Mol Divers (2014) 18:51–59
DOI 10.1007/s11030-013-9476-4

FULL-LENGTH PAPER

Efficient synthesis of 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid derivatives from aniline

Arindam Chatterjee · Stephen J. Cutler · Ikhlas A. Khan · John S. Williamson

Received: 13 August 2013 / Accepted: 19 August 2013 / Published online: 12 September 2013
© Springer Science+Business Media Dordrecht 2013

Abstract The first reported synthesis of potential kinase inhibitors, 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid derivatives starting from aniline is described. This efficient high yielding sequence was carried out in six steps without any chromatographic purification. A tandem nucleophilic aromatic substitution/cyclization reaction was used as a key step in the sequence. The versatile intermediate 2-carboxylic acid was used as a suitable precursor to access the functionalization of the C-ring, by convergent analog synthesis of several novel derivatives.

Keywords Nucleophilic aromatic substitution · Cyclization · Heterocycles · Kinase inhibitors · Convergent analog synthesis

Introduction

Thieno[3,2-*c*]quinolin-4(5*H*)-ones (**1**) are members of a highly interesting heterocyclic structural class, and have been demonstrated to be active against various biological targets. Derivatives of the central core were reported as potential anticancer agents through inhibition of several serine–threonine and tyrosine kinases including hedgehog kinase [1,2], casein kinase (CK), proviral insertion Moloney virus (PIM) kinase, and FMS-like tyrosine (Flt) kinase [3–6]. In addition, a few other analogs were effective anti-malarial agents [7] and enhancers of in-vitro α-amylase activity [8]. Since most of the known biological activities and syntheses were limited to substitutions in the A- and B-rings (Fig. 1), strategic C-ring substitutions have a great potential in the development of novel agents.

In our continued effort to explore potential kinase inhibitors, we chose C-ring-substituted 4-oxo-4,5-dihydrothieno [3,2-*c*]quinoline-2-carboxylic acid (**2**) derivatives as lead structures. The carboxylic acid function was chosen to add another point of diversity to the molecules. We observed that although the structure **2** was listed in SciFinder® [9], there was no associated reference. This motivated us to develop a new and straight-forward strategy to synthesize the versatile intermediate **2** and rapid convergent synthesis of its derivatives.

Several groups have explored the synthesis of the core structure (**1**) through transition metal-mediated synthesis with varied yields ranging from 13–86 % [5,7,10,11]. These palladium or copper-mediated transition metal syntheses are often hard to scale-up and pose issues relating to purification and overall cost. Only a few reports exist so far for the synthesis of the C-ring-substituted derivatives. Pierre et al. utilized palladium-mediated cross-coupling reaction and subsequent bromination to synthesize the 2-bromo derivative of **1** in very low yield [5,6]. A ring expansion Beckmann rearrangement was used in a multi-step synthesis of 2-phenyl-substituted derivatives of **1** in moderate yield [12]. Efforts have also been made to synthesize *N*-alkylated derivatives of **2** [2,13,14].

Electronic supplementary material The online version of this article (doi:10.1007/s11030-013-9476-4) contains supplementary material, which is available to authorized users.

A. Chatterjee · S. J. Cutler (✉) · J. S. Williamson
Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, Mississippi, MS 38677, USA
e-mail: cutler@olemiss.edu

I. A. Khan
National Center for Natural Product Research, University of Mississippi, Mississippi, MS 38677, USA

J. S. Williamson (✉)
Division of Extramural Research, National Center for Complementary and Alternative Medicine, National Institutes of Health, 6707 Democracy Blvd, Suite 401, Bethesda, MD 20892-5475, USA
e-mail: john.williamson@nih.gov

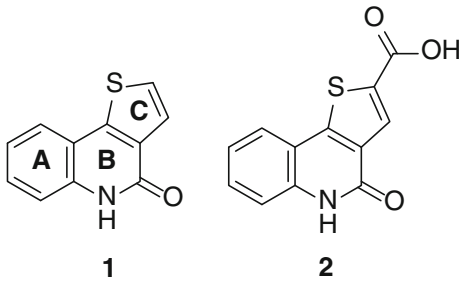
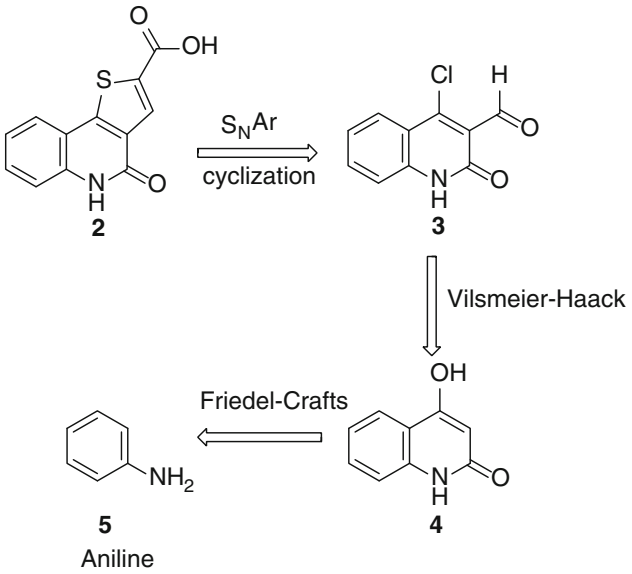


Fig. 1 Structures of **1** and **2**



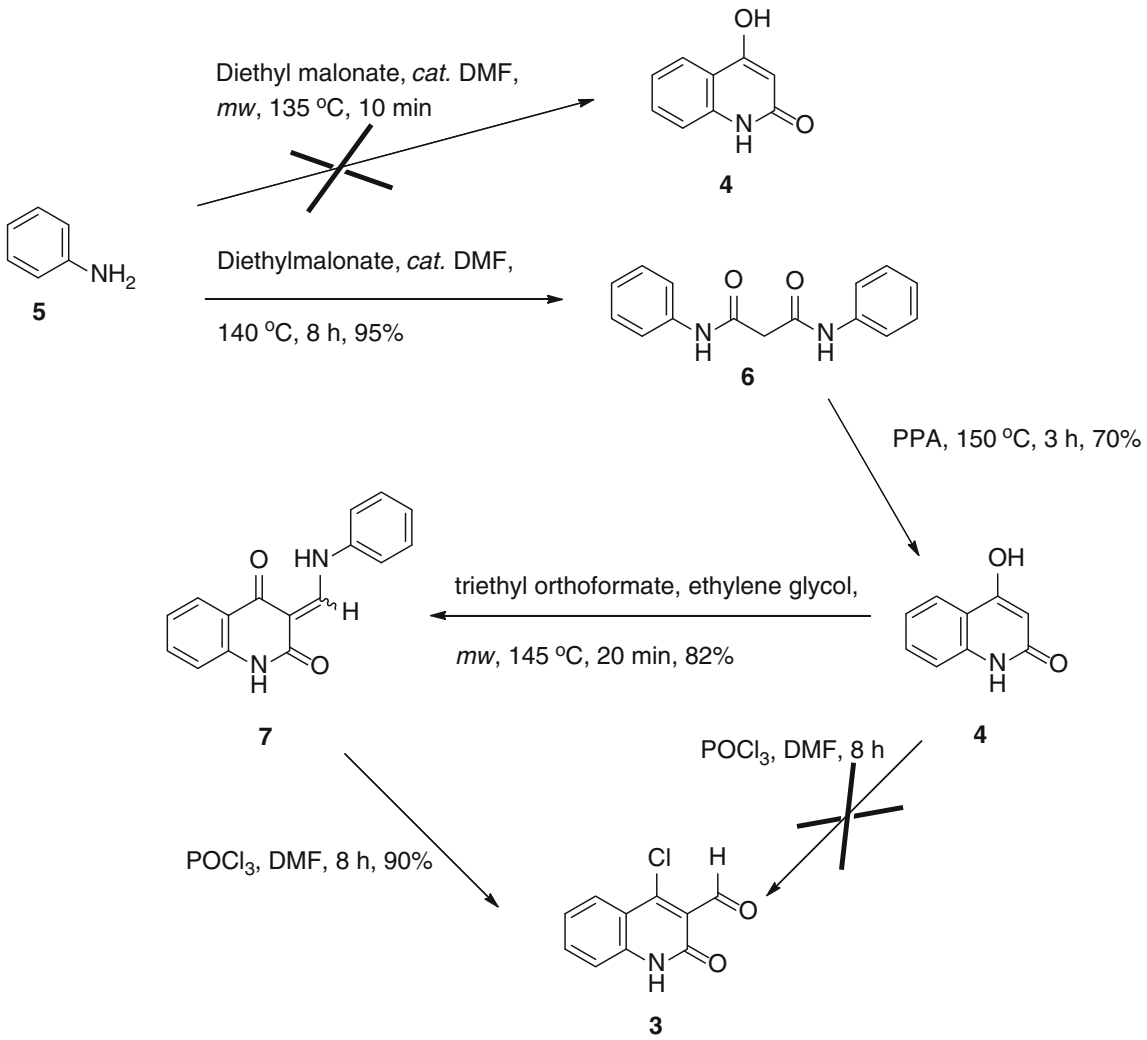
Scheme 1 Retro-synthetic approach for **2**

However, difficulty in synthesizing the unstable α-chloro aldehyde (**3**) and subsequent cyclization barred any known synthesis available for C-ring-substituted thienoquinolone moiety with free –NH lactam (**2**). Here, we report the first efficient and cost-effective method to synthesize 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid derivatives starting from aniline. Our proposed scheme starts with aniline and utilizes a sequence of Friedel–Crafts, Vilsmeier–Haack, nucleophilic aromatic substitution (S_NAr) and cyclization reactions to achieve the synthesis of the target compound (**2**). The retro-synthetic approach is described in Scheme 1.

Results and discussion

In our synthetic approach, we first attempted direct microwave conversion of commercially available aniline (**5**) and diethylmalonate to 4-hydroxyquinolin-2(1*H*)-one (**4**) [15,16]. Contrary to the reported findings, we could never repeat the synthesis of 4-hydroxyquinolin-2(1*H*)-one (**4**). Instead N^1,N^3-diphenylmalonamide (**6**) was obtained exclusively in 60 % yield. We optimized the procedure by using a varied mix of aniline and diethylmalonate with microwave and conventional heating. We found the optimum condition to be the use of a (2:1) mixture of aniline and diethylmalonate with a catalytic amount of DMF at 140 °C for 8 h to get **6** as a white solid in 95 % yield. The structure of **6** was confirmed by comparing the ^{1}H NMR and melting point (mp) with the known literature values [17]. 4-Hydroxyquinolin-2(1*H*)-one (**4**) was obtained by intra molecular Friedel–Crafts acylation of **6** by heating it with polyphosphoric acid (PPA) at 150 °C for 3 h [18]. Chromatographic purification was avoided by a simple acid–base workup, resulting in pure **4** in 74 % yield. Our attempt to convert **4** directly to the α-chloro aldehyde (**3**) failed to yield the desired product [19]. However, we were able to convert **4** to an intermediate azomethine-containing 3-((phenylamino) methylene) quinoline-2,4(1*H*, 3*H*)-dione (**7**), which was easily converted to the α-chloro aldehyde (**3**) by a Vilsmeier–Haack reaction [20] (Scheme 2).

While characterizing **7**, we noticed a striking difference between the reported ^{1}H NMR chemical shifts [20] and our observed data. We observed two new chemical shifts at 13.70 (d, J = 12.5 Hz) and 12.81 (d, J = 12.5 Hz) ppm, which collectively integrated as one proton. We speculated that **7** exists as both the (*E*)- and (*Z*)-isomers as depicted in Fig. 2, which were not reported either by Chilin et al. [20] or Fiala et al. [21]. In order to confirm our speculation, we first assigned the chemical shifts (δ in ppm) of A, B, C, and D at 25°C (Fig. 3), as follows. Three signals at 10.89–10.84 (m, 1H), 13.70 (d, J = 12.5 Hz) and 12.81 (d, J = 12.5 Hz) were exchanged by D_2O wash, confirming as −NH signals. By comparing the spectrum of **4**, the signal at 10.89–10.84 (m) was assigned to the lactam −NH. The doublet at 8.88 was assigned for H-C_{11}, from COSY, which showed correlation of the peak only with the two exchangeable signals at 13.70 and 12.81. In summary, signal D at 8.88 (d, J = 12.0 Hz, 1H, H-C_{11}), signal C at 10.89–10.84 (m, 1H, H-N_1), signal B at 13.70 (d, J = 12.5 Hz, H-N_{12}) and signal A at 12.81 (d, J = 12.5 Hz, H-N_{12}) were assigned. Since COSY showed correlations of D (H-C_{11}) with both A (H-N_{12}) and B (H-N_{12}), we wanted to investigate further to confirm whether **7** is a mixture of tautomers or two geometric isomers (*E*- and *Z*-). We designed a variable temperature NMR experiment (VTE) from 25 to 80 °C and it was observed that each signal individually coalesced with the increase in temperature (Fig. 3). But signals A and B never coalesced, confirming the presence of two different geometrical isomers (*E*- and *Z*-). In our modified conversion of **4**–**7** we used microwave irradiation at 140 °C for 40 min instead of conventional heating to obtain **7** as a mixture of the *E*- and *Z*-isomers in 82 % yield. Compound **7** was subsequently stirred with 5 equivalents of phosphorous oxychloride in DMF at room temperature for 8 h, followed by simple work-up to get 4-chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3**) as a white solid in 90 % yield. The regioselectivity of the con-



Scheme 2 Synthesis of **3**

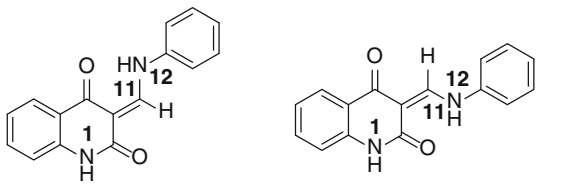


Fig. 2 Structures of *E*- and *Z*-isomers of **7**

version was confirmed by IR, indicating the presence of a carbonyl stretching at 1646 cm^{-1}corresponding to the lactam. We found that **3** was unstable at room temperature, but could be stored at −20 °C under inert atmosphere for a period of over six months.

Next, to explore the possible synthesis of ethyl 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylate (**9**), we evaluated the reaction of **3** and ethyl 2-mercaptoacetate (Scheme 3). The result of using different bases with different reaction conditions is shown in Table 1. We found that potassium carbonate (K_2CO_3) was the base of choice for the optimum conversion. Although the mechanism of this reaction has not been established experimentally, we believe the reaction went through a tandem S_NAr/cyclization, followed by elimination of water (see supplementary material). To the best of our knowledge, this is the first efficient tandem S_NAr/cyclization reaction to synthesize a C-ring-substituted thienoquinolone moiety containing a free −NH lactam. Hydrolysis of the ester (**9**) with lithium hydroxide and purification by a simple acid–base work-up produced the desired target 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid (**2**) in 96 % yield. A detailed spectral characterization of **2** was established by using ^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC, HRMS, IR and mp; purity was ascertained by HPLC analysis (see supplementary material).

Compound **2** was used as a suitable precursor to access the functionalization of the C-ring by convergent analog synthe-

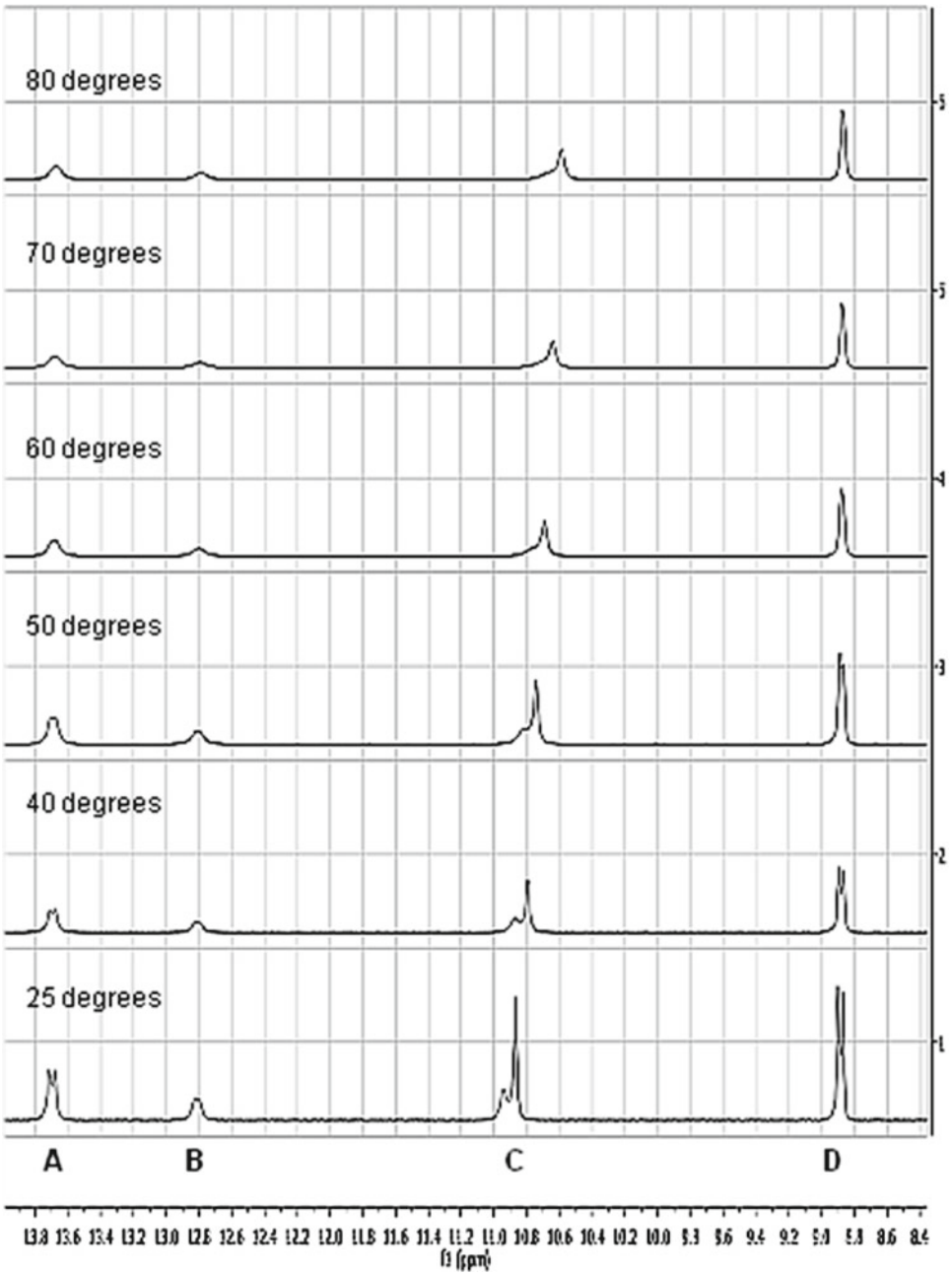


Fig. 3 VTE of compound **7**

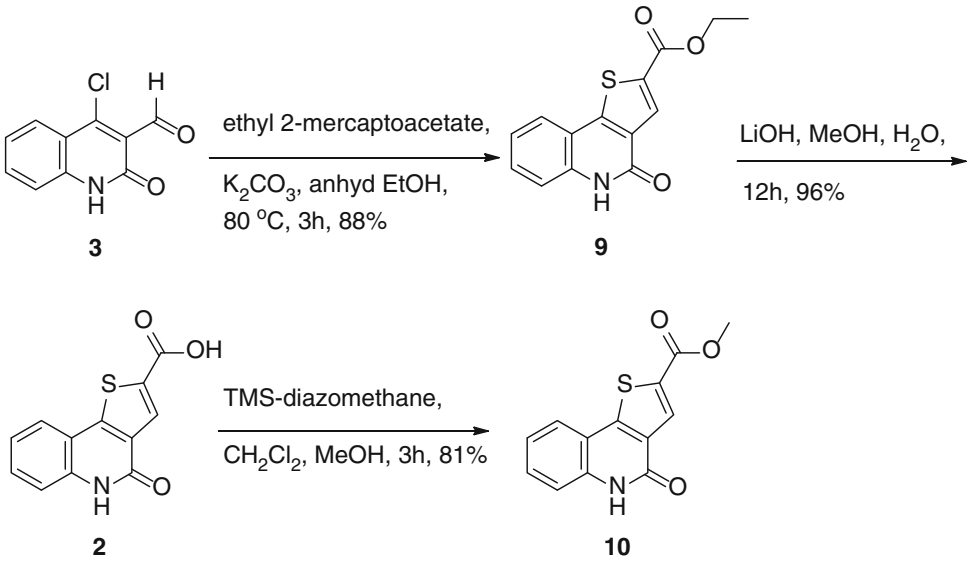
Table 1 Screening results of different bases for the synthesis of **9**

Entry	Solvent	Base	Time	Temperature (°C)	Isolated yield (%)
1	EtOH	NaOEt	3 h	80	0
2	EtOH	Na_2CO_3	3 h	80	48
3	EtOH	K_2CO_3	24 h	30	22
4	EtOH	K_2CO_3	3 h	80	88

sis. It was first converted to the corresponding methyl ester (**10**) in 81 % yield using TMS-diazomethane (Scheme 3). To further explore its use in convergent analog synthesis, **2** was easily converted to the corresponding amides (**11 a–o**) by treating the acid chloride, generated in situ with various amines (Scheme 4). We chose a broad spectrum of amines to show the generality of the conversion (Table 2). All the new compounds were characterized by ^{1}H and ^{13}C NMR, HRMS and purity was determined by HPLC analysis (see supplementary material).

In summary, a robust, cost-effective and efficient synthesis of 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid (**2**) was developed in six steps. Some interesting features were highlighted: high yields with no chromatographic purification, operational simplicity, and novelty. In this paper we also demonstrated the ease of derivatization of **2**, making

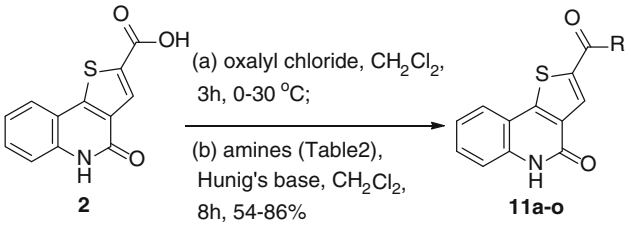
Scheme 3 Synthesis of **2** and its methyl ester



the process useful for synthesis of focused C-ring-substituted libraries. Our current effort is focused on synthetic applications of this methodology in a variety of systems.

Experimental section

Melting points were determined on an Opti-Melt automated melting point system (Stanford Research Systems) and were uncorrected. IR spectra were recorded using an Agilent model Cary 630 FT-IR. ^{1}H and ^{13}C NMR spectra were obtained on Bruker model AMX 500 and Avance 400 NMR spectrometers with standard pulse sequences, operating at 500 and 400 MHz for ^{1}H, and 125 and 100 MHz for ^{13}C respectively. The residual DMSO-d_6 solvent signals (DMSO-d_6 : $\delta_H = 2.50$ ppm and $\delta_C = 39.51$ ppm) were used as internal reference. The chemical shifts (δ) were expressed in ppm. Multiplicities were described as singlet (s), doublet (d), triplet (t), multiplet (m), and broad resonance (br). The coupling constants (J) were expressed in Hz. High-resolution mass spectra (HRMS) were recorded on a Micromass Q-TOF Agilent G1969A mass spectrometer with electro spray ionization (ESI) interface. Column chromatography was carried out on silica gel (70–230 mesh, Merck). TLC was performed on silica gel 60 F_{254} plates. Anhydrous DMF and CH_2Cl_2 were purchased in sure-seal® bottles from Aldrich. All the reagents were used without any further purification unless otherwise noted. A Biotage® Initiator microwave was used for all microwave (MW) reactions. All the HPLC analysis were performed on Waters W2690/5, with a 996 PDA detector, using X-tera C-18, 3 × 100 column and using a gradient system consisting of water (0.1 % formic acid) and acetonitrile (0.1 % formic acid).



Scheme 4 Convergent analog synthesis

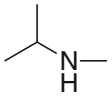
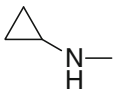
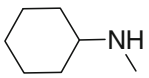
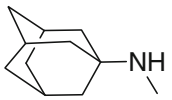
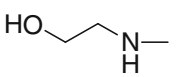
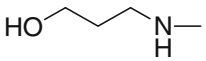
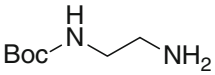
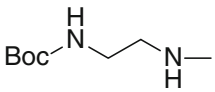
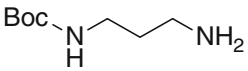
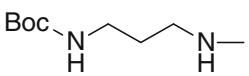
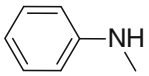
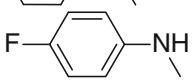
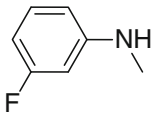
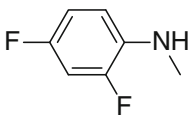
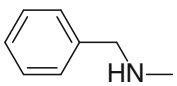
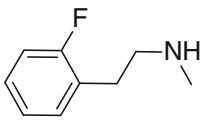
Synthesis of N^1,N^3-diphenylmalonamide **6**

A catalytic amount of DMF was added to a stirred solution of aniline (10 g, 108 mmol) and diethyl malonate (8.7 g, 54 mmol). The reaction mixture was heated at 140 °C for 8 h. The precipitated solid was filtered and washed with Et_2O to produce the title compound as a white solid (13.03 g, 95 %). Spectral data was compared with literature values [17].

Synthesis of 4-hydroxyquinolin-2(1H)-one **4**

N^1,N^3-diphenylmalonamide (**6**) (12.76 g, 50 mmol) was added in portions to a stirred solution of PPA (50 g) at 150 °C and stirred for 3 h. It was then quenched by pouring onto ice-water, resulting in precipitation. The solid was filtered and dissolved into 200 mL of 1N NaOH. Any undissolved solid was removed by filtration. The filtrate was acidified with 1N HCl to precipitate the desired product, which was filtered, washed with water and dried under vacuum to yield the title compound as a white solid (6.01 g, 74 %). Spectral data was compared with literature values [18].

Table 2 Scope of **2** in convergent synthesis of **11**

Entry	Compound	Amine	R-group	Isolated yield (%)
1	**11a**	NH_3	$-NH_2$	86
2	**11b**	Isopropylamine		80
3	**11c**	Cyclopropylamine		71
4	**11d**	Cyclohexylamine		81
5	**11e**	1-Adamantylamine		65
6	**11f**	Ethanolamine		83
7	**11g**	Propanolamine		77
8	**11h**			65
9	**11i**			75
10	**11j**	Aniline		63
11	**11k**	4-Fluoroaniline		68
12	**11l**	3-Fluoroaniline		73
13	**11m**	2,4-Difluoroaniline		54
14	**11n**	Benzylamine		66
15	**11o**	2-Fluorophenethylamine		58

Synthesis of 3-((phenylamino)methylene)quinoline-2,4(1*H*, 3*H*)-dione **7**

To a microwave vial containing aniline (0.38 g, 4.04 mmol) and triethylorthoformate (0.6 g, 4.04 mmol) in 10 mL of ethylene glycol was added 4-hydroxyquinolin-2(1*H*)-one (**4**). The reaction mixture was heated in a microwave at 140 °C for 40 min. The precipitated solid was filtered and washed with EtOH to produce the title compound as a mixture of *E*- and *Z*-isomers (0.87 g, 82 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.70 (d, $J = 12.5$ Hz), 12.81 (d, $J = 12.5$ Hz), 10.94 (s), 10.87 (s), 8.88 (d, $J = 12.0$ Hz, 1H), 7.96 (d, $J = 7.8$ Hz,

1H), 7.63–7.43 (m, 5H), 7.30 (t, $J = 6.9$ Hz, 1H), 7.24–7.08 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.72, 178.87, 165.85, 163.30, 152.96, 152.30, 141.27, 140.73, 138.44, 138.32, 133.79, 133.68, 129.92, 129.86, 126.40, 126.15, 125.97, 125.53, 121.70, 121.42, 120.35, 119.63, 118.66, 118.62, 118.49, 116.16, 115.87, 103.02, 102.32. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{15}N_2O_2$ $[M+H]^+$: 265.0977. Found: 265.0949.

Synthesis of 4-chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde **3**

To a stirred solution of 3-((phenylamino)methylene)quinoline-2,4(1*H*, 3*H*)-dione (**7**) (0.87 g, 3.29 mmol) in 10 mL of DMF at 0 °C was added $POCl_3$ (2.5 g, 16.5 mmol). The reaction mixture was stirred at 0 °C for 15 min and then stirred at ambient temperature for 8 h. It was then quenched by pouring onto ice-water, resulting in precipitation. The solid was filtered, washed with Et_2O and dried under vacuum to yield the title compound as a yellow solid (0.61 g, 90 %); mp 258−259 °C (dec); FTIR ν_{max} (cm^{-1}): 3156, 2981, 2854, 2716, 1701, 1646, 1612, 1587, 1538, 1479, 1436, 1235, 960, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.29 (s, 1H), 8.06 (d, $J = 8.3$ Hz, 1H), 7.70 (t, $J = 7.7$ Hz, 1H), 7.50–7.26 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.33, 160.37, 146.27, 139.54, 134.12, 126.66, 123.33, 122.71, 117.43, 115.92. HRMS (ESI-TOF) m/z calcd for $C_{10}H_5ClNO_2$ $[M-H]^-$: 206.0009. Found: 206.0071.

Synthesis of ethyl 4-oxo-4,5-dihydrothieno[3,2-*c*] quinoline-2-carboxylate **9**

To a stirred suspension of K_2CO_3 (1.2 g, 8.7 mmol) in 20 mL of anhydrous EtOH, was added ethyl 2-mercaptoacetate (0.52 g, 4.35 mmol). The reaction was stirred for 10 min and a suspension of 4-chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3**) (0.6 g, 2.9 mmol) in 10 mL of EtOH was added and stirred at 80 °C for 3 h. The precipitated solid was filtered, triturated with water, re-filtered, washed with EtOH and dried to yield the title compound as a white solid (0.7 g, 88 %); mp 315 − 317 °C (dec); FTIR ν_{max} (cm^{-1}): 3020, 2875, 1711, 1655, 1589, 1513, 1467, 1366, 1284, 1246, 1153, 1071, 745; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H, H^5), 8.10 (s, 1H, H^3), 7.94 (d, $J = 7.7$ Hz, 1H, H^9), 7.57 (t, $J = 7.3$ Hz, 1H, H^7), 7.43 (d, $J = 8.0$ Hz, 1H, H^6), 7.27 (t, $J = 7.1$ Hz, 1H, H^8), 4.36 (q, $J = 6.4$ Hz, 2H, H^{16}), 1.35 (t, $J = 6.7$ Hz, 3H, H^{17}). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.79, 157.48, 149.53, 137.13, 131.91, 130.72, 130.58, 123.73, 122.48, 116.25, 115.33, 61.41, 13.87. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{12}NO_3S$ $[M+H]^+$: 274.0538. Found: 274.0536. HPLC: retention time 19.26 min; purity >99 %.

Synthesis of 5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid **2**

To a stirred suspension of ethyl 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylate (**8**) (1.28 g, 4.68 mmol) in 50 mL of (1:1) MeOH-H_2O was added LiOH (0.5 g, 11.71 mmol). The mixture was stirred for 12 h, filtered and the filtrate was concentrated in vacuo to evaporate the MeOH. Acidification with 6N HCl yielded the title compound as a white precipitate. The solid was filtered, washed with water and Et_2O and dried to yield the title compound as a white solid (1.1 g, 96 %); mp 371 °C; FTIR ν_{max} (cm^{-1}): 3090, 2983, 2067, 1685, 1644, 1587, 1541, 1404, 1159, 839, 743; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.64 (s, 1H, H^{15}), 11.86 (s, 1H, H^5), 8.02 (s, 1H, H^3), 7.87 (d, $J = 7.9$ Hz, 1H, H^9), 7.53 (t, $J = 7.6$ Hz, 1H, H^7), 7.41 (d, $J = 8.4$ Hz, 1H, H^6), 7.24 (t, $J = 7.6$ Hz, 1H, H^8). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.52 (C^{14}), 157.78 (C^4), 149.48 (C^{13}), 137.14(C^{12}), 133.88 (C^2), 130.94 (C^{10}), 130.77 (C^7), 130.27 (C^3), 123.92 (C^9), 122.65 (C^8), 116.38 (C^6), 115.60 (C^{11}). HRMS (ESI-TOF) m/z calcd for $C_{12}H_8NO_3S$ $[M+H]^+$: 246.0225. Found: 246.0244. HPLC: retention time 12.58 min; purity >99 %.

Synthesis of methyl 4-oxo-4,5-dihydrothieno[3,2-*c*] quinoline-2-carboxylate **10**

TMS-diazomethane (150 μL, 0.3 mmol) was added dropwise to a stirred suspension of 5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid (**2**) (0.025 g, 0.1 mmol) in a mixture of 5 mL of CH_2Cl_2 and 1 mL of MeOH. The reaction mixture was stirred for 3 h and monitored by TLC. It was then quenched with few drops of AcOH and stirred for an additional 2 h, concentrated in vacuo to dryness and purified by column chromatography on silica gel to give the title compound as a white solid (0.021 g, 81 %); mp 314−316 °C; FTIR ν_{max} (cm^{-1}): 2877, 1718, 1591, 1468, 1430, 1286, 1251, 1153, 1071, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H, H^5), 8.08 (s, 1H, H^3), 7.91 (d, $J = 7.9$ Hz, 1H, H^9), 7.56 (t, $J = 7.6$ Hz, 1H, H^7), 7.42 (d, $J = 8.2$ Hz, 1H, H^6), 7.26 (t, $J = 7.0$ Hz, 1H, H^8), 3.90 (s, 3H, H^{16}). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.51, 157.72, 149.83, 137.28, 131.71, 131.10, 130.91, 124.09, 122.79, 116.46, 115.47, 52.85. HRMS (ESI-TOF) m/z calcd for $C_{13}H_8NO_3S$ $[M-H]^-$: 258.0225. Found: 258.0234. HPLC: retention time 14.60 min; purity >99 %.

General procedure for synthesis of carboxamides **11 a–o**

To a stirred suspension of 5-dihydrothieno[3,2-*c*]quinoline-2-carboxylic acid (**2**) (0.025 g, 0.1 mmol) in 5 mL of CH_2Cl_2 was added oxalyl chloride (0.02 g, 0.15 mmol) and two drops of DMF. The reaction mixture was stirred for 2 h and then

concentrated in vacuo. The dried suspension of the acid chloride in 10 mL of CH_2Cl_2 was added to a stirred solution of the respective amines (0.03 mmol) and Hunig's base (0.09 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was stirred for 12 h. It was then concentrated to dryness and purified on silica gel column to give the title compounds.

Representative examples of the spectral characterizations of carboxamides **11**

4-Oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide **11 a**

White solid (86 %); mp 334 °C (dec); FTIR ν_{max} (cm^{-1}): 3206, 3086, 1662, 1616, 1518, 1423, 1374, 1106, 747; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H, H^5), 8.30 (s, 2H, $H^{3,15}$), 7.88 (d, J = 7.9 Hz, 1H, H^9), 7.66 (s, 1H, H^{15}), 7.53 (t, J = 7.7 Hz, 1H, H^6), 7.43 (d, J = 8.3 Hz, 1H, H^7), 7.25 (t, J = 7.6 Hz, 1H, H^8). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.38, 157.99, 148.12, 139.86, 136.79, 131.33, 130.30, 126.20, 123.81, 122.57, 116.30, 115.80. HRMS (ESI-TOF) m/z calcd or $C_{12}H_7N_2O_2S$ $[M-H]^-$: 243.0228. Found: 243.0248. HPLC: retention time 11.09 min; purity >99 %.

N-Cyclopropyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide **11 c**

White solid (71 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H, H^5), 8.81 (s, 1H, H^{15}), 8.28 (s, 1H, H^3), 7.89 (d, J = 8.1 Hz, 1H, H^9), 7.53 (t, J = 7.9 Hz, 1H, H^7), 7.43 (d, J = 8.4 Hz, 1H, H^6), 7.25 (t, J = 7.6 Hz, 1H, H^8), 2.85 (m, 1H, H^{16}), 0.82–0.50 (m, 4H, $H^{17,18}$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.72, 158.00, 147.82, 139.47, 136.78, 131.28, 130.34, 125.54, 123.85, 122.63, 116.33, 115.80, 23.05, 5.72. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{11}N_2O_2S$ $[M-H]^-$: 283.0541. Found: 283.0549. HPLC: retention time 14.19 min; purity >96 %.

N-((3s,5s,7s)-Adamantan-1-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide **11 e**

White solid (65 %); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.76 (s, 1H, H^5), 8.44 (s, 1H, H^{15}), 8.07 (s, 1H, H^3), 7.87 (d, J = 7.8 Hz, 1H, H^9), 7.52 (t, J = 7.7 Hz, 1H, H^7), 7.42 (d, J = 8.1 Hz, 1H, H^6), 7.25 (t, J = 7.6 Hz, 1H, H^8), 2.23–1.99 (m, 9H, $H^{17,18,20,22,23,24}$), 1.78–1.57 (m, 6H, $H^{19,21,25}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.99, 158.08, 147.63, 141.16, 136.75, 131.29, 130.24, 125.71, 123.86, 122.60, 116.31, 115.87, 52.16, 40.84, 36.00, 28.89. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{21}N_2O_2S$ $[M-H]^-$: 377.1324. Found: 377.1317. HPLC: retention time 18.37 min; purity >99 %.

N-(2-Hydroxyethyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide **11 f**

White solid (83 %); mp 307−309 °C; FTIR ν_{max} (cm^{-1}): 3358, 2820, 1655, 1624, 1548, 1434, 1300, 1255, 1064, 903, 708; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H, H^5), 8.84 (s, 1H, H^{15}), 8.32 (s, 1H, H^3), 7.89 (d, J = 7.8 Hz, 1H, H^9), 7.53 (t, J = 7.6 Hz, 1H, H^7), 7.43 (d, J = 8.1 Hz, 1H, H^6), 7.25 (t, J = 7.4 Hz, 1H, H^8), 4.77 (t, J = 4.8 Hz, 1H, H^{18}), 3.53 (q, J = 5.1 Hz, 2H, H^{16}), 3.33 (q, J = 5.7 Hz, 2H, H^{17}). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.73, 158.07, 147.83, 139.73, 136.82, 131.34, 130.38, 125.54, 123.91, 122.67, 116.37, 115.85, 59.58, 42.30. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{13}N_2O_3S$ $[M+H]^+$: 289.0647. Found: 289.0627. HPLC: retention time 10.95 min; purity >99 %.

4-Oxo-N-phenyl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide **11 j**

White solid (63 %); mp 321−322 °C (dec); FTIR ν_{max} (cm^{-1}): 2728, 1638, 1536, 1512, 1321, 1254, 905, 749; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H, H^5), 10.55 (s, 1H, H^{15}), 8.64 (s, 1H, H^3), 7.93 (d, J = 7.5 Hz, 1H, H^9), 7.78 (d, J = 7.8 Hz, 2H, $H^{17,21}$), 7.55 (t, J = 7.7 Hz, 1H, H^7), 7.44 (d, J = 8.1 Hz, 1H, H^6), 7.37 (t, J = 7.9 Hz, 2H, $H^{18,20}$), 7.27 (t, J = 7.3 Hz, 1H, H^8), 7.13 (t, J = 7.4 Hz, 1H, H^{19}). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.33, 158.03, 148.54, 139.47, 138.50, 136.93, 131.36, 130.57, 128.74, 126.75, 123.99, 122.69, 120.21, 116.39, 115.74. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{12}N_2O_2S$ $[M-H]^-$: 319.0541. Found: 319.0539. HPLC: retention time 16.71 min; purity >99 %.

N-Benzyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide **11 n**

White solid (66 %); ^{1}H NMR (400 MHz, DMSO-d_6) 11.79 (s, 1H, H^5), 9.41 (s, 1H, H^{15}), 8.37 (s, 1H, H^3), 7.90 (d, J = 7.1 Hz, 1H, H^9), 7.61–7.13 (m, 8H, $H^{6-8,18-22}$), 4.49 (d, J = 6.1 Hz, 2H, H^{16}). ^{13}C NMR (125 MHz, DMSO-d_6) 160.65, 158.02, 148.02, 139.33, 139.10, 136.86, 131.35, 130.42, 128.39, 127.38, 126.96, 125.74, 123.91, 122.67, 116.38, 115.81, 42.75. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{13}N_2O_2S$ $[M-H]^-$: 333.0698 Found: 333.0733. HPLC: retention time 13.76 min; purity >99 %.

Acknowledgments This investigation was conducted with support from the Research facilities improvement program C06RR14503-01 obtained from the National Institute of Health National Center for Research Resources. The authors would like to thank Dr. Bharati Avula for the HRMS data. We would also like to thank Dr. Ronald F. Borne for careful review of this manuscript. We would like to acknowledge Dr. Mitchell Avery, Dr. Francisco Leon and Dr. Robert J. Doerksen for their helpful discussions.

References

1. Fuji N, Oguro Y, Sasaki S, Kondo S (2009) Fused heterocyclic derivative and use thereof. WO 2009107850 A2 20090903
2. Ohashi T, Oguro Y, Tanaka T, Shiokawa Z, Shibata S, Sato Y, Yamakawa H, Hattori H, Yamamoto Y, Kondo S, Miyamoto M, Tojo H, Baba A, Sasaki S (2012) Discovery of pyrrolo[3,2-*c*]quinoline-4-one derivatives as novel hedgehog signaling inhibitors. Bioorg Med Chem 20:5496–5506. doi:10.1016/j.bmc.2012.07.039
3. Chua PC, Haddach M, Nagasawa J, Pierre F (2009) Protein kinase modulators. WO 2009108912 A1 20090903
4. Pierre F, Chua PC, O'Brien SE, Siddiqui-Jain A, Bourbon P, Haddach M, Michaux J, Nagasawa J, Schwaebe MK, Stefan E, Vialettes A, Whitten JP, Chen TK, Darjania L, Stansfield R, Anderes K, Bliesath J, Drygin D, Ho C, Omori M, Proffitt C, Streiner N, Trent K, Rice WG, Ryckman DM (2011) Discovery and SAR of 5-(3-chlorophenylamino)benzo[*c*][2,6]naphthyridine-8-carboxylic acid (CX-4945), the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer. J Med Chem 54:635–654. doi:10.1021/jm101251q
5. Pierre F, Haddach M, Regan CF, Ryckman DM (2011) Condensed quiolines as protein kinase modulators. WO 2011025859 A1 20110303
6. Pierre F, Regan CF, Chevrel M-C, Siddiqui-Jain A, Macalino D, Streiner N, Drygin D, Haddach M, O'Brien SE, Rice WG, Ryckman DM (2012) Novel potent dual inhibitors of CK2 and Pim kinases with antiproliferative activity against cancer cells. Bioorg Med Chem Lett 22:3327–3331. doi:10.1016/j.bmcl.2012.02.099
7. Gorlitzer K, Gabriel B, Jomaa H, Wiesner J (2006) Synthesis of thieno[3,2-*c*]quinolin-4-ylamines and antimalarial activity. Pharmazie 61:278–284
8. Abass M (2007) Substituted quinolinones, part 10: synthesis of angular tetracyclic thieno and thiopyrano[3,2-*c*]benzo[h]quinolinones under PTC conditions as novel enzymatic enhancers. Phosphorus Sulfur Silicon Relat Elem 182:735–748. doi:10.1080/10426500601047503
9. Chemical Abstracts Service (CAS), a division of the American Chemical Society. Columbus, OH, USA. https://scifinder.cas.org
10. Bhakuni BS, Kumar A, Balkrishna SJ, Sheikh JA, Konar S, Sangit K (2012) KOtBu mediated synthesis of phenanthridinones and dibenzoazepinones. Org Lett 14:2838–2841. doi:10.1021/ol301077y
11. Rajeshkumar V, Lee T-H, Chuang S-C (2013) Palladium-catalyzed oxidative insertion of carbon monoxide to *N*-sulfonyl-2-aminobiaryls through C–H bond activation: access to bioactive phenanthridinone derivatives in one pot. Org Lett 15:1468–1471. doi:10.1021/ol4001922
12. Castle LW, Elmaaty TA (2006) A new method for the synthesis of substituted indeno[1,2-*b*]thiophene with subsequent ring expansion to form substituted thieno[3,2-*c*]quinoline. J Heterocycl Chem 43:629–631. doi:10.1002/jhet.5570430316
13. Jayashree A, Darbarwar M (1994) Synthesis of 4,5-dihydro-4(5*H*)-oxothieno[3,2-*c*]quinoline-2-carboxylicacids and their alkyl esters. Indian J Chem 33B:676–678
14. Majumdar KC, Ghosh M (2002) Tandem cyclization: one pot regioselective synthesis of thieno[3,2-*c*]quinolin-4(5*H*)-one derivatives. Tetrahedron 58:10047–10052. doi:10.1081/SCC-200051698
15. Ahmed N, Brahmbhatt KG, Sabde S, Mitra D, Singh IP, Bhutani KK (2010) Synthesis and anti-HIV activity of alkylated quinoline 2,4-diols. Bioorg Med Chem 18:2872–2879. doi:10.1016/j.bmc.2010.03.015
16. Arya K, Agarwal M (2007) Microwave prompted multigram synthesis, structural determination, and photo-antiproliferative activity of fluorinated 4-hydroxyquinolinnes. Bioorg Med Chem Lett 17:86–93. doi:10.1016/j.bmcl.2006.09.082
17. Sechi M, Azzena U, Delussu MP, Dallocchio R, Dessì A, Cosseddu A, Pala N, Neamati N (2008) Design and synthesis of bis-amide and hydrazide-containing derivatives of malonic acid as potential HIV-1 integrase inhibitors. Molecules 13:2442–2461. doi:10.3390/molecules13102442
18. Shobana N, Yeshoda P, Shanmugam P (1989) A convenient approach to the synthesis of prenyl-, furo- and pyrano-quinoline alkaloids of the rutaceae. Tetrahedron 45:757–762. doi:10.1016/0040-4020(89)80106-1
19. Khan KA, Shoeb A (1985) Chemistry of carbostyril: part I—oxidation reactions of 4-hydroxy-&4-hydroxy-1-methyl-2(1*H*)-quinolinones. Indian J Chem 24B:62–66
20. Chilin A, Marzaro G, Marza C, Via LD, Ferlin MG, Pastorini G, Guiotto A (2009) Synthesis and antitumor activity of novel amsacrine analogs: the critical role of the acridine moiety in determining their biological activity. Bioorg Med Chem 17:523–529. doi:10.1016/j.bmc.2008.11.072
21. Fiala W, Stadlbauer W (1993) Nucleophilic chlorination of 3-formyl-4-hydroxy-quinolin-2(1*H*)-ones. J Prakt Chem/Chem-Ztg 335:128–134