydes and give rise to the corresponding adduct **B.** In this nucleophilic addition reaction, there was a consensus that the DES might also assist in improving the electrophilic reactivity of the aldehydes by hydrogen bonding with its carbonyl group.[45] Subsequently, the generated hydroxyl group readily underwent the elimination reaction with the *ortho*-position hydrogen proton with the loss of one molecule of water to produce the corresponding 2-styrylquinoline derivatives **3**. In the sequences of steps, DES played dual roles of solvent and catalyst.

With the series of newly synthesized (*E*)-diethyl 2-styrylquinoline-3,4-dicarboxylate derivatives in hand, we became interested in evaluating their anti-tumor activity. Thus, a preliminary screening for their *in vitro* anti-tumor activities against human cancer cell lines A549, HT29 and T24 was conducted by the methylthiazolyldiphenyltetrazolium bromide (MTT) conversion assay using the known anti-cancer cisplatin as a reference drug. As listed in Table 2, the unsubstituted 2-styrylquinoline-3,4-dicarboxyalte (**3a**) exhibited moderate anti-proliferative activity against A549 and HT29 and poor inhibitory effect towards T24 (entry 1, Table 2). The activity was not further potentiated by the introduction of methyl, chloro, bromo and nitro substituents as in **3b–e** and **3l–o** (entries 2–5 and 12–15, Table 2), which exhibited moderate inhibitory effects. Interestingly, it was observed that the introduction of methoxy substituent appeared to be beneficial in terms of the anti-tumor activity as in compounds **3f–k**, which exhibited superior activity (entries 6–11 Table 2). Moreover, the polymethoxy substituted ones have higher inhibitory activity than the mono-substituted counterparts, and especially, the compound **3k** with the 3,4,5-trimethoxystyryl fragment had the best anti-proliferative activity against A549, HT29 and T24 cell lines with the IC_{50} values of 2.38, 4.52 and 9.86 μmol L^{-1}, respectively (entry 11, Table 2), being equipotent or even better than the reference cisplatin. Additionally, the vinylene-linked bisquinolines **3p** and **3q** were also found to exhibit satisfactory inhibition properties against the growth of three tested cancer cell lines (entries 16 and 17, Table 2), having the potential to further exploit new drug discovery.

Table 2 Anti-proliferative activity of **3a–q** against human cancer cell lines A549, HT29 and T24 (IC_{50}/μmol L^{-1})

Entry	Compd	IC_{50}[a]/μmol L^{-1} A549[b]	HT29[b]	T24[b]
1	**3a**	18.47	24.86	>40
2	**3b**	20.58	30.94	>40
3	**3c**	18.61	28.15	>40
4	**3d**	18.15	25.92	30.88
5	**3e**	23.49	>40	35.89
6	**3f**	16.85	14.12	>40
7	**3g**	8.27	13.51	18.78
8	**3h**	9.27	15.76	26.43
9	**3i**	12.84	19.56	17.69
10	**3j**	5.24	10.32	15.16
11	**3k**	2.38	4.52	9.86
12	**3l**	19.45	23.08	>40
13	**3m**	25.40	21.34	30.61
14	**3n**	>40	>40	>40
15	**3o**	>40	>40	>40
16	**3p**	6.79	8.04	16.55
17	**3q**	7.41	4.33	11.18
18	**Cisplatin**	2.73	6.82	7.69

[a] IC_{50} is defined as the drug concentration causing a 50% decrease in cell population using MTT assay as described in the Experimental section. [b] Cell lines: A549: human lung tumor; HT29: human colon tumor cells, and T24: human urinary bladder tumor cells.

It is interesting to mention that some significant anti-tumor agents, such as (*E*)-5,6,7-trimethoxy-*N*-phenyl-2-styrylquinolines,[10] combretastatin A4,[46] and its indolin-2-one-based analogue,[47] as shown in Fig. 2, also contain the 3,4,5-trimethoxyphenyl fragment as the key pharmacophore. Thus, these insights from the *in vitro* anti-tumor activity might provide valuable information for further optimization of the series of derivatives, and hopefully, contribute to the development of new and effective anti-tumor candidates.

Conclusion

In summary, we have employed the environmentally benign and non-toxic DES DMU/LTA as a mildly acidic reaction medium for the green synthesis of a new series of structurally intriguing (*E*)-diethyl 2-arylvinylquinoline-3,4-dicarboxylates *via* the direct olefination of 2-methylquinolines with aromatic aldehydes. The recyclability and biodegradability of DMU/LTA make this methodology highly sustainable and reliable. The merits of the synthetic protocol described here include experimental simplicity, the use of 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* anti-tumor activity bioassay revealed that the 3,4,5-trimethoxy substituted compound exhibited potent anti-proliferative activity against the human cancer cell lines A549, HT29 and T24, being equipotent or even better than the reference drug. These results might give an important insight into the future optimization of the series of 2-styrylquinolines. Currently, work is ongoing, mainly focusing on the further elaboration and application of these compounds, which represent an intriguing goal that we are contemplating, and these results will be a part of future reports.

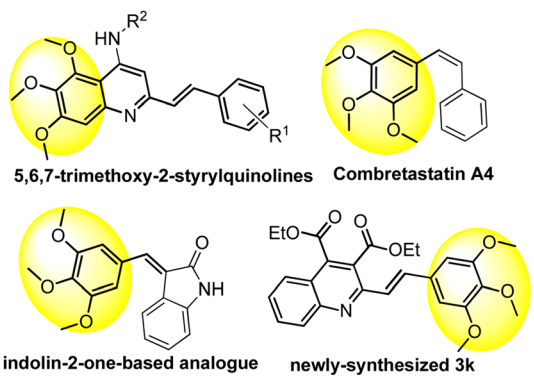


Fig. 2 Structures of some 3,4,5-trimethoxyphenyl-containing anti-tumor compounds.

Experimental section

General information

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 ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on an Agilent 400-MR spectrometer using $CDCl_3$ as the solvent. The reported chemical shifts (δ 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 ethyl acetate/petroleum ether (1 : 10) as eluent.

Preparation of deep eutectic solvent

The deep eutectic solvent 1,3-dimethylurea/L-(+)-tartaric acid was prepared as follows:[44] a mixture of 1,3-dimethylurea and L-(+)-tartaric acid with a molar ratio of 7 : 3 was heated at 100 °C in the air with stirring until a clear colourless liquid was obtained. After cooling to room temperature and vacuum drying for 5 h, the resulting 1,3-dimethylurea/L-(+)-tartaric acid deep eutectic solvent was sealed for later use.

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

Diethyl 2-methylquinoline-3,4-dicarboxylate (**1**) (0.5 mmol, 0.144 g) and respective aromatic aldehydes (**2a–o**) or 2-chloroquinoline-3-carbaldehydes (**2p** and **2q**) (0.55 mmol) was added into the medium of 1,3-dimethylurea/L-(+)-tartaric acid (7 : 3 mol mol^{-1}) (1.5 g). The resulting reaction mixture was stirred at 80 °C for 6–8 hours (as monitored by TLC). After the reaction was completed, the mixture was diluted with an equal volume of water and extracted using EtOAc (3 × 5 mL). The deep

eutectic solvent could be easily isolated after removing H_2O from the aqueous layer under a vacuum and could be further used for the next reaction run. The combined organic layer was dried over Na_2SO_4, followed by evaporation of the solvent under reduced vacuum and washing with EtOH or column chromatography over silica gel using petroleum ether/EtOAc (12 : 1) as eluent to afford the desired **3a–q**.

(*E*)-Diethyl 2-styrylquinoline-3,4-dicarboxylate (3a)

White solid, yield 83.6%, m.p. 92.4–93.8 °C. IR (KBr, cm^{-1}) ν 2981, 1740, 1704, 1246, 1194, 1027, 745; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 4.71 (q, J = 7.2 Hz, 2H, CH_2), 1.67 (t, J = 7.2 Hz, 3H, CH_3), 1.66 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{21}NO_4$: 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 82.4%, m.p. 78.2–79.5 °C. IR (KBr, cm^{-1}) ν 2972, 1731, 1546, 1379, 1255, 1203, 1080, 1027, 965, 763; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 2.57 (s, 3H, CH_3), 1.65 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{23}NO_4$: 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 84.7%, m.p. 89.3–90.8 °C. IR (KBr, cm^{-1}) ν 2981, 1722, 1546, 1379, 1246, 1194, 1027, 974, 763; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 2.59 (s, 3H, CH_3), 1.68–1.64 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{23}NO_4$: 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 71.6%; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 2.45 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 1.43–1.36 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{25}NO_4$: 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 80.7%, m.p. 108.1–110.0 °C. IR (KBr, cm^{-1}) ν 2981, 1713, 1546, 1246, 1185, 1027, 754; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 2.37 (s, 6H, CH_3), 1.54–1.52 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{25}NO_4$: 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 70.4%, m.p. 98.0–100.4 °C. IR (KBr, cm^{-1}) ν 2972, 1722, 1573, 1493, 1246, 1027, 745; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 3.87 (s, 3H, CH_3), 1.42–1.36 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{23}NO_5$: 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 77.6%. IR (KBr, cm^{-1}) ν 2981, 1731, 1546, 1379, 1246, 1045, 780; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 4.45 (q, J = 7.2 Hz, 2H, CH_2), 3.82 (s, 3H, CH_3), 1.41 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{23}NO_5$: 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 65.3%, m.p. 71.7–72.6 °C. IR (KBr, cm^{-1}) ν 2981, 1731, 1475, 1238, 1062, 780; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 3.64 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 1.18–1.13 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{25}H_{25}NO_6$: 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 66.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, CH_2), 3.72 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 1.30–1.25 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{25}H_{25}NO_6$: 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 79.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, CH_2), 3.95 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 1.47 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{25}H_{25}NO_6$: 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 83.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, CH_2), 3.91 (s, 6H, CH_3), 3.88 (s, 3H, CH_3), 1.45 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{26}H_{27}NO_7$: 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 68.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, CH_2), 4.43 (q, J = 7.6 Hz, 2H, CH_2), 1.42 (t, J = 7.6 Hz, 3H, CH_3), 1.38 (t, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{23}H_{20}ClNO_4$: 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 80.7%, m.p. 68.9–70.8 °C. IR (KBr, cm^{-1}) ν 2981, 1722, 1255, 1185, 1027, 772; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 1.44 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{20}BrNO_4$: 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 61.3%, m.p. 118.7–119.6 °C. IR (KBr, cm^{-1}) ν 2981, 1713, 1519, 1353, 1220, 772; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 4.44 (q, J = 7.2 Hz, 2H, CH_2), 1.41 (t, J = 7.6 Hz, 3H, CH_3), 1.37 (t, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{20}N_2O_6$: 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 85.8%, m.p. 161.5–162.3 °C. IR (KBr, cm^{-1}) ν 2990, 1731, 1519, 1335; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 1.44–1.38 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{20}N_2O_6$: 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%, m.p. 143.8–144.2 °C. IR (KBr, cm^{-1}) ν 2981, 1731, 1246, 1194, 1045, 737; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 4.51 (q, J = 7.2 Hz, 2H, CH_2), 1.48 (t, J = 7.2 Hz, 3H, CH_3), 1.45 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{26}H_{21}ClN_2O_4$: 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%, m.p. 158.6–161.4 °C. IR (KBr, cm^{-1}) ν 2981, 1731, 1379, 1246; ^{1}H NMR (400 MHz, $CDCl_3$) 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_2), 2.55 (s, 3H, CH_3), 1.49–1.42 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{23}ClN_2O_4$: 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 anti-proliferative 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 a 96-well culture plate at the cell density of 5×10^4 cells per well in 100 μL of culture medium at 37 °C in a 5% CO_2 incubator for 24 h seeding. The stock solutions of test compounds **3a–q** were prepared in DMSO. After incubation, the target compounds were added to the culture medium at five times the 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^{-1} 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 wavelength). The cell growth inhibition rate formula is (AC − AT)/AC × 100%. AC is the absorbance value of the blank control group; AT is the absorbance value of the experimental group. The average 50% inhibitory concentration (IC_{50}) was calculated using GraphPadPrism version 6.00 software from the non-linear curve.

Consent to participate

All authors participated directly in the current research work.

Consent to publish

The authors agree to publish the article under the Creative Commons Attribution License.

Data availability

All relevant data are within the manuscript and available from the corresponding author upon request.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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