First synthesis of novel 2,4-bis(\(E\))-styrilquinoline-3-carboxylate derivatives and their antitumor activity†

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A simple and flexible synthesis of a new series of 2,4-bis(\(E\))-styrilquinoline-3-carboxylates (3a–t) has been achieved for the first time in good yields via successive Arbuzov/Horner–Wadsworth–Emmons (HWE) reaction in one-pot using the newly-synthesized ethyl 4-(bromomethyl)-2-(chloromethyl)quinoline-3-carboxylate as the substrate. Our synthetic protocol is as attractive and powerful as it is simple, tolerates a wide range of substituents, and does not involve the use of expensive reagents or catalysts. These title compounds belong to a new class of quinoline derivatives and their antitumor activity was assessed on human cancer cell lines (A549, HT29 and T24). The MTT assay showed compounds 3h, 3k and 3t had significant inhibitory activity with IC_{50} values of 1.53, 1.38 and 2.36 \(\mu\)M against A549 and 1.50, 0.77 and 0.97 \(\mu\)M against HT29, respectively, much better than the reference cisplatin.

Introduction

Among various classes of quinoline derivatives, 2-styrylquinoline (SQ) derivatives represent a particularly fascinating class of pharmacologically active molecules, and members of this family are claimed to exhibit a broad spectrum of biological activities such as anti-HIV-1, antimicrobial, antimalarial and anti-Alzheimer activities. Especially, recent evaluation of their anti-proliferative effect on tumor cell lines have validated their importance as potential anti-tumor agents. For example, Chang et al. synthesized a range of styrylquinolines, which were proved to be useful as antitumor agents against the growth of MCF-7 (breast), NCI-H460 (lung), and SF-268 (CNS). In this respect, Mrozek-Wilczkiewicz et al. presented a similar series of compounds in a search for new anticancer agents against drug resistant lines and found that these compounds exhibited highly anti-proliferative activity against the human colon carcinoma cell lines. Recently, El-Sayed et al. reported a new series of 4,6-disubstituted 2-(4-(dimethylamino)styryl)quinolines, which exhibited significant anti-tumour activities against HepG2 and HCT116 cell lines.

Due to their striking biological activities and in order to have structurally diversified molecules for bio-screening, considerable synthetic efforts have been devoted surrounding the 2-styrylquinoline molecular template for further modification and functionalization by both organic and medicinal chemists with the aim of enhancing the potency of this privileged class of compounds. For another, quinoline carboxylates are ubiquitous heterocyclic units found extensively in many natural products and pharmaceuticals. Despite the existence of extensive reports for their synthesis and functionalization, the literature related to synthesis of styrylquinoline carboxylates found to be scarce so far. In this regard, Dabiri et al. reported a facile one-pot synthesis of (\(E\))-ethyl 4-phenyl-2-styrylquinoline-3-carboxylate derivatives through tandem Friedländer annulation and Knoevenagel condensation reaction using 1-methylimidazolium trifluoroacetate ([Hmim] TFA) as a Brønsted acidic ionic liquid as shown in Scheme 1a. Similarly, Kumar et al. recently described such synthesis with good yields by using In(OTf)_3 as the catalyst (Scheme 1b).

Promoted by the above reports and in view of structural diversity playing a prominent role towards new drug discovery, we felt that it would be a worthwhile endeavor to extend this work to look into the synthesis of 2,4-bis(styril)-substituted carboxylates.

Scheme 1 Synthetic route designed for (styril)quinoline-3-carboxylates.
derivatives for current medicinal chemistry needs. As far as we know, the routes available to specifically synthesize the bis(styryl)quinolines has remained virtually unexplored hitherto, probably due to the lack of efficient methods for their synthesis. As such, in connection with our continuing interest in the synthesis of highly valuable quinoline systems, herein we would like to report a facile one-pot synthesis and preliminary antitumor activity evaluation of a range of structurally novel and intriguing 2,4-bis((E)-styryl)quinoline-3-carboxylate derivatives through one-pot successive Arbuzov/HWE reaction sequence (Scheme 1c).

Results and discussion

2-Styrylquinoline derivatives are commonly prepared by the condensation reaction of 2-methylquinolines with aromatic aldehydes.14,15 Accordingly, in initial experimental we attempted to synthesize the desired 2,4-bis(styryl)quinoline-3-carboxylate (3a) by using ethyl 2,4-dimethylquinoline-3-carboxylate (1) obtained from literature14 as the substrate for the analogous transformations (Route 1 of Scheme 2). Although the route looked straightforward and attractive for the adaptation in our synthesis, the purported approach was ineffective in our hands, giving poor yields of highly impure products. Moreover, the protocol described for the reaction was plagued by constraints like harsh reaction conditions and the use of a large excess of aldehydes. Attempts to use other reaction conditions such as NBS/TBHP,7 NaOAc/H2O : AcOH (1 : 1),15 and Bmim[BF4]26 also failed.

As well known, arylmethyl halides are important synthetic intermediates for various transformations in organic synthesis.17 For example, they can proceed to Arbuzov reaction with phosphites to furnish phosphonates.18 On the other hand, the Horner–Wadsworth–Emmons (HWE) olefination reaction of phosphonates with aldehydes has served as the most powerful method for the construction of double bonds.19 Thus, by combination of the two name reactions some versatile methodologies for the synthesis of arylvinyl-substituted compounds have been developed.20 On the basis of these observations, we envisioned that quinoline-3-carboxylate upon bearing two active halomethyl functional groups at its 2- and 4-positions might be a feasible building block to undergo the Arbuzov reaction and subsequent HWE olefination reaction process to access structurally novel and intriguing 2,4-bis((E)-styryl)quinoline-3-carboxylate as shown in Route 2 of Scheme 2.

With this synthetic plan in mind, the first stage involved the preparation of the requisite ethyl 2,4-bis(halomethyl)quinoline-3-carboxylate. In fact, prior to the current investigation we were well aware that the preparation of bis(halomethyl)quinoline would be very interesting and attractive because such quinoline scaffold would have important potential for the flexible construction of a large range of novel and complex quinoline-based derivatives. To our knowledge, no related reports are available concerning its synthesis. To this end, we first conducted the radical bromination reaction of ethyl 2,4-dimethylquinoline-3-carboxylate (I) with N-bromosuccinimide (NBS) (2.2 equiv.) for the construction of 2,4-bis(bromomethyl)quinoline-3-carboxylate (II) as shown in Scheme 3(a). Unfortunately, the reaction was fraught with difficulties associated with excess byproducts, from which the desired bis(bromomethyl) quinoline II could not be easily separated by recrystallization or column chromatography due to their very close polarities. Further varying the amount of NBS used resulted in no improvement as well. Recently, Aitken et al.21 reported the application of benzotri fluoride as the solvent in the NBS bromination reaction of 2,3-dimethylbenzene for the efficient preparation of 2,3-bis(bromomethyl)benzene. Disappointly, by employing this method the reaction always proceeded heterogeneously and no desired product could be obtained.

By a literature survey we found that in previous work Ryabukhin et al.22a and Degtyarenko et al.22b reported independently on the synthesis of ethyl 2-chloromethyl-4-methylquinoline-3-carboxylate (IV) through chlorotrimethyl silane (TMSCl)-mediated Friedländer reaction between 2-aminoacetophenone (III) and 4-chloroacetoacetic ester. On this basis, it occurred to us that the synthetic route to the required 2,4-bis(halomethyl) quinoline might be achieved by the further radical bromination reaction of IV at its 4-methyl moiety as shown in Scheme 3(b). Thus, we first conducted the condensation reaction of III with ethyl 4-chloro-3-oxobutanoate, closely followed the literature process, in which the corresponding 2-chloromethylquinoline IV was readily obtained in 76% yield. Subsequently, the resulting IV was further subjected to the radical bromination reaction conditions with 1.1 equiv. of NBS. To our delight, in this case

Scheme 2 Synthetic route designed for 2,4-di(styryl)quinoline-3-carboxylate (3a).

Scheme 3 Synthesis of ethyl 2,4-bis(halomethyl)quinoline-3-carboxylate (I).
the radical bromination reaction proceeded well, giving the expected ethyl 4-(bromomethyl)-2-(chloromethyl)quinoline-3-carboxylate (1) in a good yield of 81% yield with a trace amount of other byproducts as observed by TLC.

With the newly-synthesized bis(halomethyl)quinoline 1 in hand, our attention was turned to its Arbuzov reaction with triethyl phosphate. Initially, ZnBr₂ was used as a catalyst in dichloromethane media at room temperature in accordance with the reaction conditions of the literature. Although the methodology is elegant and impressive, our attempt to extend this approach to our synthesis was unfruitful, and the reaction did not proceed satisfactorily, giving a poor yield of the corresponding product (27%). Interestingly, we found that by only refluxing 1 in an excess of triethyl phosphate (8 mL) without added catalyst, the Arbuzov reaction could be performed very smoothly,16 nearly quantitative conversion to the corresponding [quinolinylmethyl]phosphonate A within 3 h as monitored by TLC (R₂ = 0.64, 10% ethyl acetate/petroleum ether in a 3 time run) and LC-MS (Scheme 4). As the reaction did not involve the use of additional organic solvents and the intermediate A was obtained in nearly quantitative yield, we speculated that purification at this stage was unnecessary, and the subsequent HWE olefination reaction would proceed successfully in a one-pot manner as shown in Scheme 4.

Accordingly, we simply evaporated the excess triethyl phosphate to dryness under reduced pressure and conducted in situ the HWE olefination reaction by adding directly to the corresponding [quinolinylmethyl]phosphonate A within 3 h as monitored by TLC (R₂ = 0.64, 10% ethyl acetate/petroleum ether in a 3 time run) and LC-MS (Scheme 4). As the reaction did not involve the use of additional organic solvents and the intermediate A was obtained in nearly quantitative yield, we speculated that purification at this stage was unnecessary, and the subsequent HWE olefination reaction would proceed successfully in a one-pot manner as shown in Scheme 4.

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of 72–78% (entries 15–19). Encouraged by these results and with the aim of further diversifying our work on the synthesis of this class of 2,4-di(ferrocenylvinyl)quinoline derivatives accessible by this method, we became very interested in seeing whether ferrocenylaldehyde (2t) would exhibit a similar reactivity. Gratifyingly, ferrocenylaldehyde was equally amenable to the reaction process without any experimental difficulties, giving the corresponding 2,4-di(ferrocenylvinyl)-substituted analogue 3t in a good yield of 71% (entry 20, Table 1). The synthesized 3t would be very attractive as this class of ferrocenylvinyl heterocycles usually exhibit potent biological activities.25

Having a series of the targeted compounds 3a–t in hand, a preliminary investigation for their in vitro anti-tumor activities against human cancer cell lines such as A549, HT29 and T24 was carried out, in which the potency was expressed as inhibition rate with cisplatin as a reference. Cell viability was assessed 72 h after treatment by conducting an MTT assay. The preliminary screening results were listed in Table 2. We observed that all of the tested compounds at 2 μg ml⁻¹ concentration showed poor inhibition of cancer cell lines growth on the three studied cell lines, whereas at the concentration of 20 μg ml⁻¹ the methoxyl-substituted compounds 3d, 3e and 3h–l were observed to exert relatively good anticancer activity against A549 and HT29 compared to other substituents. Further, the presence of the substituent in the position of ortho, meta-, and/or para- of phenyl ring allowed us for the structure-activity-relationship (SAR) study. We observed that compounds 3h, 3j and 3k having methoxyl groups at both meta and para-position of the benzene ring showed better inhibitory activity (>90%). The results suggested that position of methoxyl group on meta and para-position of the styryl moiety played an important role for inhibitory activity of the compounds. The naphthyl and hetaryl-substituted compounds 3o–s displayed low activities for these types of cancer cell lines. The SAR demonstrated that the modification of phenyl ring of styryl moiety by naphthyl or heteroaromatic ring could not significantly affect the inhibitory

| Entry | R          | Product | Yielda (%) |
|-------|------------|---------|------------|
| 1     | Ph         | 3a      | 83         |
| 2     | 2-MeC₆H₄   | 3b      | 79         |
| 3     | 4-MeC₆H₄   | 3c      | 85         |
| 4     | 2-MeOC₆H₄  | 3d      | 76         |
| 5     | 4-MeOC₆H₄  | 3e      | 80         |
| 6     | 4-EtOC₆H₄  | 3f      | 71         |
| 7     | 2,4-diMeC₆H₄ | 3g     | 84         |
| 8     | 3,4-diMeOC₆H₃ | 3h   | 79         |
| 9     | 2,5-diMeOC₆H₃ | 3i    | 80         |
| 10    | 5-Piperonyl | 3j     | 75         |
| 11    | 3,4,5-TriMeOC₆H₂ | 3k | 77         |
| 12    | 2,4,5-TriMeOC₆H₂ | 3l | 70         |
| 13    | 2,6-DiClC₆H₄ | 3m | 78         |
| 14    | 4-BrC₆H₄   | 3n      | 84         |
| 15    | 1-Naphthyl  | 3o      | 75         |
| 16    | 2-Naphthyl  | 3p      | 78         |
| 17    | 2-Furyl     | 3q      | 76         |
| 18    | 2-Thienyl   | 3r      | 72         |
| 19    | 2-Pyridyl   | 3s      | 73         |
| 20    | Ferrocenyl  | 3t      | 71         |

a Isolated yield.

| Compd | A549 | HT-29 | T-24 |
|--------|------|-------|------|
|        | 2 μg ml⁻¹ | 20 μg ml⁻¹ | 2 μg ml⁻¹ | 20 μg ml⁻¹ | 2 μg ml⁻¹ | 20 μg ml⁻¹ |
| 3a     | 12.77   | 38.41  | 20.12  | 48.30    | 15.08    | 37.79   |
| 3b     | 5.50    | 62.54  | 29.96  | 52.71    | 12.92    | 28.20   |
| 3c     | 26.36   | 41.17  | 29.34  | 55.83    | 13.55    | 39.71   |
| 3d     | 21.89   | 66.83  | 27.53  | 64.75    | 14.23    | 46.84   |
| 3e     | 33.48   | 72.86  | 35.75  | 75.56    | 11.07    | 28.35   |
| 3f     | 22.05   | 65.51  | 9.16   | 48.74    | 6.94     | 31.08   |
| 3g     | 12.00   | 26.10  | 7.32   | 26.46    | 15.27    | 46.23   |
| 3h     | 28.69   | 92.65  | 51.63  | 94.76    | 8.22     | 25.72   |
| 3i     | 24.93   | 78.92  | 36.02  | 74.13    | 16.86    | 40.58   |
| 3j     | 37.30   | 94.45  | 61.46  | 92.83    | 30.19    | 53.46   |
| 3k     | 18.83   | 97.78  | 69.54  | 98.81    | 29.18    | 40.78   |
| 3l     | 49.40   | 86.66  | 43.20  | 85.51    | 33.84    | 51.70   |
| 3m     | –10.35  | –8.33  | –9.69  | –9.09    | 12.12    | 28.68   |
| 3n     | 6.81    | 37.61  | 18.33  | 47.54    | 13.66    | 32.89   |
| 3o     | 25.19   | 65.57  | 30.55  | 34.66    | 13.66    | 32.89   |
| 3p     | –5.64   | 45.30  | 9.43   | 47.94    | 14.57    | 35.81   |
| 3q     | 18.58   | 22.86  | 16.29  | 54.26    | 27.14    | 42.18   |
| 3r     | 12.11   | 13.78  | 5.23   | 43.80    | 26.51    | 39.42   |
| 3s     | –2.88   | 3.38   | 11.55  | 38.42    | 3.61     | 24.85   |
| 3t     | –6.61   | 86.17  | 60.49  | 104.17   | 15.69    | 31.29   |
| Cisplatin | 70.04 | 82.25  | 11.21  | 65.92    | 42.26    | 56.81   |
activity of the compounds. In contrast, ferroceny-substituted compound 3t was found to exhibit significant antitumor activity with the inhibitory ratios of 86.17% against A549 and 104.17% against HT29, much better than the reference cisplatin. This result indicated that introduction of a ferroceny group could also contribute to improve the antitumor properties significantly.

Basing from the above results, we decided to study the concentration-response of the potent derivatives 3h-1 and 3t by obtaining their IC_{50} (i.e., the concentration required for 50% cell viability) values in suppressing cell growth of A549 and HT-29 cells. As listed in Table 3, compounds 3h, 3k, and 3t exhibited more potent in vitro anti-cancer activity against A549 and HT29 with IC_{50} values of 1.53, 1.38, 2.36 μM and 1.50, 0.77, 0.97 μM (entries 1, 4 and 6), respectively, which were much superior to cisplatin (entry 7). The data further confirmed that the presence of methoxy substituents at both meta and para-positions of benzene ring or the introduction of ferrocene moiety played an important role in the antitumor activity of 2,4-di((E)-styryl)quinoline-3-carboxylate derivatives.

Conclusions

In conclusion, we have described an easy access to a series of structurally novel and intriguing 2,4-bis((E)-styryl)quinoline-3-carboxylate derivatives through one-pot Arbuzov/HWE reaction procedure. Experimental simplicity, inexpensive reagents and satisfactory yields would contribute to the usefulness of this method. The preliminary bioassay for their antitumor activity revealed that some of the title compounds such as 3h, 3k and 3t exerted excellent anti-cancer activity against A549 and HT29 with IC_{50} values much better than the reference cisplatin. These results might provide valuable information for designing antitumor lead compounds, and currently further work, mainly focusing on structural optimization, application and exploration of the enormous potential of these compounds, is underway in our lab.

Conflicts of interest

There are no conflicts to declare.

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