Wentao Gao*, Xingpeng Li, Yu Wang and Yang Wang

A facile synthesis of (*E*)-2-(aryl/hetaryl)vinyl-4-phenylquinoline-3-carboxylic acids

https://doi.org/10.1515/hc-2017-0139
Received July 17, 2017; accepted October 10, 2017; previously published online November 18, 2017

Abstract: New synthetic approach to (*E*)-2-aryl/hetaryl-vinyl-4-phenyl-quinoline-3-carboxylic acids was developed, featuring three different synthetic transformations, namely the Arbuzov reaction, *in situ* Horner-Emmons olefination and subsequent ester hydrolysis occurring as a one-pot procedure. The molecular structures of newly synthesized products were confirmed by spectral data and elemental analysis.

Keywords: Arbuzov reaction; ester hydrolysis; Horner-Emmons olefination; one-pot; quinoline; three-step.

Introduction

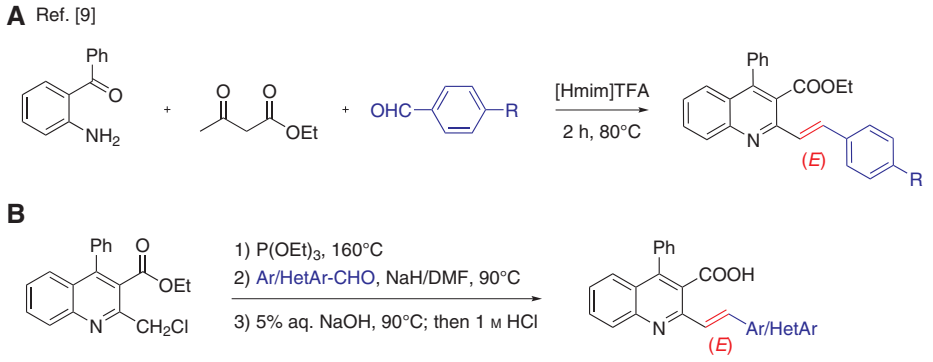
2-Styrylquinolines have received considerable interest from the medicinal community because of their well-documented biological properties such as antiproliferative activity on tumor cell lines [1], antimicrobial [2] and HIV integrase inhibitory activity [3]. Some carboxylate substituted derivatives of such molecules have been reported recently, and their biological and pharmacological properties look promising [4, 5]. For example, 2-styrylquinoline-8-carboxylic acids are active against the P388 leukemia cell line [6]. Similarly, it has been reported that 8-hydroxy-2-styrylquinoline-7-carboxylic acid derivatives exhibit potent inhibitory activity against Pim-1 kinase [7]. As a consequence, interest in the synthesis of new families of carboxylate-substituted 2-styrylquinolines continues unabated to expand the structure diversity for current medicinal chemistry needs [8]. In this regard, an impressive report [9] has described an efficient one-pot procedure for the synthesis of ethyl (*E*)-4-phenyl-2-styrylquinoline-3-carboxylate derivatives using 1-methylimidazolium trifluoroacetate ([Hmim]TFA) as a Brønsted acidic ionic liquid as shown in Scheme 1A. Even though ionic liquids offer some advantages, the tedious preparation of ionic liquids and their environmental safety are still debated. We hereby report our own results for building the (*E*)-2-aryl/hetarylvinyl-4-phenly-quinoline-3-carboxylic acids through a simple and efficient three-step one-pot reaction procedure involving Arbuzov reaction of ethyl 2-(chloromethyl)-4-phenylquinoline-3-carboxylate with some aromatic or heteroaromatic aldehydes followed by *in situ* Horner-Emmons olefination and subsequent ethyl ester hydrolysis reaction as outlined in Scheme 1B.

***Corresponding author: Wentao Gao,** Institute of Superfine Chemicals, Bohai University, Jinzhou, Liaoning 121000, China, e-mail: bhuzh@163.com
Xingpeng Li, Yu Wang and Yang Wang: Institute of Superfine Chemicals, Bohai University, Jinzhou, Liaoning 121000, China

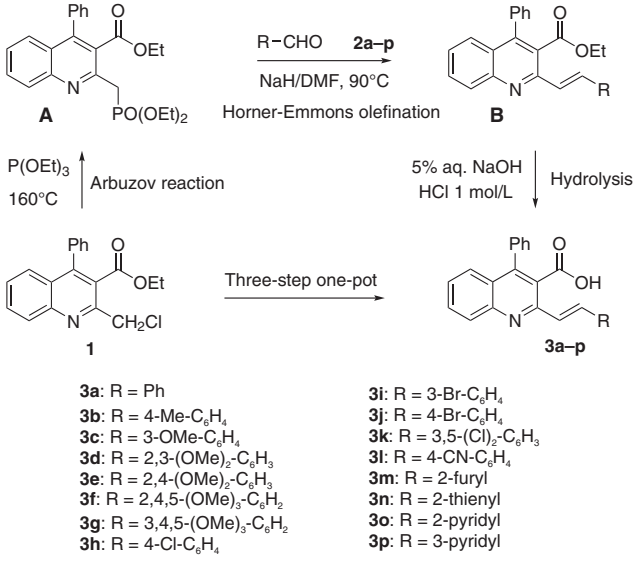
Results and discussion

The most widely used approaches to the synthesis of 2-styrylquinoline derivatives are mainly based on the Perkin-type condensation reaction of 2-methylquinolines with aldehydes in refluxing acetic anhydride, followed by hydrolysis in a pyridine water mixture [7, 10, 11]. An attempt was made by us to follow the usual methodology using the corresponding ethyl 4-phenyl-2-methylquinoline-3-carboxylate [12, 13] as the substrate for the synthesis of (*E*)-2-arylvinyl-4-phenylquinoline-3-carboxylic acids. However, the purported approach was ineffective in our hands, and the reaction did not proceed satisfactorily, giving poor yields of highly impure products. Moreover, the protocol described for this reaction was plagued by constraints like harsh reaction conditions, long reaction times and the use of a large excess of aldehydes. Therefore, the development of a simple synthesis of the target compounds is very appealing.

In the past few years, our research group has gained substantial ability in the application of ethyl 2-(halomethyl)quinoline-3-carboxylates as the valuable building blocks to reveal the synthetic potential of the platforms in accessing important quinoline scaffold derivatives [14–20]. Building on this evolving expertise and extending the applications of our previously described methodology to new substrates, we herein embarked on a facile and efficient three-step one-pot synthetic route to a variety of (*E*)-2-aryl/hetarylvinyl-4-phenylquinoline-3-carboxylic acids **3a–p** from readily available ethyl 2-(chloromethyl)-4-phenylquinoline-3-carboxylate (**1**) and various aromatic or heteroaromatic aldehydes **2a–p** as shown in Scheme 2.



Scheme 1 Synthesis of 2-styrylquinoline-3-carboxylate derivatives.



Scheme 2 Three-step one-pot synthesis of (*E*)-2-(aryl/hetaryl)vinyl-4-phenylquinoline-3-carboxylic acids **3a–p**.

The substrate **1**, which was readily obtained according to our previously described method [16], was first subjected to the Arbuzov reaction with triethyl phosphate at 160°C. After the complete conversion of the starting materials into the intermediate **A**, the excess triethyl phosphate was removed under reduced pressure. Subsequently, 1.1 equivalents of an aromatic or heteroaromatic aldehyde **2** in N,N-dimethyl formamide (DMF) and 1.1 equivalents of NaH were added to the residue and the mixture was heated to 90°C. Under these reaction conditions, an efficient Horner-Emmons olefination reaction occurred, forming the olefination intermediate **B**. It is important to mention that the use of NaH as the base is critical for this reaction because other bases such as NaOH, K_2CO_3, Et_3N, EtONa, *t*-BuOK are inferior to NaH. As the generated species **B** does not interfere with further ester hydrolysis reaction, purification at this stage is not necessary. A simple workup includes treatment of the mixture with 5% aqueous NaOH solution followed by reflux for 2 h and then acidification with 1 M hydrochloric acid. The 2-arylvinylquinoline-3-carboxylic acids **3a–p** are obtained in yields in the range of 61–82%.

To the best of our knowledge, all compounds **3a–p** have not been previously reported and the proposed structures are in full agreement with the analytical and spectroscopic data. The electronic nature and substitution at various positions of the aromatic aldehydes appear to have little impact on the reaction outcome, neither in product yield nor in reaction rate. Substituents such as Cl, Br and CN are tolerated under the reaction conditions, which could be used for further derivatizations.

Conclusions

A facile and efficient three-step one-pot procedure for the preparation of (*E*)-4-phenyl-2-styrylquinoline-3-carboxylic acid derivatives is described. Readily available starting materials, mild reaction conditions, experimental simplicity and satisfactory yields contribute to the usefulness of this method.

Experimental

The chemicals used in this work were obtained from Fluka and used without purification. Melting points (uncorrected) were determined by using a WRS-1B melting point apparatus. Infrared spectra were recorded on a Varian Scimitar 2000 series instrument using KBr pellets. The ^1H (400 MHz) and ^{13}C (100 MHz) nuclear magnetic resonance (NMR) spectra were recorded on an Agilent 400-MR spectrometer using DMSO-d_6 as the solvent. Elemental analyses were carried out on a Perkin Elmer 2400II elemental analyzer. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel GF254 using ethyl acetate/petroleum ether (2:1) as eluent.

General procedure for the preparation of (*E*)-4-phenyl-2-(aryl/hetarylvinyl)quinoline-3-carboxylic acid derivatives 3a–p

A solution of ethyl 2-(chloromethyl)-4-phenylquinoline-3-carboxylate (**1**, 0.33 g, 1 mmol) in triethyl phosphate (5 mL) was stirred at 160°C for about 1.2 h and then concentrated under reduced pressure. The residue was treated with a solution of an aromatic or heteroaromatic aldehyde (1.1 mmol) in DMF (5 mL) followed by addition of NaH (0.026 g, 1.1 mmol). The mixture was stirred at room temperature for 1 h and then at 90°C for 1.5 h. After completion of the reaction (TLC), 5% aqueous solution of sodium hydroxide (5 mL) was added and the mixture was stirred under reflux for an additional 2 h. After cooling to room temperature followed by acidification with 1 M hydrochloric acid, the precipitated crude product was crystallized from ethanol to give compound **3a–p**.

(*E*)-4-phenyl-2-styrylquinoline-3-carboxylic acid (3a) Yellow solid; yield 79%; mp 218–220°C; IR: ν 3446, 3072, 2968, 1715, 1590, 1453, 1428, 1234, 1195, 1118, 834 cm^{-1}; ^1H NMR: δ 13.29 (s br, 1H, COOH), 8.15 (d, *J* = 8.4 Hz, 1H, ArH), 8.10 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.84 (t, *J* = 7.6 Hz, 1H, ArH), 7.70 (d, *J* = 7.2 Hz, 2H, ArH), 7.53–7.59 (m, 4H, ArH), 7.42–7.48 (m, 6H, ArH), 7.38 (d, *J* = 15.6 Hz, 1H, CH=CH); ^{13}C NMR: δ 169.4, 150.1, 147.5, 145.3, 136.2, 136.1, 135.4, 131.1, 129.8, 129.6, 129.5, 129.1, 128.8, 127.8, 127.6, 126.4, 125.7, 124.5. Anal. Calcd for $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88; N, 3.99. Found: C, 81.82; H, 5.07; N, 3.82.

(*E*)-2-(4-methylstyryl)-4-phenylquinoline-3-carboxylic acid (3b) Yellow solid; yield 82%; mp 198–199°C; IR: ν 3447, 3055, 2958, 1707, 1583, 1515, 1454, 1372, 1271, 1188, 1154, 832 cm^{-1}; ^1H NMR: δ 13.58 (s br, 1H, COOH), 8.14 (d, *J* = 8.0 Hz, 1H, ArH), 8.07 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.84 (t, *J* = 7.2 Hz, 1H, ArH), 7.53–7.63 (m, 6H, ArH), 7.42–7.47 (m, 3H, ArH), 7.32 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.27 (d, *J* = 7.6 Hz, 2H, ArH), 2.35 (s, 3H, Me); ^{13}C NMR: δ 169.4, 147.5, 145.2, 139.3, 136.1, 135.5, 133.5, 131.1, 130.1, 129.8, 129.5, 129.0, 128.8, 127.8, 127.5, 126.9, 126.4, 125.6, 123.4, 21.4. Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 81.96; H, 5.41; N, 3.68.

(*E*)-2-(3-methoxystyryl)-4-phenylquinoline-3-carboxylic acid (3c) Yellow solid; yield 80%; mp 184–185°C; IR: ν 3445, 3070, 2923, 1712, 1576, 1577, 1503, 1453, 1417, 1354, 1236, 1129, 928 cm^{-1}; ^1H NMR: δ 13.62 (s br, 1H, COOH), 8.14 (d, *J* = 8.4 Hz, 1H, ArH), 8.05 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.84 (t, *J* = 7.6 Hz, 1H, ArH), 7.55–7.62 (m, 4H, ArH), 7.47 (d, *J* = 8.4 Hz, 1H, ArH), 7.38–7.44 (m, 3H, ArH), 7.36 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.28 (d, *J* = 7.6 Hz, 1H, ArH), 7.24 (s, 1H, ArH), 6.98 (d, *J* = 8.0 Hz, 1H, ArH), 3.83 (s, 3H, OMe); ^{13}C NMR: δ 169.4, 160.1, 150.1, 147.5, 145.3, 137.7, 136.1, 135.4, 131.1, 130.5, 129.8, 129.5, 129.1, 128.8, 127.7, 126.4, 125.7, 124.8, 119.8, 115.3, 113.3, 55.6. Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 79.00; H, 4.83; N, 3.46.

(*E*)-2-(2,3-dimethoxystyryl)-4-phenylquinoline-3-carboxylic acid (3d) Yellow solid; yield 76%; mp 192–194°C; IR: ν 3435, 3083, 2889, 1721, 1575, 1527, 1461, 1392, 1248, 1210, 831 cm^{-1}; ^1H NMR: δ 13.53 (s br, 1H, COOH), 8.16–8.27 (m, 4H, ArH and CH=CH), 7.44–7.57 (m, 7H, ArH and CH=CH), 7.11–7.15 (m, 3H, ArH), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe); ^{13}C NMR: δ 167.3, 151.2, 148.2, 145.6, 145.3, 143.1, 133.3, 128.9, 128.7, 127.7, 127.6, 127.5, 126.9, 126.8, 126.6, 125.5, 124.3, 123.9, 123.5, 122.8, 117.0, 111.7, 58.9, 54.0. Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40. Found: C, 75.61; H, 5.36; N, 3.19.

(*E*)-2-(2,4-dimethoxystyryl)-4-phenylquinoline-3-carboxylic acid (3e) Yellow solid; yield 72%; mp 221–222°C; IR: ν 3446, 3068, 2895, 1705, 1573, 1510, 1453, 1381, 1234, 1195, 834 cm^{-1}; ^1H NMR: δ 13.51 (s br, 1H, COOH), 8.25 (d, *J* = 15.6 Hz, 1H, ArH), 8.11 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (t, *J* = 8.0 Hz, 1H, ArH), 7.50 (d, *J* = 7.6 Hz, 1H, ArH), 7.54–7.59 (m, 4H, ArH), 7.41–7.45 (m, 3H, ArH), 7.33 (d, *J* = 15.6 Hz, 1H, CH=CH), 3.92 (s, 3H, OMe), 3.83 (s, 3H, OMe); ^{13}C NMR: δ 169.6, 162.0, 159.3, 151.0, 147.6, 144.9, 135.5, 131.2, 130.9, 129.8, 129.4, 129.3, 129.0, 128.8, 128.7, 127.2, 126.4, 125.4, 122.5, 117.7, 106.5, 99.0, 56.1, 55.8. Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40. Found: C, 76.08; H, 4.92; N, 3.53.

(*E*)-4-phenyl-2-(2,4,5-trimethoxystyryl)quinoline-3-carboxylic acid (3f) White solid; yield 76%; mp 239–241°C; IR: ν 3447, 3046, 2958, 1718, 1582, 1577, 1515, 1454, 1417, 1373, 1296, 1196, 1109, 836 cm^{-1}; ^1H NMR: δ 13.54 (s br, 1H, COOH), 8.33 (d, *J* = 16.0 Hz, 1H, CH=CH), 8.29 (d, *J* = 8.0 Hz, 1H, ArH), 7.91 (d, *J* = 7.6 Hz, 1H, ArH), 7.41 (d, *J* = 16.0 Hz, 1H, CH=CH), 7.58–7.63 (m, 4H, ArH), 7.43–7.49 (m, 3H, ArH), 7.20 (s, 1H, ArH), 6.79 (s, 1H, ArH), 3.93 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.79 (s, 3H, OMe); ^{13}C NMR: δ 172.4, 154.2, 152.3, 150.7, 143.4, 135.3, 135.0, 134.1, 133.4, 129.7, 129.4, 129.0, 128.9, 127.9, 126.8, 126.7, 125.6, 120.2, 115.7, 112.2, 98.3, 56.8, 56.7, 56.3. Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17. Found: C, 73.61; H, 5.07; N, 3.34.

(*E*)-4-phenyl-2-(3,4,5-trimethoxystyryl)quinoline-3-carboxylic acid (3g) White solid; yield 78%; mp 211–213°C; IR: ν 3443, 3054, 2968, 1723, 1575, 1578, 1505, 1480, 1396, 1239, 1110, 792 cm^{-1}; ^1H NMR: δ 13.55 (s br, 1H, COOH), 8.12 (d, *J* = 8.4 Hz, 1H, ArH), 8.04 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.84 (t, *J* = 7.6 Hz, 1H, ArH), 7.53–7.59 (m, 4H, ArH), 7.41–7.46 (m, 3H, ArH), 7.29 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.02 (s, 2H, ArH), 3.87 (s, 6H, 2OMe), 3.72 (s, 3H, OMe); ^{13}C NMR: δ 178.4, 162.6, 159.3, 156.5, 154.3, 147.9, 145.7, 145.4, 144.5, 140.9, 138.9, 138.6, 137.7, 135.6, 134.6, 114.4, 114.1, 69.6, 65.4. Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17. Found: C, 73.28; H, 5.34; N, 3.03.

(*E*)-2-(4-chlorostyryl)-4-phenylquinoline-3-carboxylic acid (3h) Yellow solid; yield 80%; mp 257–258°C; IR: ν 3452, 3072, 2962, 1718, 1579, 1490, 1455, 1414, 1372, 1291, 1120, 832 cm^{-1}; ^1H NMR: δ 13.59 (s br, 1H, COOH), 8.14 (d, *J* = 8.4 Hz, 1H, ArH), 8.06 (d, *J* = 15.6 Hz, 1H, ArH), 7.84 (t, *J* = 8.0 Hz, 1H, ArH), 7.73 (d, *J* = 8.0 Hz, 2H, ArH), 7.55-7.60 (m, 4H, ArH), 7.51 (d, *J* = 8.4 Hz, 2H, ArH), 7.42–7.48 (m, 3H, ArH), 7.37 (d, *J* = 15.6 Hz, 1H, ArH); ^{13}C NMR: δ 167.2, 147.7, 145.3, 143.2, 133.3, 133.0, 132.6, 131.8, 129.0, 127.6, 127.4, 127.3, 126.9, 126.7, 125.6, 124.3, 123.5, 123.1. Anal. Calcd for $C_{24}H_{16}ClNO_2$: C, 74.71; H, 4.18; N, 3.63. Found: C, 74.55; H, 4.36; N, 3.84.

(*E*)-2-(3-bromostyryl)-4-phenylquinoline-3-carboxylic acid (3i) Yellow solid; yield 74%; mp 190–192°C; IR: ν 3446, 1719, 1585, 1513, 1457, 1417, 1237, 1111, 786 cm^{-1}; ^1H NMR: δ 13.59 (s br, 1H, COOH), 8.13 (d, *J* = 8.4 Hz, 1H, ArH), 8.02 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.91 (s, 1H, ArH), 7.85 (t, *J* = 7.6 Hz, 1H, ArH), 7.71 (d, *J* = 8.0 Hz, 1H, ArH), 7.53–7.60 (m, 5H, ArH), 7.47 (d, *J* = 8.4 Hz, 1H, ArH), 7.41–7.45 (m, 3H, ArH), 7.38 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR: δ 167.2, 147.7, 145.3, 143.2, 133.4, 133.3, 132.6, 130.2, 129.0, 127.6, 127.5, 127.4, 126.9, 126.7, 126.6, 125.6, 124.3, 123.6, 123.2, 120.5. Anal. Calcd for $C_{24}H_{16}BrNO_2$: C, 66.99; H, 3.75; N, 3.26. Found: C, 67.20; H, 3.56; N, 3.09.

(*E*)-2-(4-bromostyryl)-4-phenylquinoline-3-carboxylic acid (3j) Yellow solid; yield 77%; mp 238–240°C; IR: ν 3460, 3038, 2980, 1714, 1578, 1497, 1423, 1399, 1290, 1233, 1165, 1126, 1056, 847 cm^{-1}; ^1H NMR: δ 13.59 (s br, 1H, COOH), 8.14 (d, *J* = 8.4 Hz, 1H, ArH), 8.05 (d, *J* = 15.6 Hz,

1H, CH=CH), 7.84 (t, *J* = 7.6 Hz, 1H, ArH), 7.63–7.68 (m, 4H, ArH), 7.55–7.60 (m, 4H, ArH), 7.47 (d, *J* = 8.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.6 Hz, 2H, ArH), 7.38 (d, *J* = 15.6 Hz, 1H, CH=CH); ^{13}C NMR: δ 169.3, 149.8, 147.5, 138.8, 135.4, 134.4, 132.0, 131.5, 131.1, 130.2, 129.8, 129.6, 129.1, 128.8, 127.8, 126.7, 126.5, 126.2, 125.8, 122.8. Anal. Calcd for $C_{24}H_{16}BrNO_2$: C, 66.99; H, 3.75; N, 3.26. Found: C, 66.80; H, 3.92; N, 3.06.

(*E*)-2-(3,5-dichlorostyryl)-4-phenylquinoline-3-carboxylic acid (3k) Orange solid; yield 74%; mp 198–200°C; IR: ν 3446, 1716, 1577, 1515, 1437, 1374, 1340, 1272, 1126, 834 cm^{-1}; ^{1}H NMR: δ 13.37 (s br, 1H, COOH), 8.13 (d, *J* = 8.4 Hz, 1H, ArH), 7.99 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.85 (t, *J* = 7.6 Hz, 1H, ArH), 7.78 (s, 2H, ArH), 7.56–7.59 (m, 5H, ArH), 7.47–7.50 (m, 2H, ArH), 7.45 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.44 (s, 1H, ArH); ^{13}C NMR: δ 169.2, 149.7, 147.4, 145.5, 140.1, 135.4, 135.1, 133.1, 131.2, 129.8, 129.6, 129.0, 128.8, 128.4, 127.9, 126.5, 126.2, 125.9. Anal. Calcd for $C_{24}H_{15}Cl_2NO_2$: C, 68.59; H, 3.60; N, 3.33. Found: C, 68.38; H, 3.79; N, 3.11.

(*E*)-2-(4-cyanostyryl)-4-phenylquinoline-3-carboxylic acid (3l) Orange solid; yield 68%; mp 261–263°C; IR: ν 3447, 2228, 1713, 1584, 1514, 1449, 1374, 1267, 1204, 1125, 832 cm^{-1}; ^{1}H NMR: δ 13.31 (s br, 1H, COOH), 8.12–8.18 (m, 2H, ArH), 8.03 (d, *J* = 7.2 Hz, 2H, ArH), 7.86 (d, *J* = 7.6 Hz, 1H, ArH), 7.82 (d, *J* = 8.0 Hz, 2H, ArH), 7.53–7.59 (m, 4H, ArH), 7.44–7.52 (m, 4H, ArH); ^{13}C NMR: δ 172.1, 154.5, 152.2, 150.2, 145.1, 140.2, 139.7, 136.0, 135.9, 135.2, 134.5, 134.4, 133.8, 133.7, 133.5, 132.8, 132.6, 131.5, 131.2, 130.6. Anal. Calcd for $C_{25}H_{16}N_2O_2$: C, 79.77; H, 4.28; N, 7.44. Found: C, 79.54; H, 4.47; N, 7.29.

(*E*)-2-(2-(furan-2-yl)vinyl)-4-phenylquinoline-3-carboxylic acid (3m) Yellow solid; yield 62%; mp 175–178°C; IR: ν 3462, 1713, 1588, 1511, 1446, 1374, 1340, 1294, 1263, 1204, 1118, 857 cm^{-1}; ^{1}H NMR: δ 13.59 (s br, 1H, COOH), 8.09 (d, *J* = 8.4 Hz, 1H, ArH), 7.94 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.80–7.84 (m, 2H, ArH), 7.51–7.58 (m, 4H, ArH), 7.40–7.46 (m, 3H, ArH), 7.17 (d, *J* = 15.6 Hz, 1H, CH=CH), 6.91 (dd, *J* = 7.2, 3.8 Hz, 1H, ArH), 6.63–6.67 (m, 1H, ArH); ^{13}C NMR: δ 174.2, 157.0, 154.5, 152.3, 149.9, 149.8, 140.1, 135.9, 134.5, 134.3, 134.2, 133.8, 133.6, 132.3, 131.2, 130.3, 128.0, 126.5, 118.8, 117.8. Anal. Calcd for $C_{22}H_{15}NO_3$: C, 77.41; H, 4.43; N, 4.10. Found: C, 77.28; H, 4.12; N, 4.31.

(*E*)-4-phenyl-2-(2-(thiophen-2-yl)vinyl)quinoline-3-carboxylic acid (3n) Yellow solid; yield 66%; mp 197–198°C; IR: ν 3446, 1719, 1583, 1493, 1452, 1417, 1373, 1291, 1263, 1201, 1123, 850 cm^{-1}; ^{1}H NMR: δ 13.65 (s br, 1H, COOH), 8.27 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.10–8.13 (m, 1H, ArH), 7.84 (dd, *J* = 7.6, 7.2 Hz, 1H, ArH), 7.64 (d, *J* = 7.6 Hz, 1H, ArH), 7.51–7.57 (m, 5H, ArH), 7.43–7.48 (m, 3H, ArH), 7.17 (d, *J* = 3.6 Hz, 1H, ArH), 7.08 (d, *J* = 15.6 Hz, 1H, CH=CH); ^{13}C NMR: δ 174.1, 154.5, 152.2, 150.0, 146.2, 140.2, 135.9, 135.5, 134.5, 134.2, 134.0, 133.8, 133.7, 133.5, 133.3, 132.7, 132.3, 131.2, 130.3, 127.9. Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92. Found: C, 74.14; H, 4.08; N, 3.76.

(*E*)-4-phenyl-2-(2-(pyridin-2-yl)vinyl)quinoline-3-carboxylic acid (3o) Yellow solid; yield 61%; mp 181–182°C; IR: ν 3446, 2915, 1715, 1582, 1508, 1449, 1402, 1380, 1336, 1286, 1240, 1116, 874 cm^{-1}; ^{1}H NMR: δ 13.64 (s br, 1H, COOH), 8.67 (d, *J* = 3.6 Hz, ArH), 8.16 (d, *J* = 8.4 Hz, 1H, ArH), 8.12 (d, *J* = 15.6 Hz, 1H, ArH), 7.97 (d, *J* = 15.6 Hz, 1H, ArH), 7.87 (dd, *J* = 7.6, 7.6 Hz, 2H, ArH), 7.70 (d, *J* = 7.6 Hz, 1H, ArH), 7.54–7.60 (m, 4H, ArH), 7.44–7.50 (m, 3H, ArH), 7.36–7.39 (m, 1H, ArH); ^{13}C NMR: δ 167.2, 151.8, 148.2, 147.5, 145.4, 143.1, 135.5, 133.2, 132.8, 129.0, 127.6, 127.5, 127.2, 126.9, 126.7, 125.8, 125.7, 124.3, 123.7, 122.9, 121.9. Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.67; H, 4.39; N, 7.74.

(*E*)-4-phenyl-2-(2-(pyridin-3-yl)vinyl)quinoline-3-carboxylic acid (3p) Yellow solid; yield 64%; mp 195–196°C; IR: ν/cm^{-1}: 3461, 1710, 1581, 1581, 1511, 1463, 1406, 1379, 1320, 1132, 874; ^{1}H NMR: δ 13.54 (s br, 1H, COOH), 8.88 (s, 1H, ArH), 8.57 (d, *J* = 4.4 Hz, 1H, ArH), 8.13–8.16 (m, 2H, ArH), 8.09 (d, *J* = 16.0 Hz, 1H, CH=CH), 7.85 (d, *J* = 7.6 Hz, 1H, ArH), 7.55–7.60 (m, 4H, ArH), 7.41–7.50 (m, 5H, ArH); ^{13}C NMR: δ 165.4, 148.0, 147.9, 147.6, 145.6, 144.7, 133.1, 132.0, 130.7, 130.0, 129.4, 127.5, 127.4, 127.0, 126.7, 125.8, 125.0, 124.4, 124.1, 123.4, 122.2. Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.18; H, 4.35; N, 8.11.

Acknowledgments: This work was supported by the National Natural Science Foundation of China (Grants 21476028 and 21402011) and the Natural Science Foundation of Liaoning Province (Grant 201602006).

References

[1] Chang, F.; Chen, W.; Wang, C.; Tzeng, C.; Chen, Y. Synthesis and antiprolife- rative evaluations of certain 2-phenylvinylquinoline (2-styrylquinoline) and 2-furanylvinylquinoline derivatives. *Bioorg. Med. Chem.* **2010**, *18*, 124–133.

[2] Cieslik, W.; Musiol, R.; Nycz, J. E.; Jampilek, J.; Vejsova, M.; Wolf, M.; Machura, B.; Polansk, J. Contribution to investigation of antimicrobial activity of styrylquinolines. *Bioorg. Med. Chem.* **2012**, *20*, 6960–6968.

[3] Leonard, J. T.; Roy, K. Exploring molecular shape analysis of styrylquinoline derivatives as HIV-1 integrase inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 81–92.

[4] Zouhiri, F.; Danet, M.; Bénard, C.; Normand-Bayle, M.; Mouscadet, J. F.; Leh, H.; Thomas, C. M.; Mbemba, G.; d'Angelo, J.; Desmaële, D. HIV-1 replication inhibitors of the styrylquinoline class: introduction of an additional carboxyl group at the C-5 position of the quinoline. *Tetrahedron Lett.* **2005**, *46*, 2201–2205.

[5] Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. Investigating biological activity spectrum for novel quinoline analogues. *Bioorg. Med. Chem.* **2007**, *15*, 1280–1288.

[6] Podeszwa, B.; Niedbala, H.; Polanski, J.; Musiol, R.; Tabak, D.; Finster, J.; Serafin, K.; Milczarek, M.; Wietrzyk, J.; Boryczka, S.; et al. Investigating the antipro-liferative activity of quinoline-5,8-diones and styrylquinolinecarboxylic acids on tumor cell lines. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6138–6141.

[7] Sliman, F.; Blairvacq, M.; Durieu, E.; Meijer, L.; Rodrigo, J.; Desmaële, D. Identification and structure – activity relationship of 8-hydroxy-quinoline-7-carboxylic acid derivatives as inhibitors of Pim-1 kinase. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2801–2805.

[8] Musiol, R.; Podeszwa, B.; Finster, J.; Niedbala, H.; Polanski, J. An efficient microwave-assisted synthesis of structurally diverse styrylquinolines. *Monatsh. Chem.* **2006**, *137*, 1211–1217.

[9] Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Nikcheh, M. S. A new and efficient one-pot procedure for the synthesis of 2-styrylquinolines. *Tetrahedron Lett.* **2008**, *49*, 5366–5368.

[10] Normand-Bayle, M.; Bénard, C.; Zouhiri, F.; Mouscadet, J. F.; Leh, H.; Thomas, C. M.; Mbemba, G.; Desmaëlea, D.; d'Angelo,

J. New HIV-1 replication inhibitors of the styryquinoline class bearing aroyl/acyl groups at the C-7 position: synthesis and biological activity. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4019–4022.

[11] Nosova, E. V.; Stupina, T. V.; Lipunova, G. N.; Charushin, V. N. Synthesis and fluorescent properties of 2-styryl-6,7-difluoro-8-hydroxyquinoline and its Zn(II) complex. *J. Fluorine Chem.* **2013**, *150*, 36–38.

[12] Aspiotis, R.; Deschênes, D.; Dubé, D.; Girard, Y.; Huang, Z.; Laliberté, F.; Liu, S.; Papp, R.; Nicholson, D. W.; Young, R. N. The discovery and synthesis of highly potent subtype selective phosphodiesterase 4D inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5502–5505.

[13] Wu, L. H.; Yang, D. Q. Synthesis, characterization and single crystal structure of ethyl 2-(substituted-piperazin-1-ylmethyl)-quinoline-3-carboxylate derivatives. *Chin. J. Org. Chem.* **2009**, *29*, 1122–1128.

[14] Gao, W. T.; Jiang, Y.; Li, Y.; Li, F.; Yan, Y. A Novel and facile synthesis of 2-(benzofuran-2-yl)benzo[*h*]-quinoline-3-carboxylic acid derivatives. *Chin. J. Chem.* **2012**, *30*, 822–826.

[15] Gao, W. T.; Zhao, Z. G.; Li, Y.; Yan, Y.; Li, F. Synthesis and cyclization of 8-formyl-2-(phenoxymethyl)-quinoline-3-carboxylic acids. *Chin. J. Chem.* **2012**, *30*, 1127–1132.

[16] Gao, W. T.; Lin, G. H.; Li, Y.; Tao, X. Y.; Liu, R.; Sun, L. J. An efficient access to the synthesis of novel 12-phenylbenzo[6,7] oxepino[3,4-*b*]quinolin-13(6*H*)-one derivatives. *Beilstein J. Org. Chem.* **2012**, *8*, 1849–1857.

[17] Chang, M. Q.; Gao, F.; Li, Y.; Gao, W. T. Synthesis and keto–enol tautomerism of ethyl 4-oxo-3,4-dihydro-1-pyrano[3,4-*b*] quinoline-3-carboxylate. *Chem. Pap.* **2013**, *67*, 437–443.

[18] Gao, W. T.; Li, Y.; Wang, S. T. A facile synthesis of bisquinoline derivatives via the Williamson reaction. *Res. Chem. Intermed.* **2014**, *40*, 669–679.

[19] Gao, W. T.; Xing, X. D.; Li, Y.; Lan, S. A novel construction of quino-fused tropone skeleton: first synthesis of 12*H*-benzo[4,5] cyclohepta[1,2-*b*]quinolin-12- one derivatives. *Tetrahedron* **2014**, *70*, 2180–2189.

[20] Li, K.; Fu, X. B.; Zhao, Y. N.; Gao, W. T. A facile synthesis of novel pyrrolo[3,4 -*b*]quinolin-1-one derivatives. *Res. Chem. Intermed.* **2016**, *42*, 4273–4287.