Synthesis of Novel Ethyl (substituted)phenyl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-Carboxylates as Potential Anticancer Agents

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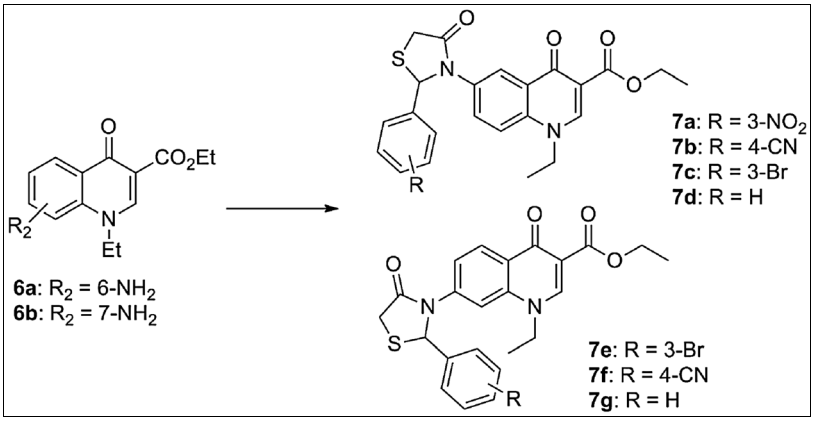


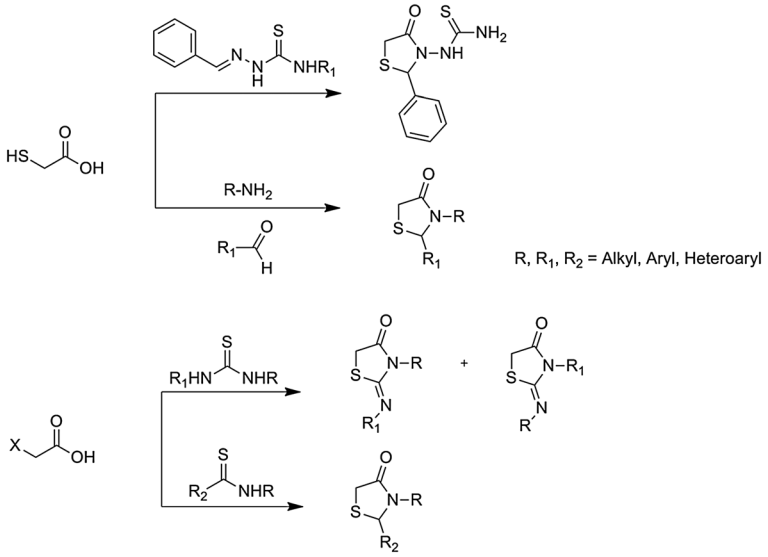
A series of ethyl (substituted)phenyl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylates (**7a–g**) has been prepared from reactions between aminoquinolones **6** with arenealdehydes and mercaptoacetic acid. The critical intermediates, **6**a and **6b**, were obtained from appropriate amines by a sequence of steps involving (i) reaction with diethylethoxymethylenemalonate, (ii) thermal cyclization in diphenyl ether, (iii) ethylation and (iv) Pd/C catalyzed reduction. New compounds **7a–g** were fully identified and characterized by NMR (^{1}H and ^{13}C) and specifically for **7d** by X-ray crystallography. Compounds **7b–f** were found not to exhibit activity at 10 uM concentrations against gastric ascitis (AGP-01), gastric adenocarcinoma kind intestinal (ACP-02), colon (HCT-116) and murine melanome (B16F10) cancer cells. However, none exhibited cytotoxicity against normal cells human fibroblast (MRC-5), murine fibroblast (NIH3T3) and normal human melanocyte (Melan-A).

INTRODUCTION

Cancer still remains a threat to men's health, representing the leading cause of death in economically developed countries and the second in developing countries [1,2]. In 2008, 7.6 million people died from cancer, around 13% of all deaths worldwide. It is projected a continuous rise in the number of cases, with an expectation of 13 million deaths in 2030 [3]. In the last years, many efforts have been made to develop new strategies for finding effective ways of treating this disease, which include an increase in the understanding of the biological process involved in cancer survival and also the search for more selective and potent chemotherapeutic agents [4].

In this context, thiazolidinones represent an important class of heterocyclic compounds that have attracted special attention lately because of their chemical properties and diverse biological activities [5]. The thiazolidinone core is a very versatile scaffold, which can be easily modified at positions 2-, 3- and 5- of the heterocyclic ring allowing the synthesis of a large number of derivatives [6]. This core has also been reported as an important pharmacophore with a wide range of biological activities, such as antimicrobial [7,8], antiviral [9], antiprotozoal [10], analgesic [11], antitubercular [12], anticancer [13] and anticonvulsant [14]. Thiazolidinones are obtained through various synthetic procedures from primary amines or hydrazines in one- or two-step reactions with aldehydes or ketones and mercaptoacetic acid [5]. Such reactions proceed through an initial imine formation, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization and elimination of water. *N*,*N*′-dicyclohexylcarbodiimide can promote dehydration but

Scheme 1. Synthesis of 4-thiazolidinones from α-haloacetic and α-mercaptoacetic acids.



azeotropic distillation is the most common protocol applied for water removal. 4-Thiazolidinones can also be prepared through cyclization reactions of imines, thiosemicarbazides, thiourea and thioamides with α-haloacetic and α-mercaptoacetic acids [15] as shown in Scheme 1. These reactions have also been carried out using microwave and ultrasound irradiation [16,17]. Our research group has a vast experience on the synthesis of 1,3-thiazolidin-4-ones from amines through cyclization with aldehydes and thioglycolic acid in one-pot conditions [12,17–19].

The quinolone scaffold has also been widely explored because of its various pharmacological activities [20–23]. Indeed, there are a considerable number of quinolone-based molecules in the market as anti-infective agents, and others are currently being studied for their potential activity as antitumoral [24], antiviral [25], anti-ischemic [26], antiparasitic [27] and anxiolytic [28] agents. Recently, our research group has published a review article highlighting recent developments on potentially active quinolones against cancer and tuberculosis [22].

The most common protocols for the synthesis of quinolones include the Gould–Jacobs reaction [29] and the Grohe–Heitzer cycloacylation [30].

Thus, in continuation of our efforts on the synthesis of some pharmacologically important heterocycles [12,17–19,24,31], a novel series of ethyl aryl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylates was designed (Fig. 1), synthesized (Scheme 2) and evaluated against three human cancer cell lines.

RESULTS AND DISCUSSION

The target compounds **7a–g** were synthesized as shown in Scheme 2, following procedures used previously in our laboratory. Quinolones **4a–b** were obtained through the classic Gould–Jacobs procedure [20,29]. The procedure consists of treating anilines **1** with diethylethoxymethylenemalonate **2** to give the enamines **3**, which were thermally cyclized in diphenyl ether. *N*-Ethylation of quinolones **4** was achieved using ethyl bromide and K_2CO_3 in DMF. Key intermediates **6a** and **6b** were obtained in moderate to good yields (60–70%) by Pd/C catalyzed reduction of **5**. This type of reduction in the presence of Pd/C is unprecedented for this system. It is noteworthy that the previously reported nitro group reduction of quinolones **5a–b** employing the classic methodology with iron and aqueous ammonium chloride 0.05 M [33,34] was tested and found to be a poor option

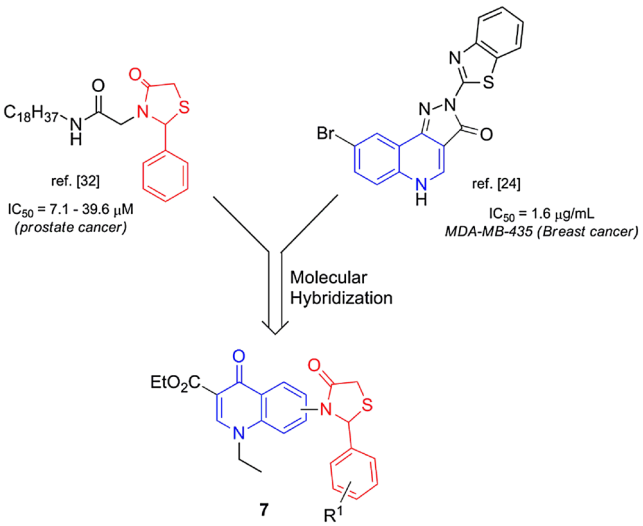
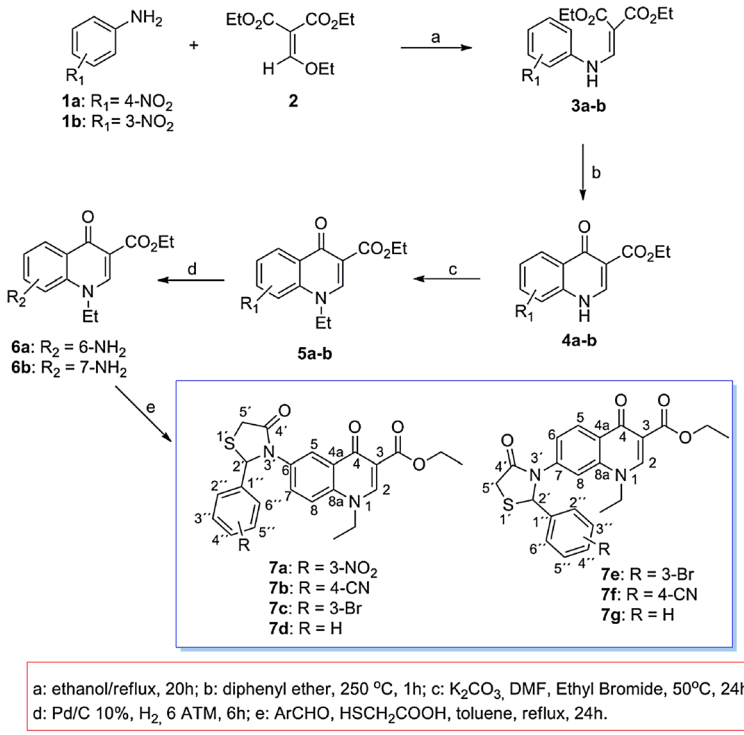


Figure 1. A design for synthesis of ethyl aryl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylates.

Scheme 2. Synthesis of ethyl (substituted)phenyl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylates **7a–g**.



because of the partial solubility in water of the respective aminoquinolone **6a–b**. This fact has made the isolation and purification of the desired amine difficult, leading to low yields (15–20%) after tedious work up. Ethyl (substitutedphenyl)-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate derivatives **7a–g** were obtained from reactions of amines **6**, arenealdehydes and mercaptoacetic acid (1:1:3) in one-pot under reflux in toluene using a Dean–Stark trap (Scheme 2). The molar ratio of 1:1:3 of amine, arenealdehyde and mercaptoacetic acid was determined to be optimal leading to 35–56% yields of pure products (Table 1).

Characterization was achieved in all cases from NMR and IR spectral and ESI-MS data, and in the case of **7d** additionally by a single crystal structure determination. Two-dimensional NMR techniques (COSY, heteronuclear single-quantum correlation and heteronuclear multiple-bond correlation) were used to identify the signals for the new compounds. As an example, the ^{1}H NMR spectrum of compound **7b** exhibits a singlet at 8.62 ppm for H2, a broad singlet at 6.74 ppm for H2′, and a double doublet at 4.12 ppm (J = 15.7; 1.4 Hz) and a doublet at 3.94 ppm (J = 15.7 Hz), respectively, for the diastereotopic hydrogens, H5′a and H5′b. Methylenic hydrogens (NCH_2CH_3) are identified as a quartet at 4.33 ppm (J = 7.1 Hz) (Fig. 2). In addition, phenyl signals were assigned. The ^{13}C NMR spectrum exhibits signals at 148.8, 62.4 and 32.5 ppm for C2, C2′ and C5′, respectively. The three carbonyl groups could be identified in the ^{13}C NMR spectrum by the peaks at 172.1 ppm (C4), 170.8 ppm (C4′) and 164.4 ppm (CO_2Et) (Fig. 3).

Table 1

Yields and selected physical properties of compounds **7a–g**.

Substance	R[a]	Yield (%)	P.F. (°C)	ESI-MS *m/z* %
7a	3-NO_2	56	111–112	468.3 ($[M+H]^+$; 100)
7b	4-CN	52	145–147	448.3 ($[M+H]^+$; 100)
7c	3-Br	41	193–195	501.1 ($[M+H]^+$; 100), based on ^{79}Br
7d	H	40	104–105	423.3 ($[M+H]^+$; 100)
7e	3-Br	37	184–185 (d)	501.1 ($[M+H]^+$; 100), based on ^{79}Br
7f	4-CN	43	134–136	448.2 ($[M+H]^+$; 100)
7g	H	35	97–100	423.2 ($[M+H]^+$; 100)

[a]Quinolones **7a–d** bear the thiazolidinone moiety at position 6.
Quinolones **7e–g** bear the thiazolidinone moiety at position 7.

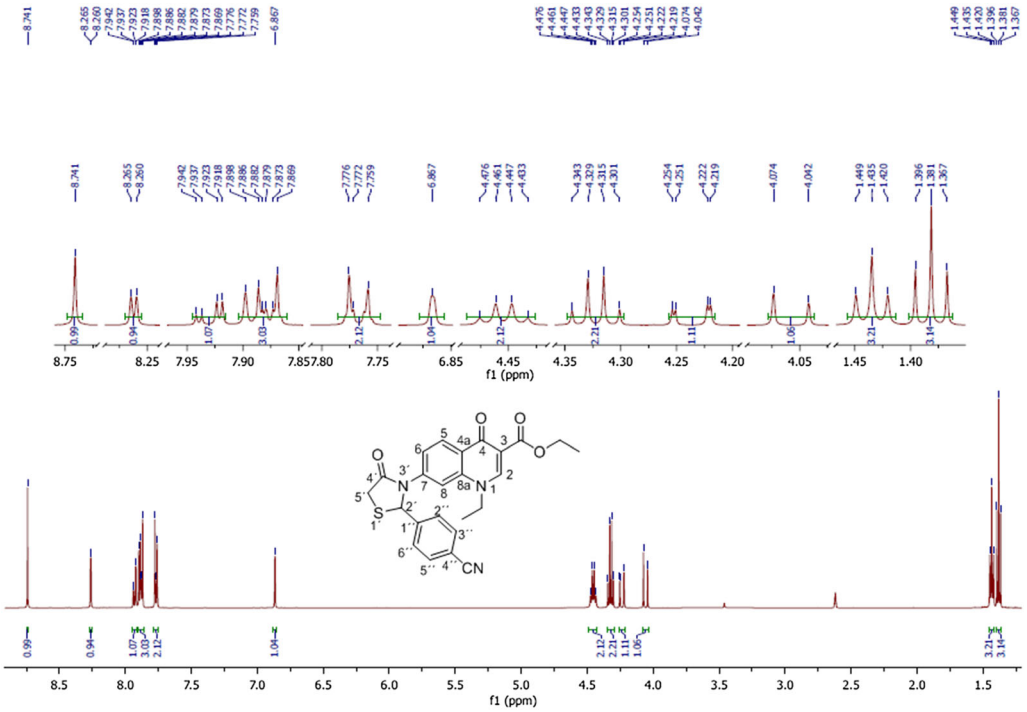


Figure 2. ^{1}H NMR spectrum of compound **7b** (500.00 MHz, DMSO-d_6).

Recrystallization of **7d** from moist EtOH led to the isolation of the mixed solvate, [(**7d**)$_2$·(H$_2$O)$_2$(EtOH)], the structure of which was determined by X-ray crystallography form data collected at 120 K [35–37]. The asymmetric unit of [(**7d**)$_2$·(H$_2$O)$_2$(EtOH)], consists of a single molecule of **7d** and a single disordered water molecule [occupancy ratio = 60:40] and a half molecule of the EtOH solvate disordered equally over two symmetry related sites. Figure 4a shows the atom arrangements and numbering scheme for the molecule **7d** in [(**7d**)$_2$·(H$_2$O)$_2$(EtOH). Bond lengths and angles in **7d** are in the expected regions and are not discussed further.

The oxothiazolidinyl ring has an envelope shape with a flap at the sulfur atom. Overall, the molecule of **7d** is far from planar, see Figure 4b. The phenyl ring, [C1–C6], is nearly orthogonal to both the 4-oxo-1,4-dihydroquinolinyl, and oxothiazolidinyl rings are shown by the angles

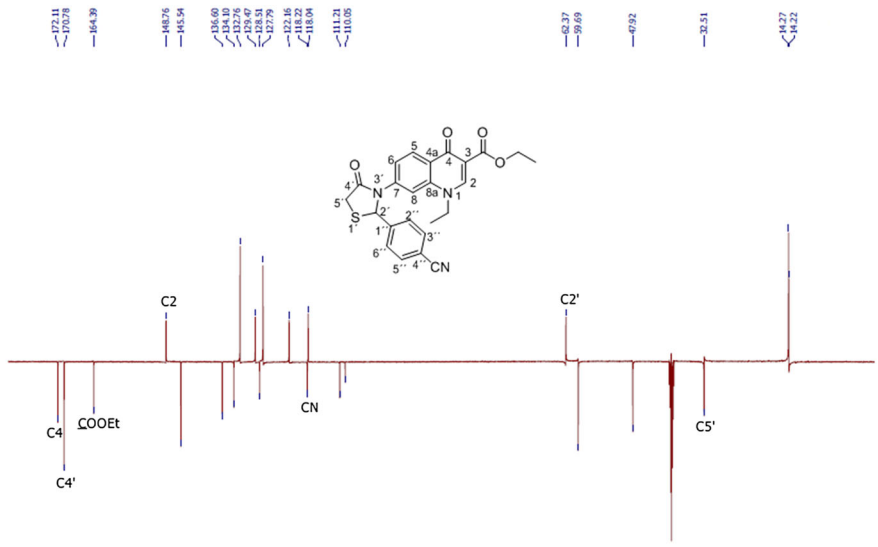


Figure 3. ^{13}C NMR spectrum of compound **7b** (125.00 MHz, DMSO-d_6).

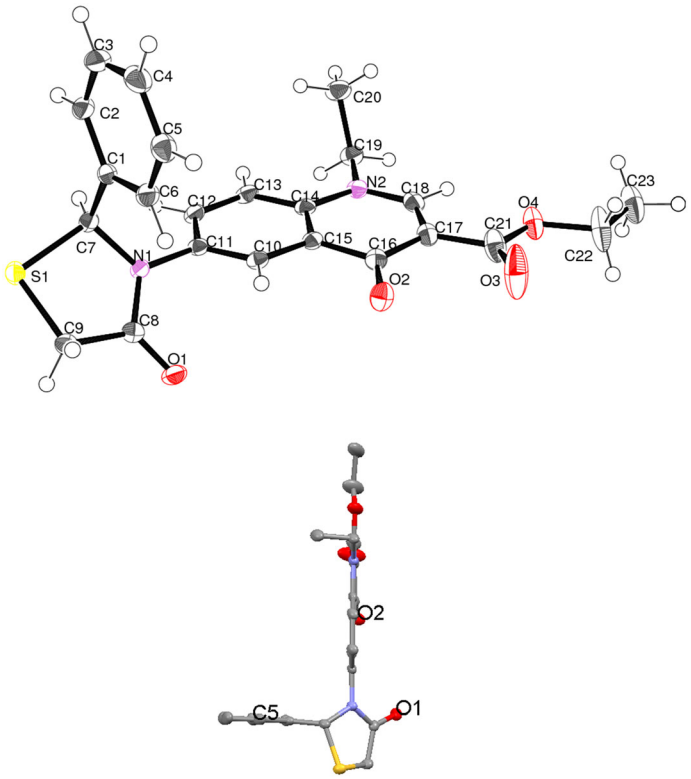


Figure 4. (*a*) Atom arrangements and numbering scheme for the molecule of **7d** in the mixed solvate [(**7d**)$_2$·(H$_2$O)$_2$(EtOH)]; (*b*) view of the molecule of **7d** looking down the plane of the 4-oxo-1,4-dihydroquinolinyl moiety.

between the best planes of 88.52(3) and 82.76(4)°, respectively, through the rings. The angles between the planes through the 4-oxo-1,4-dihydroquinolinyl and oxothiazolidinyl rings is 46.26(5)°. Of interest, the carbonyl group at C16 and that in the CO_2Et group at C17 have a *cis*-arrangement, and this appear suitably sited for **7d** to act as a chelating ligand. Direct links between the molecules involve weak C–H–O and C–H–π hydrogen bonds and by π–π stacking arrangements. While the disorder involving the solvate molecules complicates the discussion of the intermolecular interactions, it is apparent that molecules of **7d** are linked indirectly via the solvate molecules, utilizing strong O–H–O hydrogen bonds [35].

Compounds **7b–f** were evaluated *in vitro* for their anticancer activities against gastric ascitis (AGP-01), gastric adenocarcinoma kind intestinal (ACP-02), colon (HCT-116) and murine melanome (B16F10) cancer cells. None of these derivatives exhibited activity at 10 uM concentration. In addition, none of these compounds exhibited cytotoxicity against the normal cells human fibroblast (MRC-5), murine fibroblast (NIH3T3) and normal human melanocyte (Melan-A), in spite of the lack of anticancer activity. Title compounds will be evaluated on their antibacterial activity.

CONCLUSION

A series of new ethyl (substituted)phenyl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate derivatives has been synthesized in moderate yields from commercially available materials. The compounds were generally characterized from spectroscopic data and specifically for **7d**, as the mixed solvate, [(**7d**)$_2$·(H$_2$O)$_2$(EtOH)], by X-ray diffraction. Compounds **7b–f** were not cytotoxic to normal cells. Despite the lack of anticancer activity, the quinolone core is known to possess antibacterial activity; therefore, these structures are also potential antibacterials.

EXPERIMENTAL

General. All reagents and solvents were used as obtained from commercial suppliers without further purification. Melting points were determined on a Fisatom 430 instrument and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1420 spectrometer in potassium bromide disks. Hydrogenation reactions were performed on a Berghof BR-300 reactor. Mass spectra (ESI-MS) were recorded on a ZQ-4000 single quadrupole mass spectrometer. NMR spectra were recorded on Bruker Avance 500 or on Varian Unity 300 e 500 spectrometers in deuterated dimethyl sulfoxide. The progress of the reactions was monitored by thin-layer

chromatography with F_{254} silica gel precoated sheets (Merck), using chloroform/methanol (9:1) mixture as eluent, and visualized under UV light. All the chemicals were purchased and used without further purification.

General procedure for the synthesis of ethyl (substituted) phenyl-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate derivatives (7a–g). The quinolone derivatives **4** were prepared by treating the appropriate aniline (50 mmol) with diethyl ethoxymethylenemalonate (50 mmol) under reflux in ethanol (10 mL) for 20 h to obtain the enamine derivatives, which were cyclized in refluxing diphenyl ether for 1 h. The quinolones **4** (4 mmol) were ethylated using ethyl bromide (40 mmol) and K_2CO_3 (10 mmol) in DMF (15 mL) at 50 °C for 24 h leading to compounds **5**. Key intermediates **6** were obtained after catalytic hydrogenation of ethylquinolones **5** (4 mmol) with Pd/C 10% (220 mg) in a Paar reactor under 6 atm H_2 pressure in toluene (150 mL) after 6 h. A solution of an arenealdehyde (0.78 mmol) and 6-aminoquinolone (**6a** or **6b**) (0.78 mmol) in toluene (30 mL) was reflux for 6 h under Dean–Stark conditions. Mercaptoacetic acid (2.34 mmol) was added, and the mixture refluxed for 16 h. The reaction mixture was washed with an aqueous saturated solution of $KHCO_3$ (5 × 50 mL), dried over Na_2SO_4 and evaporated to obtain a solid, that was either washed with ethyl ether (for **7b**, **7f** and **7g**) or recrystallized from ethyl ether : ethyl acetate (1:1) (for **7a** and **7e**) or from methanol/water (8:2) (for **7c** and **7d**).

Ethyl 1-ethyl-6-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (7a). This compound was obtained as yellow powder; yield: 56%; mp: 111–112 °C; IR (KBr): C═O 1722, C═O 1693, C═O 1609, Nitro 1530, Nitro 1352 cm^{-1}; ^1H NMR (500.00 MHz, DMSO-d_6) δ (ppm): 8.61 (s, 1H, H2); 8.29 (dd, 1H, J = 2.0 Hz, H2″), 8.15 (d, 1H, J = 2.3 Hz, H5), 8.08 (ddd, 1H, J = 8.2; 2.3; 0.9 Hz, H4″), 7.98–7.94 (m, 1H, H6″), 7.81 (dd, 1H, J = 9.1; 2.5 Hz, H7), 7.78 (d, 1H, J = 9.0 Hz, H8), 7.61 (dd, 1H, J = 8.0 Hz, H5″), 6.85 (br, 1H, H2′), 4.33 (q, 2H, J = 7.1 Hz, NCH_2CH_3), 4.20 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 4.5 (dd, 1H, J = 15.7; 1.4 Hz, H5′a), 3.96 (d, 1H, J = 15.8 Hz, H5′ b), 1.31 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 1.27 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125.0 MHz, DMSO-d_6) δ (ppm): 171.8 (C4), 170.5 (C4′), 164.1 (COOEt), 148.5 (C2), 147.5 (3″), 142.1 (C1″), 136.4 (C8a), 133.7 (C6), 133.2 (Ph), 130.2 (Ph), 129.3 (C7), 128.2 (C4a), 123.2 (Ph), 122.1 (C5), 121.3 (Ph), 118.0 (C8), 109.7 (C3), 61.7 (C2′), 59.4 (OCH_2CH_3), 47.6 (NCH_2CH_3), 32.2 (C5′), 14.0 (OCH_2CH_3), 13.9 (NCH_2CH_3); ESI-MS (*m/z*; %): 468.3 ($[M + H]^+$; 100).

Ethyl 1-ethyl-6-(2-(4-cyanophenyl)-4-oxothiazolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (7b). This compound was obtained as yellow powder; yield: 52%; mp 145–147 °C; IR (KBr): CN 2226, C═O 1698, C═O 1683, C═O 1608 cm^{-1}; ^1H NMR (500.00 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 1H, H2), 8.14 (d, 1H, J = 2.5 Hz, H5), 7.81 (dd, 1H, J = 9.2; 2.5 Hz, H7), 7.78–7.74 (m, 3H, 3″ and H8), 7.67–7.63 (m, 2H, 2″);, 6.75 (bs, 1H, H2′), 4.33 (q, 2H, J = 7.1 Hz, NCH_2CH_3), 4.20 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.12 (dd, 1H, J = 15.7; 1.4 Hz, H5′a), 3.94 (d, 1H, J = 15.7 Hz, H5′b), 1.31 (t, 3H, J = 7.1 Hz, NCH_2CH_3); 1.26 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125.0 MHz, DMSO-d_6) δ (ppm): 172.1 (C4), 170.8 (C4′), 164.4 (CO_2Et), 148.8 (C2), 145.5 (C1″), 136.6 (C8a), 134.1 (C6), 132.8 (C3″), 129.5 (C7), 128.5 (C4a), 127.8 (2″), 122.2 (C5), 118.2 (CN), 118.0 (C8), 111.2 (C4″), 110.1 (C3), 62.4 (C2′), 59.7 (OCH_2CH_3), 47.9 (NCH_2CH_3), 32.5 (C5′), 14.3 (OCH_2CH_3), 14.2 (NCH_2CH_3); ESI-MS (*m/z*; %): 448.2 ($[M + H]^+$; 100).

Ethyl 6-(2-(3-bromophenyl)-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (7c). This compound was obtained as yellow powder; yield: 41%; mp: 193–195 °C; IR (KBr): C═O 1722, C═O 1682, C═O 1611 cm^{-1}; ^1H NMR (500.00 MHz, DMSO-d_6) δ (ppm): 8.64 (s, 1H, H2), 8.13 (s, 1H,), 7.80 (s, 2H), 7.66 (s, 1H); 7.45 (d, 1H, J = 7.8 Hz), 7.41 (d, 1H, J = 7.9 Hz, H4″), 7.25 (dd, 1H, J = 7.9 Hz, H5″), 6.66 (br, 1H, H2′), 4.35 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 4.20 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.13 (d, 1H, J = 15.5 Hz, H5′b), 3.92 (d, 1H, J = 15.7 Hz, H5′a), 1.31 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 1.27 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125.0 MHz, DMSO-d_6) δ (ppm): 172.2 (C4), 170.8 (C4′), 164.5 (COOEt), 148.9 (C2), 142.8 (C1″), 136.6 (C8a), 134.2 (C6), 131.5 (Ph), 131.0 (Ph), 129.7 (Ph), 129.6 (Ph), 128.6 (C4a), 126.0 (Ph), 122.4 (C5), 121.9 (Ph), 118.1 (C8), 110.0 (C3), 62.3 (C2′), 59.8 (OCH_2CH_3), 48.0 (NCH_2CH_3), 32.6 (C5″), 14.4 (OCH_2CH_3), 14.3 (NCH_2CH_3); ESI-MS (*m/z*; %): 501.1 ($[M + H]^+$; 100), based on ^{79}Br.

Ethyl 1-ethyl-4-oxo-6-(4-oxo-2-phenylthiazolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (7d). This compound was obtained as yellow powder; yield: 40%; mp: 104–105 °C; IR (KBr): C═O 1726, C═O 1690, C═O 1611 cm^{-1}; ^1H NMR (500.00 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 1H, H2), 8.11 (d, 1H, J = 1.6 Hz, H5), 7.79 (dd, 1H, J = 9.3, 2.0 Hz, H7), 7.76 (d, 1H, J = 9.2 Hz, H8), 7.41 (d, 2H, J = 7.5 Hz, H2″), 7.28 (dd, 2H, J = 7.5 Hz, H3″), 7.21 (t, 1H, J = 7.3 Hz, H4″), 6.64 (br, 1H, H2′), 4.33 (q, 2H, J = 7.0 Hz, NCH_2CH_3), 4.20 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.07 (d, 1H, J = 15.9 Hz, H5′ b), 3.93 (d, 1H, J = 15.7 Hz, H5′a), 1.30 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 1.26 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125.0 MHz, DMSO-d_6) δ (ppm): 172.2 (C4), 171.0 (C4′), 164.5 (COOEt), 148.9 (C2), 139.8 (C1″), 136.5 (C8a), 134.5 (C6), 129.8 (C7), 128.8 (Ph), 128.6 (C4a), 128.5 (Ph), 127.0 (Ph), 122.5 (C5), 118.0 (C8), 109.9 (C3), 63.3 (C2′), 59.8 (OCH_2CH_3), 48.0 (NCH_2CH_3), 32.7 (C5″), 14.4 (OCH_2CH_3), 14.3 (NCH_2CH_3); ESI-MS (*m/z*; %): 423.3 ($[M + H]^+$; 100).

Ethyl 7-(2-(3-bromophenyl)-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (7e). This compound was obtained as yellow powder; yield: 37%; mp: 184–185 °C (d); IR (KBr): C═O 1719, C═O 1690, C═O 1603 cm^{-1}; ^1H NMR (500.00 MHz, DMSO-d_6) δ (ppm): 8.64 (s, 1H, H2), 8.14 (d, 1H, J = 8.7 Hz, H6), 7.71 (s, 2H, H8 and H2″), 7.53 (d, 1H, J = 8.3 Hz, H5), 7,47 (d, 1H, J = 7.6 Hz, H4″), 7.41 (d, 1H, J = 7.8 Hz, H6″), 7.24 (dd, 1H, J = 7.8 Hz, H5″), 6.78 (br, 1H, H2′), 4.38–4.25 (m, 2H, NCH_2CH_3), 4.20 (q, 2H, J = 7,0 Hz, OCH_2CH_3), 4.13 (d, 1H, J = 15.9 Hz, H5′b), 3.97 (d, 1H, J = 15.9 Hz, H5′a), 1.27–1.23 (m, 6H, NCH_2CH_3 e OCH_2CH_3); ^{13}C NMR (125.0 MHz, DMSO-d_6) δ (ppm): 172.2 (C4), 171.0 (C4′), 164.6 (COOEt), 149.6 (C2), 142.6 (C1″), 141.3 (Ph), 138.8 (8a), 131.7 (Ph), 131.1 (Ph), 129.9 (Ph), 127.2 (C5), 126.1 (Ph), 126.1 (Ph), 122.0 (Ph), 121.6 (C6), 113.0 (C8), 110.4 (C3), 62.1 (C2′), 59.9 (OCH_2CH_3), 48.1 (NCH_2CH_3), 32.9 (C5″), 14.4 (OCH_2CH_3), 14.3 (NCH_2CH_3); ESI/MS (*m/z*; %): 501.1 ($[M + H]^+$; 100), based on ^{79}Br.

Ethyl 7-(2-(4-cyanophenyl)-4-oxothiazolidin-3-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (7f). This compound was obtained as yellow powder; yield: 43%, mp: 134–136 °C; IR (KBr): CN 2227, C═O 1705, C═O 1612 cm^{-1}; ^1H NMR (300.00 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 1H, H2), 8.14 (d, 1H, J = 8.7 Hz, H5), 7.78–7.72 (m, 3H, H8 and H3″), 7.69–7.64 (m, 2H, H2″), 7.50 (dd, 1H, J = 8.8, 1.8 Hz, H6), 6.86 (br, 1H, H2′), 4.38–4.23 (m, 2H, NCH_2CH_3), 4.19 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.12 (dd, 1H, J = 15.9, 1.2 Hz, H5′b), 3.97 (d, 1H,

J = 15.9 Hz, H5′a), 1.25 (t, 3H, NCH_2CH_3) , 1.24 (t, 3H, OCH_2CH_3); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ (ppm): 172.3 (C4), 171.0 (C4′), 164.6 (COOEt), 149.6 (C2), 145.4 (C1″), 141.2 (Ph), 138.8 (C8a) , 132.9 (C3″), 127.9 (C2″), 126.7 (C5), 126.1 (Ph), 121.4 (C6), 118.4 (CN), 113.0 (C8), 111.4 (C4″), 110.5 (C3), 62.3 (C2′), 59.9 (OCH_2CH_3), 48.2 (NCH_2CH_3), 32.9 (C5′), 14.4 (OCH_2CH_3), 14.2 (NCH_2CH_3); ESI/MS (*m/z*): 448.2 ($[M + H]^+$; 100).

Ethyl 1-ethyl-4-oxo-7-(4-oxo-2-phenylthiazolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (7g). This compound was obtained as yellow powder; yield: 35%, mp: 98–101 °C; IR (KBr): C═O 1720, C═O 1692, C═O 1605 cm^{-1}; ^1H NMR (500.00 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 1H, H2), 8.12 (d, 1H, J = 8.7 Hz, H5), 7.70 (s, 1H, H8), 7.51 (dd, 1H, J = 8.8, 1.2 Hz, H6), 7.45 (d, 2H, J = 7.4 Hz, H2″), 7.28 (t, 2H, J = 7.5 Hz, H3″), 7.21 (t, 1H, J = 7.3 Hz, H4″), 6.78 (br, 1H, H2′), 4.36–4.17 (m, 2H, NCH_2CH_3), 4.19 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.09 (d, 1H, J = 15.7 Hz, H5′ b), 3.97 (d, 1H, J = 15.9 Hz, H5′a), 1.25 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 1.22 (t, 3H, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (125,0 MHz, DMSO-d_6) δ (ppm): 172.1 (C4), 171.0 (C4′), 164.5 (COOEt), 149.4 (C2), 141.5 (Ph), 139.6 (Ph), 138.7 (C8a), 128.8 (Ph), 128.6, 127.0 (C5), 125.9 (Ph), 121.6 (C6), 112.9 (C8), 110.3 (C3), 63.0 (C2′), 59.7 (OCH_2CH_3), 48.0 (NCH_2CH_3), 32.9 (C5′), 14.3 (OCH_2CH_3), 14.2 (NCH_2CH_3); ESI/MS (*m/z*): 423.2 ($[M + H]^+$; 100).

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