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ORIGINAL PAPER

# Synthesis, X-ray crystallographic study, and biological evaluation of coumarin and quinolinone carboxamides as anticancer agents

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**Abstract** A series of coumarin and quinolinone-3-aminoamide derivatives was synthesized and evaluated for its potency in inhibition of cancer cell growth. The structure of *N*-[2-(dimethylamino) ethyl]-4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxamide was unambiguously confirmed by X-ray diffraction analysis, which revealed the *cis* conformation of the amide bond resulting from the presence of two intramolecular hydrogen bonds.

**Keywords** Heterocycles · Antitumor agents · X-ray structure determination · Aminoamides

## Introduction

Coumarins comprise a vast group of natural and synthetic compounds which have proven to possess diverse biological and pharmacological activities. Among these, cytotoxicity has made them "targeted molecules" in the research of anticancer agents. A review presenting the broad range of effects of coumarins on tumors, as shown by in vitro and in vivo experiments and clinical studies, was published a few years ago [1]. So far, the results for different coumarins with various tumor lines are often contradictory. This fact indicates that there is still a long way to go until researchers reach a consensus about which cytotoxic agents will be suitable for clinical treatment.

Natural or synthetic coumarins with simple structures, such as esculetin, osthole, and the synthetic 7-hydroxy-6-nitrocoumarin (Fig. 1) are well-known to exhibit notable anticancer activities [2–6]. In particular, osthole has proved to be very effective against liver tumors. Moreover, the widely known warfarin, marketed for more than 50 years as an anticoagulant, has been reported [7] to improve the survival of patients with small-cell lung cancer even though this has not been confirmed, and metal complexes of niffcoumar with lanthanides have proven to exhibit anticancer activity [8, 9].

The presence of different substituents enhances some biological abilities of these compounds. In particular, coumarins bearing an amide bond at C-3 of the heterocyclic nucleus have been identified as potent tumor-specific cytotoxic agents [10]. In a previous work, the growth inhibitory properties of novel coumarin sulfonamides were described using a panel of cancer cell lines [11]. In addition, the natural product novobiocin, a 3-amidocoumarin, has attracted the interest of scientists due to its antitumor activity [12] through inhibition of the heat-shock protein 90 (hsp90).

N-substituted quinolinone analogues also constitute an important source for pharmaceutical and agrochemical industries. Vesnarinone, a 3,4-dihydroquinolinone used as a cardiotonic agent, was found to be a unique antiproliferative, differentiation-inducing and apoptosis-inducing drug against several human malignancies, including leukemia and several solid tumors [13–15].

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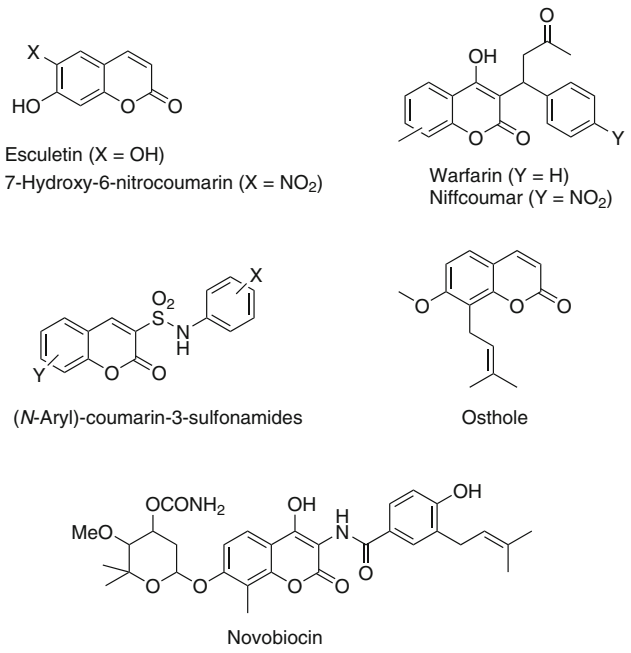



**Fig. 1** Coumarin derivatives known as anticancer agents

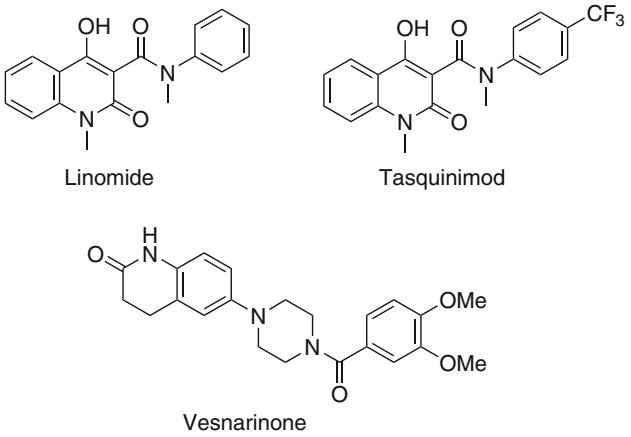



**Fig. 2** Quinolinone derivatives known as anticancer agents

On the other hand, quinolinone carboxamides have been more extensively examined (Fig. 2). As an example, linomide (or roquinimex) is a quinoline-3-carboxamide molecule which has been proven to inhibit the process of angiogenesis, which is a vital step in tumor development [16].

Second generation quinoline-3-carboxamide compounds were synthesized and investigated as to whether they could maintain their anti-angiogenesis abilities without inducement of a proinflammatory response. The compound tasquinimod was proven to be 30–60 times more potent than linomide in rat prostate cancer models and to exhibit a therapeutic effective oral dose as low as 0.5–1 μM [17].

## Results and discussion

### *Chemistry*

The well known anticancer activities of coumarin and quinolinone-3-carboxamides motivated us to prepare a compound library to examine their potency as antitumor agents. Particular attention was paid to the side chain at C-3 position of the heterocyclic nucleus. Diamines bearing two free amino groups (ethylenediamine, hexamethylenedimine, 1,8-diamineoctane, and *o*-phenylenediamine) were used, as well as diamines with tertiary amine groups (*N*,*N*-dimethyethylenediamine and 1-(2-aminoethyl)piperidine). Concerning the heterocyclic ring, *N*-phenyl-, *N*-methyl-4-hydroxyquinolinones, and 4-hydroxycoumarins were used.

The starting materials, methyl coumarin-3-carboxylate and quinolinones were synthesized following published methodologies. The first were prepared using the *N*-hydroxysuccinimide protocol [18] and the latter using the HOBt method [19].

Schemes 1 and 2 illustrate the approach to the synthesis of the aminoamides. In the case of free aminoamides, the diamine and the heterocycle were dissolved in toluene and heated to produce the target molecules as insoluble solids [20, 21]. The products were obtained in high yields and with very good purities after typical filtration and washing procedures using toluene and diethyl ether. The amines were used in three fold excess to avoid formation of unwanted diamides.

However, in the case of substituted aminoamides this process was unsuccessful. These products were obtained by the reaction of the reagents in polar protic solvent (methanol) or in solvent free conditions, depending on the substituents. After careful treatment with the appropriate solvent, the final products were obtained as pure solids or crystals.

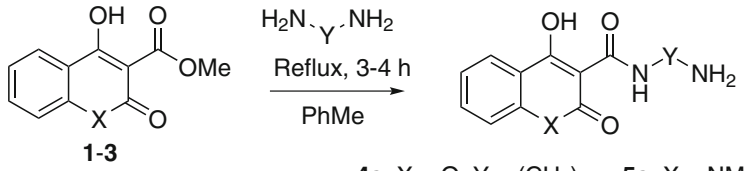
### *Structure elucidation*

In order to elucidate the structures and the conformation of the molecules, we studied them by means of $^{1}H$ and $^{13}C$ NMR spectroscopy and X-ray single crystal crystallography. The NMR spectra showed that the 4-hydroxy was the predominant tautomer in chloroform as solvent, as only one enolic hydrogen was observed for all compounds.

Crystals of compound **6** were obtained by adding ethanol to the crude oily product, without recrystallization. Parameters for X-ray crystallography data collection and refinement are summarized in Table 1.

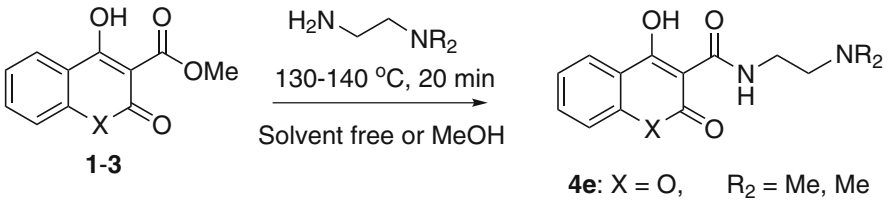
The molecular structure, along with the numbering scheme, is shown in Fig. 3. Concerning the heterocyclic

**Scheme 1**




**4a**: X = O, Y = $(CH_2)_2$ **5a**: X = NMe, Y = $(CH_2)_2$
**4b**: X = O, Y = $(CH_2)_6$ **5b**: X = NMe, Y = $(CH_2)_6$
**4c**: X = O, Y = $(CH_2)_8$ **5c**: X = NMe, Y = *o*-$C_6H_4$
**4d**: X = O, Y = *o*-$C_6H_4$

**Scheme 2**




**4e**: X = O, $R_2$ = Me, Me
**4f**: X = O, $R_2$ = piperidinyl
**6**: X = NPh, $R_2$ = Me, Me

part of the molecule, it is noteworthy that the bond C(2)–O(26) is double (1.240(2)Å) and the bond N(1)–C(2) has a partial double bond character (1.394(2)Å). The double bond character of the bonds C(3)–C(4) (1.386(3)Å) and C(7)–O(8) (1.263(2)Å) and the longer than double bond length of the C(4)–O(15) (1.320(2)Å) strongly proves that the 4-hydroxy is also the dominant tautomer in a solid state. Finally, the bond C(7)–N(9) (1.323(3)Å) has obvious double bond character, as expected from an amide bond (Table 2).

The benzene ring is tilted at 72.48(2)° to the fused rings (which are close to planar). The amide bond has the *cis* conformation, due to the existence of two intramolecular H-bonds as shown in the picture. There is possibly also a third (N9–N12); the N–H–N angle is quite acute but it accounts for the orientation of the pendant amine (Table 3). Intermolecular interactions including π-π stacking of the fused rings (average interplanar distance 3.63 Å, symmetry operation x−1, y, z) and C–H ··· π interaction involving the phenyl ring (C18–H ··· centroid 2.99 Å under symmetry operation −1−x, 1−y, −z) are observed (Fig. 4).

*Biological evaluation*

The biological evaluation of the investigated compounds was based on their anticancer activity according to in vitro NCI standards ($GI_{50}$, TGI, or $LC_{50}$). The molecules examined are amides at position 3 of quinolinone and coumarin compounds bearing functional groups on the amide chain, and a study of their traits reveals two things: (a) the relationship of nitrogen (quinolinone) or oxygen (coumarin) atom on the heterocyclic nucleus versus anticancer activity and (b) the relevance of the amide chain bearing different functionalities to anticancer activity of the molecule.

The cancer cell lines that we applied were DU 145 and PC3 for prostate cancer, HCT-15 for colon cancer, MCF 7 for breast cancer, IGROV-1 for ovarian cancer, SKHep1 for liver cancer, and HL-60 (TB) for leukemia cancer. The results are presented in Table 4.

From these results it is apparent that there are a few compounds that exhibit $GI_{50}$ values below 50 % (compound **4c** for prostate cancer cell line PC3 and liver cancer cell line SKHep1, compound **5b** for colon cancer cell line HCT 15), or around 50 % (compound **4b** for liver cancer cell line SKHep1, compound **4e** for prostate cancer cell line DU 145, compound **5a** for prostate cancer cell line PC3); furthermore, compound **4c** exhibits very good activity against prostate cancer cell line DU 145 with a value of $GI_{50}$ of 8.14 μM. The next stages in this project will be: (a) synthesis of novel functionalized derivatives of coumarins and quinolinones and their in vitro biological evaluation and (b) synthesis of a larger quantity of compound **4c** in order to perform further in vitro and in vivo experiments (e.g. xenografts).

**Table 1** Crystal data and structure refinement for *N*-[2-(dimethylamino) ethyl]-4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxamide (**6**)

| Parameter | |
|---|---|
| Empirical formula | $C_{20}H_{21}N_3O_3$ |
| Formula weight | 351.40 |
| Temperature/K | 150 (2) |
| Wavelength/Å | 0.71073 |
| Crystal system | Triclinic |
| Space group | P-1 |
| Unit cell dimensions/Å | $a = 5.7259$ (5) |
| | $b = 10.9384$ (10) |
| | $c = 14.0120$ (13) |
| Volume/Å$^3$ | 861.21 (14) |
| $Z$ | 2 |
| Density (calculated)/Mg m$^{-3}$ | 1.355 |
| Absorption coefficient/mm$^{-1}$ | 0.093 |
| $F$(000) | 372 |
| Crystal size/mm$^3$ | 0.39 × 0.10 × 0.04 |
| Crystal description | Pale yellow lath |
| Theta range for data collection | 1.89° to 26.00° |
| Index ranges | −7 <=h <=7, −13 <=k <=13, −17 <=l <=17 |
| Reflections collected | 9,939 |
| Independent reflections | 3,372 [$R$(int) = 0.0425] |
| Completeness to theta = 26.00° | 99.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9963 and 0.9647 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data/restraints/parameters | 3,372/0/241 |
| Goodness-of-fit on $F^2$ | 1.041 |
| Final $R$ indices [I > 2sigma(I)] | $R1 = 0.0476$, w$R2 = 0.1084$ |
| $R$ indices (all data) | $R1 = 0.0792$, w$R2 = 0.1230$ |
| Largest diff. peak and hole/e Å$^{-3}$ | 0.179 and −0.197 |

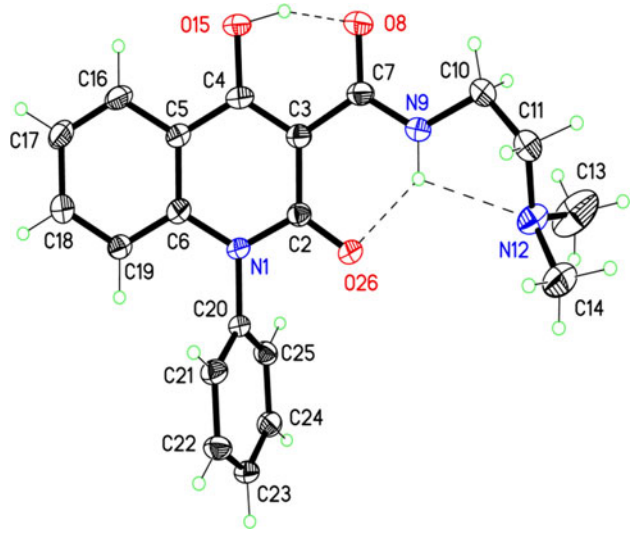



**Fig. 3** Molecular structure of *N*-[2-(dimethylamino)ethyl]-4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxamide (**6**). Displacement ellipsoids for nonhydrogen atoms are drawn at the 50 % probability level. The intramolecular hydrogen bonds are shown *dashed*

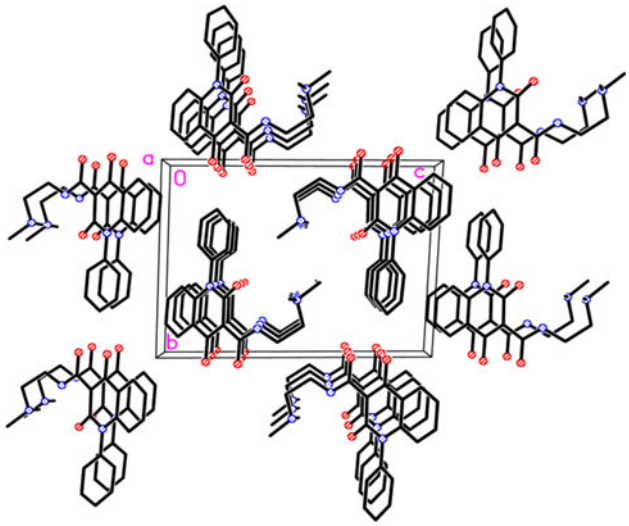



**Fig. 4** Crystal packing diagram of **6**, viewed down the b axis

**Table 2** Bond lengths for **6**

| Bond | Length/Å | Bond | Length/Å |
|---|---|---|---|
| N(1)–C(2) | 1.394 (2) | N(9)–C(10) | 1.453 (3) |
| N(1)–C(6) | 1.400 (2) | C(10)–C(11) | 1.510 (3) |
| N(1)–C(20) | 1.448 (2) | C(11)–N(12) | 1.448 (3) |
| C(2)–O(26) | 1.240 (2) | N(12)–C(13) | 1.450 (3) |
| C(2)–C(3) | 1.446 (3) | N(12)–C(14) | 1.454 (3) |
| C(3)–C(4) | 1.386 (3) | C(16)–C(17) | 1.375 (3) |
| C(3)–C(7) | 1.471 (3) | C(17)–C(18) | 1.387 (3) |
| C(4)–O(15) | 1.320 (2) | C(18)–C(19) | 1.375 (3) |
| C(4)–C(5) | 1.443 (3) | C(20)–C(21) | 1.382 (3) |
| C(5)–C(6) | 1.399 (3) | C(20)–C(25) | 1.383 (3) |
| C(5)–C(16) | 1.405 (3) | C(21)–C(22) | 1.395 (3) |
| C(6)–C(19) | 1.398 (3) | C(22)–C(23) | 1.380 (3) |
| C(7)–O(8) | 1.263 (2) | C(23)–C(24) | 1.383 (3) |
| C(7)–N(9) | 1.323 (3) | C(24)–C(25) | 1.386 (3) |

**Table 3** Hydrogen bonds for **6**

| Bond D–H···A | Length D-H/Å | Length H···A/Å | Length D···A/Å | Angle DHA/° |
|---|---|---|---|---|
| N(9)–H(9)···O(26) | 0.90 (2) | 1.97 (2) | 2.669 (2) | 134 (2) |
| O(15)–H(15)···O(8) | 0.99 (3) | 1.51 (3) | 2.445 (2) | 156 (2) |
| N(9)–H(9)···N(12) | 0.90 (2) | 2.40 (2) | 2.784 (3) | 106.4 (18) |

## Conclusion

In summary, tertiary and primary coumarin and quinolinone-3-carboxamide derivatives were synthesized and characterized. The structure of compound **6** was

**Table 4** In vitro screening table: summary results from the in vitro drug screening

| Compound | Stock conc./mM | Values | HCT-15 | DU 145 | PC3 | MCF 7 | IGROV-1 | SKHep1 | HL-60 (TB) |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | 20 | $LC_{50}$ | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| | | TGI | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| | | $GI_{50}$ | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| **4b** | 20 | $LC_{50}$ | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| | | TGI | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| | | $GI_{50}$ | | 86.6 | 71.1 | | 86.8 | 55.4 | |
| **4c** | 20 | $LC_{50}$ | | 47.5 | >100.0 | | >100.0 | >100.0 | >100.0 |
| | | TGI | | 20.5 | >100.0 | | >100.0 | >100.0 | >100.0 |
| | | $GI_{50}$ | | 8.14 | 41.8 | | 77.0 | 38.2 | >100.0 |
| **4d** | 20 | $LC_{50}$ | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| | | TGI | | >100.0 | >100.0 | | >100.0 | >100.0 | |
| | | $GI_{50}$ | | 93.5 | 75.7 | | >100.0 | 71.3 | |
| **4e** | 20 | $LC_{50}$ | >100.0 | >100.0 | >100.0 | | 100.0 | >100.0 | >100.0 |
| | | TGI | >100.0 | >100.0 | >100.0 | | 100.0 | >100.0 | >100.0 |
| | | $GI_{50}$ | >100.0 | 53.8 | >100.0 | | 100.0 | >100.0 | 100.0 |
| **5a** | 20 | $LC_{50}$ | >100.0 | | >100.0 | >100.0 | | >100.0 | |
| | | TGI | >100.0 | | >100.0 | >100.0 | | >100.0 | |
| | | $GI_{50}$ | >100.0 | | 53.6 | >100.0 | | 97.6 | |
| **5b** | 20 | $LC_{50}$ | >100.0 | | >100.0 | >100.0 | | >100.0 | |
| | | TGI | >100.0 | | >100.0 | >100.0 | | >100.0 | |
| | | $GI_{50}$ | 39.2 | | 83.2 | 65.8 | | 61.1 | |
| **4f** | 20 | $LC_{50}$ | >100.0 | | | >100.0 | | >100.0 | |
| | | TGI | >100.0 | | | >100.0 | | >100.0 | |
| | | $GI_{50}$ | >100.0 | | | >100.0 | | >100.0 | |
| **6** | 20 | $LC_{50}$ | >100.0 | | | >100.0 | | >100.0 | |
| | | TGI | 100.0 | | | 100.0 | | 100.0 | |
| | | $GI_{50}$ | 79.7 | | | 100.0 | | 79.5 | |
| **5c** | 20 | $LC_{50}$ | | | 100.0 | | 100.0 | 100.0 | |
| | | TGI | | | 100.0 | | 100.0 | 100.0 | |
| | | $GI_{50}$ | | | 100.0 | | 83.0 | 61.9 | |

For each experimental agent: $LC_{50}$ is the concentration of drug resulting in 50 % reduction in measured protein, TGI the concentration resulting in total growth inhibition, and $GI_{50}$ the concentration resulting in growth inhibition of 50 %

determined by X-ray crystal structural analysis. In the solid state this compound demonstrated an edge-to-face interaction involving the phenyl ring and π-π stacking interactions of the fused rings, thus forming chains. One N–H ··· O hydrogen bond and one O–H ··· O hydrogen bond, both intramolecular, favoring the *cis* conformation of amide bond were observed as expected.

Compounds were evaluated for cytostatic activities against various cancer cell lines. Compound **4c** exhibited higher inhibitory effects against DU 145 prostate cancer cell line ($GI_{50} < 10$ μM).

Our future plans include synthesis of novel functionalized derivatives of coumarins and quinolinones and their in vitro biological evaluation and synthesis of a larger quantity of compound **4c**, in order to perform further in vitro and in vivo experiments.

## Experimental

All reagents were purchased from Aldrich, Fluka, and Acros and used without further purification. Dry tetrahydrofuran (THF) was distilled from $Na/Ph_2CO$. Melting points were determined with a Gallenkamp MFB-595 melting point apparatus. NMR spectra were recorded with a Varian Gemini-2000 300 MHz spectrometer operating at 300 MHz ($^1H$) and 75 MHz ($^{13}C$). Chemical shifts are reported in ppm relative to $CDCl_3$ ($^1H$: $\delta = 7.26$ ppm, $^{13}C$: $\delta = 77.16$ ppm). Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyzer. Compounds **4a–4f** [21], **4e**, **4f** [24], and **5a–5c** [20], were prepared using slightly modified literature methods.

Cell viability was assessed at the beginning of each experiment by the trypan blue dye exclusion method, and

was always greater than 95 %. Cells were seeded into 96-well microtiter plates in 100 $mm^3$ of medium at the corresponding density (3,500–30,000 cells per well) and subsequently, the plates were incubated at standard conditions for 24 h to allow the cells to resume exponential growth prior to addition of the agents to be tested. Then in order to measure the cell population, cells in one plate were fixed in situ with trichloroacetic acid (TCA) followed by sulforhodamine B solution (SRB) staining, as described elsewhere. To determine the activity, each compound was dissolved in dimethyl sulfoxide (DMSO) and then was added at 10-fold dilutions (from 100 to 0.01 μM), and incubation continued for an additional period of 48 h. The assay was terminated by addition of cold TCA followed by SRB staining and absorbance measurement at 540 nm in a DAS plate reader, to determine (1) the $GI_{50}$, the concentration required in the cell culture to inhibit cell growth by 50 %, (2) TGI, the concentration that is required to completely inhibit cell growth, and (3) the $LC_{50}$, the concentration that is needed in culture to kill 50 % of the cellular population as described [23].

The standard experimental procedure comprises of the following steps: (a) the experimental compounds were dissolved in DMSO, purchased from Sigma-Aldrich, at a final stock concentration of 20 mM. (b) Dilutions of 20 $mm^3$ of the final stock solution with the medium to final concentrations of 100, 10, and 1 μM followed in order to examine the cytotoxicity effect. (c) In parallel, DMSO control studies were performed by preparing DMSO control solutions of 20 $mm^3$ of DMSO diluted with the medium to final concentrations of 100, 10, and 1 μM, concentrations at which DMSO did not show any cellular cytotoxicity.

*N-[2-(Dimethylamino)ethyl]-4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxamide*
(**6**, $C_{20}H_{21}N_3O_3$)
4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxylic acid methyl ester (0.40 mmol) was dissolved in the minimum amount of *N,N*-dimethylethylenediamine under heat at 130 °C (0.48–1.20 mmol) in a 10 $cm^3$ round bottom flask. The dark brown solution was gently stirred and refluxed at 130 °C for 20 min. Then the amine was allowed to distill (b.p. 104–106 °C) for 40 min. The gummy solid was washed with ethanol and refrigerated overnight to afford the desired products as yellow needle crystals, which were filtered and washed twice with a small volume of diethyl ether. Yellow crystalline solid; yield 83 %; m.p.: 192–193 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.40$ (s, 6H, $N(CH_3)_2$), 2.68 (t, $J = 6.6$ Hz, 2H, $CH_2CH_2NCH_3$), 3.61 (q, $J = 6.6$ Hz, 2H, $CH_2CH_2NCH_3$), 6.63 (d, $J = 8.1$ Hz, 1H, Ar), 7.26-7.28 (m, 3H, Ar), 7.45 (t, $J = 8.1$ Hz, 1H, Ar), 7.52-7.63 (m, 3H, Ar), 8.24 (d, $J = 8.1$ Hz, 1H, Ar), 10.23 (br, 1H, NH), 17.15 (br, 1H, OH) ppm; $^{13}$C (75 MHz, $CDCl_3$): $\delta = 36.5$ ($CH_2CH_2NCH_3$), 45.0 ($NCH_3$), 57.8 ($CH_2CH_2NCH_3$), 97.0 (C-3), 116.2, 122.8, 125.4, 129.2, 129.3, 130.4, 133.4, 137.3, 141.0 (Ar), 160.1 (C-2), 171.5 (CONH), 172.5 (C-4) ppm.

Diffraction data were collected at 150 (2) K on a Bruker Apex II CCD diffractometer using MoKα radiation ($\lambda = 0.71073$ Å). All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters, and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to O or N were located from difference maps and their coordinates refined [22].

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 856973. Copies of the data can be obtained, free of charge, through application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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