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Article

Synthesis, Characterization and Evaluation of *in vitro* Antitumor Activities of Novel Chalcone-Quinolinone Hybrid Compounds

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Chalcone-quinolinone hybrid compounds, as well as the synthesis of such compounds, have few reports in the literature. Such compounds may be quite useful in therapeutics, since various biological activities are reported for both chalcones and quinolinones. In the present work, several novel chalcone-quinolinone compounds have been synthesized. The reaction conditions developed allowed to obtain the compounds in a single step of synthesis from the chalcones. The products precipitated pure and were isolated by filtration. The yields of such reactions, from 45 to 94%, were promising. The product structures were confirmed by nuclear magnetic resonance (NMR) and electrospray ionization mass spectrometry (ESI-MS) techniques. Their antitumor activities were evaluated in HCT-116 (colon) cell lines by the 3-(4,5-dimethyl-2-thiazole)-2,5-diphenyl-2-*H*-tetrazolium bromide (MTT) test. The half maximal inhibitory concentration (IC_{50}) values obtained for the most active chalcones were between 2.9 and 7.5 and for active quinolinone was 19.3 mg L^{-1}. The antitumor activities results suggest that the class of compounds studied has potential for use in cancer research.

Keywords: chalcone-quinolinone hybrids, chacone sulfonamide, Claisen-Schmidt condensation, antitumor activity

Introduction

Several chalcones and chalcone analogs have been found in nature or have been synthesized, and sundry biological activities have been reported for this class of compound. Some reviews[1-4] summarize the synthetic routes and applications of chalcones. Anticancer activities of synthetic and natural chalcones, and chalcone analogs, are reported in the literature,[5-18] involving diverse mechanisms related to various aspects of cancer progression.

A wide range of biological activities of quinolinones has also been reported, such as the inhibitory activity of GSK-3β and antimicrobial,[19] anti-HIV,[20] antimalarial[21] and antitumor activity.[22] However, the synthesis of chalcone-quinolinone compounds, possessing the moiety shown in the Figure 1, is rarely described in the literature, and only one study reports the biological activity of such compounds; in this case inhibition of *Trypanosoma cruzi* *trans*-sialidase.[23] Our search in the Scifinder®,[24] for the sub-structure shown in Figure 1, resulted in only 11 different structures.

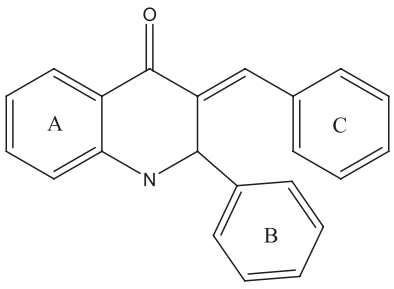

Figure 1. Sub-structure of chalcone-quinolinone searched on Scifinder® database.[24]

Kim *et al*.[23] described the synthesis of two compounds with this nucleus via acid catalysis in methanol. All compounds synthesized had identical substituents in rings B and C.[23] Saito *et al*.[25] reported the synthesis of a compound with these nuclei, exploiting the reactivity of an alkyne

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group. Rings B and C also come from the same aldehyde added to the reaction system.[25] Black *et al*.[26] started from an acetophenone with N at the *ortho* position and reacted with an aldehyde, by a Claisen-Schmidt condensation reaction, using an amide and sodium hydride as a basic catalyst to obtain the final compounds in two steps, with different substituted aldehydes. Ma *et al*.[27] also started from an acetophenone with N at the *ortho* position and reacting with aldehyde. The yield was 29%, and rings B and C had identical substituents. Wang *et al*.[28] synthesized a series of similar compounds via acid catalysis starting from an alkyne group, with nitrogen in the *ortho* position of the ring. The substituents of rings B and C were identical.

In recent years, our research group has been dedicated to synthesis, characterization and antitumor evaluation of chalcone derivatives.[29-34] The bioactivity of these compounds is associated with cellular thiols as glutathione reduced (GSH). Therefore, our group reported the reaction of Mannich bases and hydroxychalcone with GSH and the stereochemistry of non-enzyme nucleophilic addition of GSH to hydroxychalcone and Mannich base derivative at different pH.[32,33] Among these derivatives, the sulfonamide chalcones have been synthesized and evaluated against several strains of human cancer with relevant results.[29-31] The synthesis of 3-(*p*-nitrobenzylidene) quinolinone, with nitro group in rings B and C, reported by de Castro *et al*.,[31] motivated the subsequent study of chalcone-quinolinones. Therefore, the aim of this work was the development of a synthetic route for chalcone-quinolinone synthesis in such a way as to incorporate different substituents in B and C rings and evaluate the antitumor activity of these compounds against HCT-116 (colon) human tumor cell lines.

Experimental

General procedures

Nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance III 500 spectrometer (Rheinstetten, Germany) operating at 11.75 T, observing ^{1}H at 500.13 MHz and ^{13}C at 125.76 MHz. The spectrometer was equipped with a 5 mm inverse-detection three-channel (^{1}H, ^{2}H, ^{13}C and XBB) and 5 mm broadband observe (BBO) probes. The samples (ca. 10 mg) were dissolved in 600 µL of deuterated chloroform ($CDCl_3$), containing tetramethylsilane (TMS) as the internal standard. Complete signal assignment was also obtained by correlation spectroscopy (COSY), heteronuclear multiple bond correlation (HMBC) and heteronuclear single quantum correlation (HSQC) experiments.

The degree of purity of the compounds was determined by the ^{1}H spectra, from the proportion of the areas between the peaks assigned to the structure and the total area of all peaks attributed to the material under analysis. For compounds **16**, **22**, **31**, **32**, **33**, **34** and **35**, in which considerable amounts of solvent were in evidence, the degree of purity was calculated on the dry basis, i.e., disregarding the peaks of the solvents.

Mass spectrometric (MS) analyses were performed using a MicroTOF-Q® III spectrometer (Bruker Daltonics, Bremen, Germany) equipped with a commercial ESI (electrospray ionization) ion source. Analyses were by direct infusion (3 µL min^{-1}) after extraction under acetonitrile and 1 mM formic acid. All analyses were carried out in positive mode. The configuration of the ESI(+) was: nitrogen gas nebulizer with a temperature of 200 °C, pressure of 0.4 bar and a drying gas flow of 4 L min^{-1}; voltage in the capillary of –4 kV; temperature of 200 °C in the transfer capillary; end plate offset of –500 V; 35 V skimmer and –1.5 V collision voltage. Each spectrum was acquired using two microscans and processed using Data Analysis Software (Bruker Daltonics, Bremen, Germany).

The infrared spectroscopy analyses were performed at the State University of Goiás, CCET campus, in Anápolis, Goiás, on a PerkinElmer, Frontier Dual Range FT-IR/MIR Spectrometer (Massachusetts, USA), read in ATR (attenuated total reflectance) apparatus. The melting points were determined with the solid supported on glass coverslips and subjected to heating in a melting point apparatus (Karl Kolb, Frankfurt a.M., Germany).

Synthesis of compounds **1** to **9**

Compounds **1** to **9** were synthesized using the methodology reported by de Castro *et al*.[29] with apropriate reagents.

1-(2-(Phenylsulfonylamine)phenyl)ethanone (**1**)

White crystalline solid, yield 63.8%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 2.56 (s, 3H), 7.08 (ddd, *J* 7.98, 7.33, 1.18 Hz, 1H), 7.42-7.46 (m, 2H), 7.46 (dddd, *J* 8.44, 7.34, 1.56, 0.41 Hz, 1H), 7.51-7.54 (m, 1H), 7.70 (ddd, *J* 8.40, 1.15, 0.45 Hz, 1H), 7.80 (ddd, *J* 8.01, 1.59, 0.46 Hz, 1H), 7.84-7.87 (m, 2H), 11.50 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 28.2, 119.2, 122.4, 122.8, 127.2, 129.0, 131.9, 133.0, 135.0, 139.5, 139.9, 202.4; HRMS (high-resolution mass spectrometry) calculated for $C_{14}H_{14}NO_3S$ 276.0694, found 276.0725.

(*E*)-3-(2-Methoxyphenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**2**)

Yellow crystalline solid, yield 93.5%, purity of 99.1%, mp 118-120 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.94 (s,

3H), 6.96 (d, *J* 8.35 Hz, 1H), 7.00 (t, *J* 7.53 Hz, 1H), 7.13 (ddd, *J* 1.13, 7.35, 7.88 Hz, 1H), 7.36-7.44 (m, 4H), 7.46 (d, *J* 15.65 Hz, 1H), 7.46-7.49 (m, 1H), 7.57 (dd, *J* 1.58, 7.68 Hz, 1H), 7.75 (dd, *J* 0.85, 8.30 Hz, 1H), 7.82-7.84 (m, 2H), 7.85 (dd, *J* 1.40, 8.10 Hz, 1H), 8.00 (d, *J* 15.65 Hz, 1H), 11.30 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.6, 111.4, 120.6, 120.8, 122.7, 123.1, 123.5, 125.0, 127.3, 129.0, 129.4, 130.7, 132.3, 132.8, 134.1, 139.5, 139.9, 141.7, 159.0, 193.3; IR (ATR) ν / cm^{-1} 1632 (m), 1489 (m), 1328 (m), 934 (m), 749 (s); HRMS calculated for $C_{22}H_{20}NO_4S$ 394.1113, found 394.1002.

(*E*)-3-(2-Bromophenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**3**)

Yellow crystalline solid, yield 77.4%, purity of 96.7%, mp 151-153 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.15 (ddd, *J* 1.19, 7.39, 7.99 Hz, 1H), 7.26 (d, *J* 15.55 Hz, 1H), 7.26-7.30 (m, 1H), 7.35-7.37 (m, 1H), 7.38-7.46 (m, 3H), 7.50 (ddd, *J* 1.53, 7.40, 8.35 Hz, 1H), 7.65-7.67 (m, 2H), 7.77 (dd, *J* 1.05, 8.40 Hz, 1H), 7.82-7.85 (m, 3H), 7.99 (d, *J* 15.55 Hz, 1H), 11.10 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 120.9, 123.2, 124.6, 124.9, 126.1, 127.3, 127.8, 127.9, 129.0, 130.8, 131.8, 132.9, 133.7, 134.5, 139.4, 139.9, 144.3, 192.7; IR (ATR) ν / cm^{-1} 1641 (m), 1493 (m), 1330 (m), 932 (m), 751 (s); HRMS calculated for $C_{21}H_{16}BrNO_3SNa$ 463.9932, found 463.9837.

(*E*)-3-(4-Ethoxyphenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**4**)

Yellow crystalline solid, yield 76.1%, purity of 98.1%, mp 137-140 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.45 (t, *J* 7.00 Hz, 3H), 4.09 (q, *J* 7.00 Hz, 2H), 6.91-6.94 (m, 2H), 7.13 (ddd, *J* 1.25, 7.38, 7.88 Hz, 1H), 7.20 (d, *J* 15.50 Hz, 1H), 7.35-7.39 (m, 2H), 7.40-7.44 (m, 1H), 7.47 (ddd, *J* 1.45, 7.40, 8.38 Hz, 1H), 7.53-7.56 (m, 2H), 7.65 (d, *J* 15.50 Hz, 1H), 7.75 (dd, *J* 1.03, 8.33 Hz, 1H), 7.80-7.84 (m, 3H), 11.22 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 14.7, 63.8, 115.0, 119.5, 120.9, 123.2, 125.3, 127.0, 127.3, 129.0, 130.4, 130.5, 132.8, 134.0, 139.5, 139.7, 146.1, 161.6, 192.7; IR (ATR) ν / cm^{-1} 1637 (m), 1497 (m), 1329 (s), 927 (m), 761 (s); HRMS calculated for $C_{23}H_{21}NO_4SNa$ 430.1089, found 430.1103.

(*E*)-3-(4-Methoxyphenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**5**)

Yellow crystalline solid, yield 87.7%, purity of 98.8%, mp 124-126 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.93-6.96 (m, 2H), 7.13 (ddd, *J* 1.09, 7.26, 7.99 Hz, 1H), 7.21 (d, *J* 15.50 Hz, 1H), 7.35-7.39 (m, 2H), 7.40-7.44 (m, 1H), 7.47 (ddd, *J* 1.53, 7.43, 8.25 Hz, 1H), 7.54-7.57 (m, 2H), 7.65 (d, *J* 15.50 Hz, 1H), 7.75 (dd, *J* 0.98, 8.48 Hz, 1H), 7.81-7.84 (m, 3H), 11.22 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.5, 114.6, 119.7, 120.9, 123.2, 125.2, 127.2, 127.3, 129.0, 130.4, 130.5, 132.8, 134.0, 139.5, 139.7, 146.0, 162.1, 192.7; IR (ATR) ν / cm^{-1} 1639 (m), 1494 (m), 1329 (m), 924 (m), 755 (m); HRMS calculated for $C_{22}H_{19}NO_4SNa$ 416.0932, found 416.0833.

(*E*)-3-(2-Chlorophenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**6**)

Yellow crystalline solid, yield 79.9%, purity of 98.1%, mp 150-152 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.14 (ddd, *J* 1.04, 7.41, 7.94 Hz, 1H), 7.32 (d, *J* 15.60 Hz, 1H), 7.31-7.34 (m, 1H), 7.35-7.41 (m, 3H), 7.42-7.47 (m, 2H), 7.50 (ddd, *J* 1.56, 7.31, 8.36 Hz, 1H), 7.69 (dd, *J* 1.73, 7.63 Hz, 1H), 7.77 (dd, *J* 0.85, 8.30 Hz, 1H), 7.81-7.84 (m, 3H), 8.03 (d, *J* 15.55 Hz, 1H), 11.10 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 120.9, 123.2, 124.7, 124.7, 127.2, 127.3, 127.8, 129.0, 130.5, 130.8, 131.6, 132.8, 132.9, 134.5, 135.7, 139.4, 139.9, 141.7, 192.7; IR (ATR) ν / cm^{-1} 1641 (m), 1494 (m), 1331 (m), 932 (m), 747 (s); HRMS calculated for $C_{21}H_{16}ClNO_3SNa$ 420.0437, found 420.0327.

(*E*)-3-(4-Chlorophenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**7**)

Yellow crystalline solid, yield 70.9%, purity of 98.2%, mp 150-155 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.14 (ddd, *J* 1.16, 7.34, 7.94 Hz, 1H), 7.33 (d, *J* 15.55 Hz, 1H), 7.37-7.42 (m, 4H), 7.43-7.46 (m, 1H), 7.50 (ddd, *J* 1.55, 7.40, 8.40 Hz, 1H), 7.52-7.55 (m, 2H), 7.63 (d, *J* 15.55 Hz, 1H), 7.75 (dd, *J* 1.08, 8.33 Hz, 1H), 7.82-7.85 (m, 3H), 11.18 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 120.7, 122.5, 123.2, 124.6, 127.3, 129.0, 129.4, 129.7, 130.6, 132.9, 132.9, 134.5, 137.0, 139.5, 140.0, 144.5, 192.5; IR (ATR) ν / cm^{-1} 1641 (m), 1492 (m), 1329 (m), 928 (m), 756 (m); HRMS calculated for $C_{21}H_{17}ClNO_3S$ 398.0618, found 398.0462.

(*E*)-3-(3-Nitrophenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**8**)

Yellow crystalline solid, yield 39.7%, purity of 98.4%, mp 190-195 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.17 (t, *J* 7.70 Hz, 1H), 7.40-7.43 (m, 2H), 7.46-7.47 (m, 1H), 7.50 (d, *J* 15.55 Hz, 1H), 7.53 (t, *J* 8.03 Hz, 1H), 7.64 (t, *J* 7.95 Hz, 1H), 7.72 (d, *J* 15.60 Hz, 1H), 7.76 (d, *J* 8.35 Hz, 1H), 7.85 (d, *J* 7.50 Hz, 2H), 7.89 (d, *J* 7.80 Hz, 2H), 8.28 (dd, *J* 1.18, 8.08 Hz, 1H), 8.47 (t, *J* 1.80 Hz, 1H), 11.18 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 120.5, 122.3, 123.2, 124.0, 124.7, 125.0, 127.3, 129.1, 130.2, 130.8, 133.0, 134.5, 135.0, 136.2, 139.5, 140.2, 142.7, 148.8, 192.0; IR (ATR) ν / cm^{-1} 1646 (m), 1450 (m), 1333 (m), 930 (m), 747 (m); HRMS calculated for $C_{21}H_{17}N_2O_5S$ 409.0858, found 409.0562.

(*E*)-3-(4-Bromophenyl)-1-(2-(phenylsulfonylamine)phenyl) prop-2-en-1-one (**9**)

Yellow crystalline solid, yield 52.0%, purity of 97.1%, mp 157-159 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.14 (ddd, *J* 1.15, 7.35, 7.90 Hz, 1H), 7.34 (d, *J* 15.55 Hz, 1H), 7.37-7.40 (m, 2H), 7.42-7.47 (m, 3H), 7.49 (ddd, *J* 1.54, 7.34, 8.41 Hz, 1H), 7.55-7.58 (m, 2H), 7.61 (d, *J* 15.55 Hz, 1H), 7.75 (dd, *J* 0.80, 8.35 Hz, 1H), 7.81-7.84 (m, 3H), 11.17 (s, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 120.7, 122.6, 123.2, 124.6, 125.4, 127.3, 129.0, 129.9, 130.6, 132.4, 132.9, 133.3, 134.5, 139.4, 140.0, 144.5, 192.5; IR (ATR) ν / cm^{-1} 1640 (m), 1489 (m), 1331 (m), 924 (m), 751 (s); HRMS calculated for $C_{21}H_{17}BrNO_3S$ 442.0113, found 442.0004.

Synthesis of compounds **10** to **41**

Chalcones **10** to **41** (1.0 mmol) and benzaldeyde (2.0 mmol) were dissolved in 15 mL of basic ethanol (56.1 mg of potassium hydroxide dissolved) and reacted (25 °C) for 48 h. The solution was filtered and the precipitate was rinsed with 15 mL of ethanol. The precipitate was dissolved in dichloromethane (10 mL) and this solution was extracted with water. The organic phase was allowed to evaporate slowly, yielding the product. The compounds **14**, **16**, **17**, **23**, **27**, **31**, **32** and **33** were further purified by recrystalization by dissolving in dicloromethane and exposing to ethyl ether vapor.

(*E*)-3-(3-Nitrobenzylidene)-2-(4-ethoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**10**)

Pale yellow crystalline solid, yield 78.1%, purity of 98.6%, mp 187-189 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.37 (t, *J* 6.98 Hz, 3H), 3.96 (q, *J* 7.02 Hz, 2H), 6.48 (d, *J* 0.75 Hz, 1H), 6.79-6.82 (m, 2H), 7.09-7.12 (m, 2H), 7.24-7.27 (m, 2H), 7.28-7.34 (m, 3H), 7.40-7.42 (m, 1H), 7.54-7.59 (m, 4H), 7.70 (dd, *J* 0.98, 8.13 Hz, 1H), 7.92 (dd, *J* 1.73, 7.83 Hz, 1H), 8.04 (t, *J* 1.95 Hz, 1H), 8.28 (ddd, *J* 0.88, 2.25, 8.23 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 14.8, 59.6, 63.4, 114.9, 124.4, 125.2, 127.2, 127.4, 128.0, 128.1, 128.4, 128.5, 128.9, 129.0, 130.3, 133.5, 133.5, 134.5, 135.0, 135.3, 136.7, 137.6, 139.0, 148.5, 159.2, 182.4; IR (ATR) ν / cm^{-1} 1675 (m), 1603 (m), 1475 (m), 1349 (s), 1306 (w), 1242 (s); HRMS calculated for $C_{30}H_{25}N_2O_6S$ 541.1433, found 541.1026.

(*E*)-3-(4-Nitrobenzylidene)-2-(4-ethoxyphenyl)-2,3-dihydro-1-phenylsulfonyl)-quinolin-4(1*H*)-one (**11**)

Pale yellow crystalline solid, yield 78.1%, purity of 99.1%, mp 208-209 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.37 (t, *J* 7.00 Hz, 3H), 3.96 (q, *J* 7.02 Hz, 2H), 6.53 (d, *J* 0.75 Hz, 1H), 6.78-6.81 (m, 2H), 7.10-7.12 (m, 2H), 7.22-7.26 (m, 2H), 7.28-7.34 (m, 5H), 7.53 (tt, *J* 1.23, 7.49 Hz, 1H), 7.57 (ddd, *J* 1.66, 7.36, 8.16 Hz, 1H), 7.59 (s, 1H), 7.71 (dd, *J* 0.98, 8.18 Hz, 1H), 7.90 (dd, *J* 1.63, 7.83 Hz, 1H), 8.25-8.28 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 14.8, 59.5, 63.5, 114.9, 124.2, 127.2, 127.4, 128.1, 128.2, 128.5, 128.8, 129.0, 130.6, 133.4, 134.0, 135.0, 136.7, 137.5, 139.0, 139.9, 148.1, 159.2, 182.3; IR (ATR) ν / cm^{-1} 1677 (m), 1601 (m), 1472 (w), 1344 (s), 1306 (w), 1250 (s); HRMS calculated for $C_{30}H_{25}N_2O_6S$ 541.1433, found 541.1332.

(*E*)-3-(4-Bromobenzylidene)-2-(4-ethoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**12**)

Pale yellow crystalline solid, yield 76.6%, purity of 98.4%, mp 196-198 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.36 (t, *J* 7.00 Hz, 3H), 3.95 (q, *J* 7.00 Hz, 2H), 6.55 (d, *J* 0.60 Hz, 1H), 6.76-6.79 (m, 2H), 7.03-7.06 (m, 2H), 7.10-7.13 (m, 2H), 7.19-7.23 (m, 2H), 7.27-7.31 (m, 3H), 7.49 (tt, *J* 1.20, 7.46 Hz, 1H), 7.50 (s, 1H), 7.54 (ddd, *J* 1.73, 7.30, 8.20 Hz, 1H), 7.53-7.56 (m, 2H), 7.70 (dd, *J* 0.90, 8.15 Hz, 1H), 7.88 (dd, *J* 1.63, 7.83 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 14.8, 59.6, 63.4, 114.7, 124.9, 127.2, 127.9, 128.3, 128.5, 128.5, 128.8, 128.9, 131.4, 131.5, 132.4, 132.6, 133.2, 134.6, 137.5, 138.6, 139.0, 159.0, 182.7; IR (ATR) ν / cm^{-1} 1676 (m), 1608 (m), 1474 (w), 1355 (s), 1305 (w), 1245 (s); HRMS calculated for $C_{30}H_{25}BrNO_4S$ 574.0688, found 574.0327.

(*E*)-3-(4-Chlorobenzylidene)-2-(4-ethoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**13**)

Pale yellow crystalline solid, yield 66.2%, purity of 98.0%, mp 190-192 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.36 (t, *J* 7.00 Hz, 3H), 3.95 (q, *J* 7.00 Hz, 2H), 6.56 (d, *J* 0.60 Hz, 1H), 6.77-6.80 (m, 2H), 7.10-7.13 (m, 4H), 7.19-7.23 (m, 2H), 7.27-7.32 (m, 3H), 7.37-7.40 (m, 2H), 7.49 (tt, *J* 1.25, 7.45 Hz, 1H), 7.52 (s, 1H), 7.54 (ddd, *J* 1.66, 7.36, 8.19 Hz, 1H), 7.71 (dd, *J* 1.05, 8.20 Hz, 1H), 7.89 (dd, *J* 1.65, 7.80 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 14.8, 59.6, 63.4, 114.7, 127.2, 127.9, 128.3, 128.5, 128.5, 128.8, 128.9, 129.4, 131.3, 131.3, 132.2, 133.2, 134.6, 136.4, 137.6, 138.6, 138.9, 159.0, 182.7; IR (ATR) ν / cm^{-1} 1677 (m), 1609 (m), 1474 (w), 1354 (s), 1306 (w), 1247 (s); HRMS calculated for $C_{30}H_{25}ClNO_4S$ 530.1193, found 530.1083.

(*E*)-3-(3-Nitrobenzylidene)-2-(4-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**14**)

Pale yellow to white amorphous solid, yield 93.6%, purity of 96.3%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.50 (s, 1H), 6.81-6.84 (m, 2H), 7.11-7.13 (m, 2H),

7.24-7.29 (m, 2H), 7.30-7.34 (m, 3H), 7.42 (d, *J* 7.70 Hz, 1H), 7.54-7.58 (m, 3H), 7.59 (s, 1H), 7.71 (d, *J* 8.10 Hz, 1H), 7.93 (dd, *J* 1.50, 7.80 Hz, 1H), 8.04 (t, *J* 1.98 Hz, 1H), 8.28 (dd, *J* 1.88, 8.23 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.2, 59.5, 114.5, 124.4, 125.2, 127.2, 127.4, 128.0, 128.1, 128.5, 128.6, 128.9, 129.0, 130.3, 133.5, 133.5, 134.5, 135.0, 135.3, 136.7, 137.5, 139.0, 148.5, 159.8, 182.4; IR (ATR) ν / cm^{-1} 1673 (m), 1606 (m), 1477 (w), 1348 (s), 1305 (m), 1257 (m); HRMS calculated for $C_{29}H_{23}N_2O_6S$ 527.1277, found 527.1193.

(*E*)-3-(4-Nitrobenzylidene)-2-(4-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**15**)

Yellow crystalline solid (390 mg, 74.1%), purity of 97.8%, mp 211-213 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.54 (s, 1H), 6.80-6.83 (m, 2H), 7.10-7.13 (m, 2H), 7.22-7.26 (m, 2H), 7.29-7.34 (m, 5H), 7.53 (tt, *J* 1.17, 7.46 Hz, 1H), 7.57 (ddd, *J* 1.65, 7.43, 8.13 Hz, 1H), 7.60 (s, 1H), 7.71 (dd, *J* 0.95, 8.25 Hz, 1H), 7.91 (dd, *J* 1.65, 7.85 Hz, 1H), 8.25-8.28 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.3, 59.5, 114.5, 124.2, 127.2, 127.4, 128.1, 128.4, 128.5, 128.8, 129.0, 130.6, 133.4, 134.0, 135.1, 136.7, 137.5, 139.0, 139.9, 148.1, 159.8, 182.3; IR (ATR) ν / cm^{-1} 1674 (m), 1600 (m), 1476 (w), 1353 (s), 1304 (m), 1250 (s); HRMS calculated for $C_{29}H_{23}N_2O_6S$ 527.1277, found 527.1229.

(*E*)-3-(4-Bromobenzylidene)-2-(4-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)quinolin-4(1*H*)-one (**16**)

Pale yellow crystalline solid, yield 44.6%, purity of 98.2%, mp 137-139 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.56 (s, 1H), 6.78-6.81 (m, 2H), 7.03-7.06 (m, 2H), 7.10-7.13 (m, 2H), 7.19-7.23 (m, 2H), 7.29 (dt, *J* 1.07, 7.50 Hz, 1H), 7.30-7.33 (m, 2H), 7.48-7.51 (m, 1H), 7.51 (s, 1H), 7.53-7.57 (m, 3H), 7.71 (dd, *J* 0.85, 8.20 Hz, 1H), 7.89 (dd, *J* 1.63, 7.78 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.2, 59.6, 114.3, 124.9, 127.2, 127.3, 127.9, 128.3, 128.5, 128.7, 128.8, 128.9, 131.3, 131.5, 132.4, 132.5, 133.3, 134.7, 137.5, 138.7, 138.9, 159.6, 182.7; IR (ATR) ν / cm^{-1} 1677 (m), 1607 (m), 1474 (w), 1354 (s), 1306 (w), 1247 (s); HRMS calculated for $C_{29}H_{23}BrNO_4S$ 560.0531, found 560.0422.

(*E*)-3-(4-Chlorobenzylidene)-2-(4-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)quinolin-4(1*H*)-one (**17**)

Pale yellow crystalline solid, yield 47.5%, purity of 98.4%, mp 166-167 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.57 (s, 1H), 6.78-6.81 (m, 2H), 7.10-7.13 (m, 4H), 7.19-7.23 (m, 2H), 7.28-7.33 (m, 3H), 7.37-7.40 (m, 2H), 7.49 (tt, *J* 1.23, 7.48 Hz, 1H), 7.53 (s, 1H), 7.55 (ddd, *J* 1.65, 7.38, 8.18 Hz, 1H), 7.71 (dd, *J* 0.80, 8.15 Hz, 1H), 7.89 (dd, *J* 1.58, 7.83 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.2, 59.6, 114.3, 127.2, 127.3, 127.9, 128.3, 128.4, 128.7, 128.8, 128.9, 129.4, 131.2, 131.3, 132.1, 133.2, 134.7, 136.4, 137.5, 138.6, 138.9, 159.6, 182.7; IR (ATR) ν / cm^{-1} 1671 (m), 1605 (m), 1475 (w), 1355 (s), 1303 (m), 1253 (m); HRMS calculated for $C_{29}H_{23}ClNO_4S$ 516.1036, found 516.0902.

(*E*)-3-(3-Nitrobenzylidene)-2-(4-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**18**)

Pale yellow crystalline solid, yield 90.4%, purity of 98.3%, mp 212-215 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.49 (s, 1H), 7.09-7.11 (m, 2H), 7.24-7.30 (m, 4H), 7.32-7.37 (m, 3H), 7.36-7.39 (m, 1H), 7.55-7.61 (m, 3H), 7.62 (s, 1H), 7.70 (dd, *J* 0.83, 8.18 Hz, 1H), 7.91 (dd, *J* 1.55, 7.80 Hz, 1H), 8.02 (t, *J* 1.93 Hz, 1H), 8.30 (dd, *J* 2.18, 8.28 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.4, 124.6, 125.1, 127.2, 127.7, 127.9, 128.2, 128.4, 128.9, 129.1, 129.4, 130.4, 132.8, 133.7, 134.3, 134.9, 135.1, 135.2, 135.4, 137.4, 138.8, 148.5, 182.0; IR (ATR) ν / cm^{-1} 1674 (m), 1613 (m), 1478 (w), 1353 (s), 1305 (m), 1237 (m); HRMS calculated for $C_{28}H_{20}ClN_2O_5S$ 531.0781, found 531.0540.

(*E*)-3-(4-Nitrobenzylidene)-2-(4-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**19**)

Yellow crystalline solid, yield 81.9%, purity of 98.5%, mp 224-226 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.55 (s, 1H), 7.09-7.12 (m, 2H), 7.22-7.26 (m, 2H), 7.27-7.29 (m, 2H), 7.29-7.32 (m, 2H), 7.33-7.36 (m, 3H), 7.54 (tt, *J* 1.25, 7.50 Hz, 1H), 7.59 (ddd, *J* 1.68, 7.35, 8.18 Hz, 1H), 7.63 (s, 1H), 7.71 (dd, *J* 1.00, 8.20 Hz, 1H), 7.90 (dd, *J* 1.60, 7.75 Hz, 1H), 8.27-8.29 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.4, 124.3, 127.2, 127.7, 127.9, 128.2, 128.4, 128.9, 129.1, 129.4, 130.5, 133.3, 133.6, 134.9, 135.3, 137.3, 138.8, 139.6, 148.3, 181.9; IR (ATR) ν / cm^{-1} 1673 (m), 1602 (m), 1480 (w), 1354 (s), 1298 (m), 1255 (w); HRMS calculated for $C_{28}H_{29}ClN_2O_5SNa$ 553.0601, found 553.0601.

(*E*)-3-(4-Bromobenzylidene)-2-(4-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**20**)

Pale yellow crystalline solid, yield 76.1%, purity of 98.2%, mp 202-204 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.57 (s, 1H), 7.00-7.03 (m, 2H), 7.10-7.12 (m, 2H), 7.19-7.23 (m, 2H), 7.24-7.27 (m, 2H), 7.31 (dt, *J* 1.13, 7.59 Hz, 1H), 7.34-7.37 (m, 2H), 7.50 (tt, *J* 1.21, 7.48 Hz, 1H), 7.53 (s, 1H), 7.54-7.58 (m, 3H), 7.71 (dd, *J* 0.80, 8.20 Hz, 1H), 7.88 (dd, *J* 1.58, 7.78 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.5, 125.2, 127.2, 127.5, 128.1, 128.1, 128.4, 129.0, 129.0, 129.3, 130.7, 131.4, 132.3,

132.5, 133.4, 134.6, 134.9, 135.6, 137.3, 138.7, 139.3, 182.3; IR (ATR) ν / cm^{-1} 1674 (m), 1608 (m), 1487 (m), 1359 (m), 1304 (m), 1237 (m); HRMS calculated for $C_{28}H_{19}BrClNO_3SNa$ 585.9855, found 585.9952.

(*E*)-3-(4-Chlorobenzylidene)-2-(4-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**21**)

Pale yellow crystalline solid, yield 75.9%, purity of 99.3%, mp 192-195 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.58 (s, 1H), 7.07-7.10 (m, 2H), 7.10-7.12 (m, 2H), 7.19-7.23 (m, 2H), 7.24-7.27 (m, 2H), 7.31 (ddd, *J* 1.14, 7.36, 7.79 Hz, 1H), 7.34-7.37 (m, 2H), 7.38-7.41 (m, 2H), 7.50 (tt, *J* 1.60, 7.80 Hz, 1H), 7.56 (s, 1H), 7.56 (ddd, *J* 1.68, 7.35, 8.18 Hz, 1H), 7.71 (dd, *J* 0.93, 8.18 Hz, 1H), 7.88 (dd, *J* 1.60, 7.80 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.4, 127.2, 127.5, 128.0, 128.1, 128.3, 129.0, 129.0, 129.3, 129.6, 130.6, 131.2, 131.9, 133.4, 134.6, 134.8, 135.6, 136.7, 137.3, 138.7, 139.2, 182.3; IR (ATR) ν / cm^{-1} 1675 (m), 1609 (m), 1475 (w), 1358 (m), 1302 (m), 1237 (m); HRMS calculated for $C_{28}H_{20}Cl_2NO_3S$ 520.0541, found 520.0569.

(*E*)-3-(3-Nitrobenzylidene)-2-(4-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**22**)

Pale yellow to white crystalline solid, yield 93.3%, purity of 98.4%, mp 206-208 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.47 (s, 1H), 7.08-7.11 (m, 2H), 7.24-7.28 (m, 2H), 7.28-7.30 (m, 2H), 7.34 (ddd, *J* 1.11, 7.41, 7.74 Hz, 1H), 7.36-7.38 (m, 1H), 7.43-7.45 (m, 2H), 7.55-7.61 (m, 3H), 7.62 (s, 1H), 7.70 (dd, *J* 1.03, 8.18 Hz, 1H), 7.91 (dd, *J* 1.62, 7.83 Hz, 1H), 8.03 (t, *J* 1.32 Hz, 1H), 8.30 (ddd, *J* 0.84, 2.21, 8.24 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.4, 123.1, 124.6, 125.1, 127.2, 127.7, 127.9, 128.2, 128.4, 129.1, 129.2, 130.4, 132.4, 132.8, 133.7, 134.2, 135.1, 135.2, 135.9, 137.3, 137.4, 138.8, 148.5, 182.0; IR (ATR) ν / cm^{-1} 1675 (m), 1599 (m), 1478 (w), 1353 (s), 1305 (w), 1236 (m); HRMS calculated for $C_{28}H_{20}BrN_2O_5S$ 575.0276, found 575.0129.

(*E*)-3-(4-Nitrobenzylidene)-2-(4-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**23**)

Pale yellow crystalline solid, yield 93.5%, purity of 98.3%, mp 229-231 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.53 (s, 1H), 7.10-7.12 (m, 2H), 7.23-7.27 (m, 2H), 7.28-7.32 (m, 4H), 7.33 (dd, *J* 1.08, 7.59 Hz, 1H), 7.43-7.46 (m, 2H), 7.54 (tt, *J* 1.16, 7.45 Hz, 1H), 7.59 (ddd, *J* 1.66, 7.36, 8.14 Hz, 1H), 7.64 (s, 1H), 7.72 (dd, *J* 0.73, 8.08 Hz, 1H), 7.90 (dd, *J* 1.55, 7.85 Hz, 1H), 8.27-8.30 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.4, 123.1, 124.3, 127.2, 127.7, 127.9, 128.2, 128.4, 129.1, 129.2, 130.5, 132.4, 133.2, 133.6, 135.3, 135.8, 137.3, 137.4, 138.8, 139.6, 148.3, 181.9; IR (ATR) ν / cm^{-1} 1677 (m), 1598 (m), 1485 (m), 1347 (s), 1301 (m), 1238 (m); HRMS calculated for $C_{28}H_{20}BrN_2O_5S$ 575.0276, found 575.0358.

(*E*)-3-(4-Bromobenzylidene)-2-(4-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**24**)

Pale yellow crystalline solid, yield 82.5%, purity of 98.9%, mp 205-206 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.55 (s, 1H), 7.00-7.03 (m, 2H), 7.10-7.12 (m, 2H), 7.19-7.23 (m, 2H), 7.27-7.30 (m, 2H), 7.31 (ddd, *J* 1.09, 7.44, 7.74 Hz, 1H), 7.40-7.43 (m, 2H), 7.50 (tt, *J* 1.23, 7.48 Hz, 1H), 7.53 (s, 1H), 7.54-7.58 (m, 3H), 7.71 (dd, *J* 0.95, 8.20 Hz, 1H), 7.88 (dd, *J* 1.55, 7.80 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.5, 122.8, 125.2, 127.2, 127.5, 128.1, 128.1, 128.4, 129.0, 129.3, 130.6, 131.4, 132.2, 132.3, 132.5, 133.4, 134.9, 136.1, 137.3, 138.7, 139.3, 182.3; IR (ATR) ν / cm^{-1} 1674 (m), 1608 (m), 1484 (m), 1359 (m), 1302 (m), 1236 (m); HRMS calculated for $C_{28}H_{20}Br_2NO_3S$ 607.9531, found 607.9590.

(*E*)-3-(4-Chlorobenzylidene)-2-(4-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**25**)

Pale yellow crystalline solid, yield 78.6%, purity of 97.8%, mp 198-200 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.56 (s, 1H), 7.07-7.10 (m, 2H), 7.10-7.12 (m, 2H), 7.19-7.23 (m, 2H), 7.28-7.31 (m, 2H), 7.31 (dt, *J* 1.10, 7.55 Hz, 1H), 7.38-7.43 (m, 4H), 7.50 (tt, *J* 1.25, 7.46 Hz, 1H), 7.56 (s, 1H), 7.54-7.58 (m, 1H), 7.71 (dd, *J* 0.78, 8.18 Hz, 1H), 7.88 (dd, *J* 1.60, 7.80 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.5, 122.8, 127.2, 127.5, 128.1, 128.1, 128.3, 129.0, 129.3, 129.6, 130.5, 131.2, 131.9, 132.2, 133.4, 134.9, 136.1, 136.7, 137.3, 138.7, 139.3, 182.3; IR (ATR) ν / cm^{-1} 1675 (m), 1610 (m), 1485 (m), 1358 (m), 1303 (m), 1237 (m); HRMS calculated for $C_{28}H_{20}BrClNO_3S$ 564.0036, found 563.9741.

(*E*)-3-(3-Nitrobenzylidene)-2-(2-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**26**)

Pale yellow amorphous solid, yield 92.9%, purity of 98.7%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.71 (dt, *J* 1.08, 7.49 Hz, 1H), 6.81 (dd, *J* 1.60, 7.70 Hz, 1H), 6.89 (s, 1H), 6.99 (dd, *J* 0.85, 8.35 Hz, 1H), 7.13-7.16 (m, 2H), 7.24-7.30 (m, 3H), 7.36 (ddd, *J* 2.50, 5.95, 7.80 Hz, 1H), 7.47-7.50 (m, 1H), 7.50-7.54 (m, 3H), 7.54 (s, 1H), 7.58 (t, *J* 7.93 Hz, 1H), 7.93 (t, *J* 2.10 Hz, 1H), 7.96-7.98 (m, 1H), 8.25 (ddd, *J* 1.09, 2.21, 8.19 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.7, 56.1, 111.8, 120.4, 124.2, 124.4, 125.9, 127.5, 127.5, 127.7, 128.8, 129.0, 129.3, 129.4, 129.9, 130.5, 133.3, 134.6, 134.6, 135.5, 135.6, 135.8, 137.4, 139.5, 148.5, 157.4, 182.6; IR (ATR) ν / cm^{-1} 1670 (m), 1601 (m), 1489 (m), 1351 (s), 1300 (m), 1251

(m); HRMS calculated for $C_{29}H_{22}N_2O_6SNa$ 549.1096, found 549.0998.

(*E*)-3-(4-Nitrobenzylidene)-2-(2-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**27**)

Pale yellow crystalline solid, yield 88.1%, purity of 97.6%, mp 212-213 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.73 (dt, *J* 0.97, 7.51 Hz, 1H), 6.84 (dd, *J* 1.60, 7.70 Hz, 1H), 6.87 (s, 1H), 6.96 (dd, *J* 0.80, 8.35 Hz, 1H), 7.13-7.15 (m, 2H), 7.24-7.28 (m, 3H), 7.28-7.31 (m, 2H), 7.36 (ddd, *J* 2.11, 6.29, 7.81 Hz, 1H), 7.51-7.56 (m, 3H), 7.54 (s, 1H), 7.96 (dd, *J* 1.35, 7.90 Hz, 1H), 8.23-8.26 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.8, 56.3, 111.9, 120.6, 124.1, 126.0, 127.5, 127.5, 127.7, 128.8, 129.2, 129.4, 130.5, 130.7, 133.3, 134.7, 135.0, 135.6, 137.3, 139.4, 140.2, 147.9, 157.4, 182.6; IR (ATR) ν / cm^{-1} 1673 (m), 1599 (m), 1475 (w), 1349 (s), 1298 (m), 1239 (m); HRMS calculated for $C_{29}H_{23}N_2O_6S$ 527.1277, found 527.1089.

(*E*)-3-(4-Bromobenzylidene)-2-(2-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)quinolin-4(1*H*)-one (**28**)

Pale yellow crystalline solid, yield 76.9%, purity of 98.3%, mp 234-237 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.69 (dt, *J* 0.93, 7.51 Hz, 1H), 6.82 (dd, *J* 1.50, 7.60 Hz, 1H), 6.91 (s, 1H), 6.93 (dd, *J* 0.70, 8.20 Hz, 1H), 7.01-7.04 (m, 2H), 7.13-7.16 (m, 2H), 7.20-7.25 (m, 3H), 7.32 (dt, *J* 1.20, 7.48 Hz, 1H), 7.46 (s, 1H), 7.46-7.55 (m, 5H), 7.93 (dd, *J* 1.58, 7.83 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.8, 56.4, 111.9, 120.5, 124.5, 126.4, 127.3, 127.5, 127.6, 128.7, 128.8, 129.4, 129.5, 130.2, 131.6, 132.2, 132.3, 132.9, 133.1, 134.3, 137.4, 137.6, 139.4, 157.6, 183.0; IR (ATR) ν / cm^{-1} 1673 (m), 1604 (m), 1477 (vw), 1349 (m), 1298 (m), 1244 (m); HRMS calculated for $C_{29}H_{23}BrNO_4S$ 560.0531, found 560.0431.

(*E*)-3-(4-Chlorobenzylidene)-2-(2-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)quinolin-4(1*H*)-one (**29**)

Pale yellow crystalline solid, yield 78.7%, purity of 98.8%, mp 219-221 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.69 (dt, *J* 1.10, 7.54 Hz, 1H), 6.83 (dd, *J* 1.55, 7.70 Hz, 1H), 6.92 (s, 1H), 6.93 (dd, *J* 0.95, 8.35 Hz, 1H), 7.08-7.11 (m, 2H), 7.13-7.15 (m, 2H), 7.20-7.25 (m, 3H), 7.32 (ddd, *J* 1.29, 7.26, 7.71 Hz, 1H), 7.35-7.37 (m, 2H), 7.48 (s, 1H), 7.48 (tt, *J* 1.28, 7.43 Hz, 1H), 7.49 (ddd, *J* 1.59, 7.21, 8.14 Hz, 1H), 7.54 (dd, *J* 1.13, 8.13 Hz, 1H), 7.93 (dd, *J* 1.53, 7.78 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 55.8, 56.4, 111.9, 120.5, 126.4, 127.3, 127.5, 127.6, 128.7, 128.8, 129.2, 129.4, 129.5, 130.2, 131.4, 132.2, 132.5, 133.1, 134.3, 136.1, 137.5, 137.5, 139.4, 157.6, 183.0; IR (ATR) ν / cm^{-1} 1674 (m), 1603 (m), 1476 (vw), 1349 (s), 1299 (m), 1244 (m); HRMS calculated for $C_{29}H_{23}ClNO_4S$ 516.1036, found 516.0979.

(*E*)-3-(3-Nitrobenzylidene)-2-(3-nitrophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**30**)

Pale yellow amorphous solid, yield 83.8%, purity of 99.1%, mp 217-219 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.63 (s, 1H), 7.13-7.16 (m, 2H), 7.27-7.30 (m, 2H), 7.35 (ddd, *J* 1.09, 7.41, 7.79 Hz, 1H), 7.40-7.43 (m, 1H), 7.55 (t, *J* 7.95 Hz, 1H), 7.57-7.60 (m, 1H), 7.60 (ddd, *J* 1.65, 7.47, 8.18 Hz, 1H), 7.62 (t, *J* 7.98 Hz, 1H), 7.72 (s, 1H), 7.75 (dd, *J* 0.95, 8.20 Hz, 1H), 7.84 (tdd, *J* 0.94, 1.89, 7.79 Hz, 1H), 7.93 (dd, *J* 1.58, 7.83 Hz, 1H), 8.03 (t, *J* 1.98 Hz, 1H), 8.16 (dddd, *J* 0.70, 1.05, 2.23, 8.20 Hz, 1H), 8.21 (t, *J* 2.48 Hz, 1H), 8.31 (ddd, *J* 0.85, 2.20, 8.25 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.3, 122.3, 124.0, 124.8, 124.9, 127.2, 127.9, 127.9, 128.3, 128.4, 129.2, 130.4, 130.5, 132.1, 133.5, 133.9, 134.2, 134.9, 135.4, 137.2, 138.2, 138.6, 139.4, 148.6, 148.9, 181.4; IR (ATR) ν / cm^{-1} 1675 (m), 1604 (m), 1478 (w), 1359 (m), 1305 (m); HRMS calculated for $C_{28}H_{19}N_3O_7SNa$ 564.0841, found 564.0779.

(*E*)-3-(4-Nitrobenzylidene)-2-(3-nitrophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**31**)

Pale yellow crystalline solid, yield 85.9%, purity of 98.9%, mp 235-237 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.69 (s, 1H), 7.12-7.15 (m, 2H), 7.25-7.29 (m, 2H), 7.33-7.37 (m, 3H), 7.54-7.59 (m, 2H), 7.61 (ddd, *J* 1.69, 7.34, 8.16 Hz, 1H), 7.73 (s, 1H), 7.77 (dd, *J* 0.73, 8.18 Hz, 1H), 7.83 (tdd, *J* 0.96, 1.93, 7.80 Hz, 1H), 7.91 (dd, *J* 1.43, 7.73 Hz, 1H), 8.15-8.17 (m, 1H), 8.22 (t, *J* 2.55 Hz, 1H), 8.29-8.32 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.2, 122.2, 124.1, 124.5, 127.2, 127.8, 128.0, 128.3, 128.4, 129.2, 130.4, 130.4, 132.4, 133.4, 133.8, 135.5, 137.0, 138.2, 138.5, 139.1, 139.3, 148.4, 148.8, 181.4; IR (ATR) ν / cm^{-1} 1682 (m), 1599 (m), 1475 (w), 1345 (s), 1301 (m), 1240 (m); HRMS calculated for $C_{28}H_{19}N_3O_7SNa$ 564.0841, found 564.0804.

(*E*)-3-(4-Bromobenzylidene)-2-(3-nitrophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**32**)

Pale yellow amorphous solid, yield 73.7%, purity of 98.9%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.71 (s, 1H), 7.02-7.06 (m, 2H), 7.12-7.15 (m, 2H), 7.22-7.26 (m, 2H), 7.33 (dt, *J* 1.08, 7.59 Hz, 1H), 7.50-7.55 (m, 2H), 7.58 (ddd, *J* 1.66, 7.39, 8.14 Hz, 1H), 7.57-7.60 (m, 2H), 7.63 (s, 1H), 7.76 (dd, *J* 0.75, 8.20 Hz, 1H), 7.81 (tdd, *J* 0.96, 1.91, 7.84 Hz, 1H), 7.89 (dd, *J* 1.50, 7.80 Hz, 1H), 8.12-8.15 (m, 1H), 8.24 (t, *J* 2.35 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.4, 122.4, 123.8, 125.5, 127.3, 127.8, 128.1, 128.3, 128.3, 129.1, 129.8, 130.2, 131.3, 132.1, 132.7,

133.5, 133.7, 135.1, 137.0, 138.4, 139.5, 140.2, 148.8, 181.7; IR (ATR) ν / cm^{-1} 1677 (m), 1606 (m), 1478 (w), 1349 (s), 1301 (m), 1240 (m); HRMS calculated for $C_{28}H_{20}BrN_2O_5S$ 575.0276, found 575.0102.

(*E*)-3-(4-Chlorobenzylidene)-2-(3-nitrophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**33**)

Pale yellow amorphous solid, yield 73.1%, purity of 99.1%, mp 207-210 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.72 (s, 1H), 7.10-7.13 (m, 2H), 7.13-7.16 (m, 2H), 7.21-7.25 (m, 2H), 7.32 (dt, *J* 1.05, 7.59 Hz, 1H), 7.41-7.43 (m, 2H), 7.49-7.54 (m, 2H), 7.57 (ddd, *J* 1.66, 7.41, 8.11 Hz, 1H), 7.65 (s, 1H), 7.76 (dd, *J* 0.63, 8.18 Hz, 1H), 7.81 (tdd, *J* 0.95, 1.90, 7.85 Hz, 1H), 7.89 (dd, *J* 1.60, 7.85 Hz, 1H), 8.11-8.14 (m, 1H), 8.24 (t, *J* 2.53 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 59.3, 122.4, 123.8, 127.3, 127.8, 128.1, 128.2, 128.3, 129.1, 129.7, 129.7, 130.2, 131.2, 131.7, 133.5, 133.6, 135.1, 137.0, 137.1, 138.4, 139.5, 140.1, 148.8, 181.7; IR (ATR) ν / cm^{-1} 1674 (m), 1605 (m), 1478 (w), 1348 (s), 1302 (m), 1238 (m); HRMS calculated for $C_{28}H_{20}ClN_2O_5S$ 531.0781, found 531.0619.

(*E*)-3-(3-Nitrobenzylidene)-2-(2-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**34**)

Pale yellow to white amorphous solid, yield 79.4%, purity of 98.5%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.74 (dd, *J* 1.53, 7.83 Hz, 1H), 6.86 (s, 1H), 7.01 (dt, *J* 1.32, 7.63 Hz, 1H), 7.11-7.14 (m, 2H), 7.14 (ddd, *J* 1.60, 7.43, 7.83 Hz, 1H), 7.27-7.31 (m, 2H), 7.38 (ddd, *J* 1.51, 7.06, 7.76 Hz, 1H), 7.44 (tdd, *J* 0.85, 1.70, 7.70 Hz, 1H), 7.51 (ddd, *J* 0.45, 1.50, 8.05 Hz, 1H), 7.53-7.58 (m, 2H), 7.63 (t, *J* 7.98 Hz, 2H), 7.66 (s, 1H), 7.74 (dd, *J* 1.28, 7.98 Hz, 1H), 7.91 (ddd, *J* 0.50, 1.58, 7.78 Hz, 1H), 7.99 (t, *J* 1.98 Hz, 1H), 8.29 (ddd, *J* 0.90, 2.20, 8.23 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 60.8, 124.6, 124.7, 124.9, 127.3, 127.8, 128.1, 128.2, 128.7, 129.4, 130.1, 130.1, 130.4, 130.6, 133.7, 133.9, 134.8, 134.9, 135.0, 135.2, 136.2, 136.4, 137.1, 139.1, 148.7, 182.2; IR (ATR) ν / cm^{-1} 1672 (m), 1599 (m), 1471 (m), 1351 (s), 1294 (m), 1242 (m); HRMS calculated for $C_{28}H_{20}BrN_2O_5S$ 575.0276, found 575.0015.

(*E*)-3-(4-Nitrobenzylidene)-2-(2-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**35**)

Pale yellow crystalline solid, yield 69.7%, purity of 99.7%, mp 207-209 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.74 (dd, *J* 1.58, 7.88 Hz, 1H), 6.90 (s, 1H), 7.01 (dt, *J* 1.30, 7.60 Hz, 1H), 7.11-7.14 (m, 2H), 7.14 (dt, *J* 1.63, 7.73 Hz, 1H), 7.25-7.29 (m, 2H), 7.31-7.34 (m, 2H), 7.37 (ddd, *J* 1.51, 7.06, 7.74 Hz, 1H), 7.51 (ddd, *J* 0.55, 1.53, 8.08 Hz, 1H), 7.52-7.56 (m, 2H), 7.66 (s, 1H), 7.72 (dd, *J* 1.33, 7.98 Hz, 1H), 7.90 (ddd, *J* 0.51, 1.59, 7.76 Hz, 1H), 8.28-8.31 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 60.7, 124.4, 124.8, 127.4, 127.8, 128.1, 128.2, 128.6, 129.3, 130.0, 130.1, 130.5, 130.6, 133.6, 134.4, 134.9, 135.0, 136.2, 136.4, 137.1, 139.1, 139.8, 148.3, 182.2; IR (ATR) ν / cm^{-1} 1677 (m), 1596 (m), 1471 (m), 1343 (s), 1295 (m), 1239 (m); HRMS calculated for $C_{28}H_{20}BrN_2O_5S$ 575.0276, found 575.0035.

(*E*)-3-(4-Bromobenzylidene)-2-(2-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**36**)

Pale yellow crystalline solid, yield 55.6%, purity of 98.6%, mp 219-221 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.74 (dd, *J* 1.48, 7.83 Hz, 1H), 6.91 (s, 1H), 6.98 (dt, *J* 1.23, 7.61 Hz, 1H), 7.03-7.06 (m, 2H), 7.09-7.13 (m, 3H), 7.22-7.26 (m, 2H), 7.34 (ddd, *J* 3.55, 5.05, 7.75 Hz, 1H), 7.49-7.53 (m, 3H), 7.56 (s, 1H), 7.56-7.59 (m, 2H), 7.70 (dd, *J* 1.23, 7.98 Hz, 1H), 7.86-7.89 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 60.9, 124.8, 125.1, 127.2, 127.6, 128.0, 128.1, 128.5, 129.3, 130.2, 130.3, 130.3, 131.4, 131.5, 132.5, 132.6, 133.5, 134.7, 134.8, 136.4, 136.4, 139.0, 139.1, 182.6; IR (ATR) ν / cm^{-1} 1675 (m), 1605 (m), 1474 (w), 1351 (s), 1292 (m), 1239 (m); HRMS calculated for $C_{28}H_{20}Br_2NO_3S$ 607.9531, found 607.9454.

(*E*)-3-(4-Chlorobenzylidene)-2-(2-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**37**)

Pale yellow crystalline solid, yield 47.1%, purity of 98.8%, mp 204-205 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.75 (dd, *J* 1.75, 7.85 Hz, 1H), 6.91 (s, 1H), 6.98 (dt, *J* 1.48, 7.60 Hz, 1H), 7.09-7.13 (m, 5H), 7.22-7.26 (m, 2H), 7.34 (ddd, *J* 3.35, 5.23, 7.75 Hz, 1H), 7.40-7.43 (m, 2H), 7.49-7.53 (m, 3H), 7.59 (s, 1H), 7.70 (dd, *J* 1.38, 7.98 Hz, 1H), 7.86-7.89 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 60.9, 124.8, 127.2, 127.6, 128.0, 128.1, 128.5, 129.3, 129.6, 130.2, 130.3, 130.3, 131.3, 131.4, 132.0, 133.5, 134.7, 134.8, 136.4, 136.7, 139.0, 139.1, 182.6; IR (ATR) ν / cm^{-1} 1676 (m), 1605 (m), 1474 (w), 1351 (s), 1293 (m), 1239 (m); HRMS calculated for $C_{28}H_{19}BrClNO_3SNa$ 585.9855, found 585.9566.

(*E*)-3-(3-Nitrobenzylidene)-2-(2-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**38**)

Pale yellow to white amorphous solid, yield 81.7%, purity of 98.9%, mp 224-226 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.76 (dd, *J* 1.68, 7.83 Hz, 1H), 6.91 (s, 1H), 6.98 (dt, *J* 1.40, 7.65 Hz, 1H), 7.12-7.14 (m, 2H), 7.24 (dt, *J* 1.52, 7.75 Hz, 1H), 7.28-7.32 (m, 2H), 7.38 (ddd, *J* 1.76, 6.76, 7.76 Hz, 1H), 7.42 (tdd, *J* 0.85, 1.70, 7.70 Hz, 1H), 7.51-7.58 (m, 4H), 7.63 (t, *J* 8.08 Hz, 1H), 7.64 (s, 1H), 7.93 (dd, *J* 1.40, 7.70 Hz, 1H), 7.97 (t, *J* 2.00 Hz, 1H), 8.29 (ddd, *J* 0.94, 2.19, 8.14 Hz, 1H); ^{13}C NMR (125.76 MHz,

$CDCl_3$) δ 58.6, 124.6, 124.6, 126.8, 127.8, 127.9, 128.1, 128.7, 129.3, 129.8, 129.8, 130.3, 130.4, 131.4, 133.7, 133.7, 134.8, 135.0, 135.2, 136.6, 137.1, 139.1, 148.6, 182.2; IR (ATR) ν / cm^{-1} 1670 (m), 1609 (m), 1474 (w), 1352 (s), 1295 (m), 1245 (m); HRMS calculated for $C_{28}H_{20}ClN_2O_5S$ 531.0781, found 531.0478.

(*E*)-3-(4-Nitrobenzylidene)-2-(2-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**39**)

Pale yellow amorphous solid, yield 79.5%, purity of 97.1%, mp 216-219 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.76 (dd, *J* 1.55, 7.85 Hz, 1H), 6.94 (s, 1H), 6.98 (td, *J* 1.28, 7.64 Hz, 1H), 7.12-7.14 (m, 2H), 7.23 (ddd, *J* 1.59, 7.49, 7.96 Hz, 1H), 7.26-7.32 (m, 4H), 7.37 (ddd, *J* 1.91, 6.66, 7.74 Hz, 1H), 7.51-7.57 (m, 4H), 7.65 (s, 1H), 7.92 (ddd, *J* 0.55, 1.50, 7.78 Hz, 1H), 8.27-8.30 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 58.5, 124.3, 126.8, 127.8, 127.9, 128.1, 128.7, 129.2, 129.7, 129.8, 130.4, 131.3, 133.6, 134.2, 134.8, 134.9, 135.1, 136.6, 137.1, 139.1, 139.8, 148.3, 182.2; IR (ATR) ν / cm^{-1} 1679 (m), 1597 (m), 1474 (w), 1340 (s), 1295 (m), 1244 (m); HRMS calculated for $C_{28}H_{19}ClN_2O_5SNa$ 553.0601, found 553.0431.

(*E*)-3-(4-Bromobenzylidene)-2-(2-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**40**)

Pale yellow crystalline solid, yield 64.8%, purity of 98.3%, mp 229-231 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.76 (dd, *J* 1.58, 7.83 Hz, 1H), 6.94 (dt, *J* 1.32, 7.61 Hz, 1H), 6.95 (s, 1H), 7.01-7.04 (m, 2H), 7.10-7.13 (m, 2H), 7.20 (dt, *J* 1.55, 7.73 Hz, 1H), 7.23-7.26 (m, 2H), 7.35 (ddd, *J* 2.60, 5.98, 7.75 Hz, 1H), 7.48-7.54 (m, 4H), 7.55 (s, 1H), 7.56-7.58 (m, 2H), 7.88-7.91 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 58.7, 125.1, 126.7, 127.7, 127.9, 128.6, 129.2, 129.9, 130.0, 130.2, 131.2, 131.4, 132.5, 132.5, 133.4, 134.7, 134.9, 135.0, 136.6, 139.0, 139.1, 182.6; IR (ATR) ν / cm^{-1} 1674 (m), 1603 (m), 1474 (w), 1358 (m), 1294 (m), 1238 (m); HRMS calculated for $C_{28}H_{20}BrClNO_3S$ 564.0036, found 563.9567.

(*E*)-3-(4-Chlorobenzylidene)-2-(2-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1*H*)-one (**41**)

Pale yellow crystalline solid, yield 57.6%, purity of 99.2%, mp 226-228 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.76 (dd, *J* 1.35, 7.75 Hz, 1H), 6.95 (dt, *J* 1.30, 7.58 Hz, 1H), 6.96 (s, 1H), 7.08-7.11 (m, 2H), 7.11-7.13 (m, 2H), 7.20 (ddd, *J* 1.51, 7.44, 7.96 Hz, 1H), 7.23-7.26 (m, 2H), 7.35 (ddd, *J* 2.46, 6.09, 7.76 Hz, 1H), 7.40-7.43 (m, 2H), 7.49-7.54 (m, 4H), 7.57 (s, 1H), 7.89-7.91 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 58.7, 126.7, 127.7, 128.0, 128.6, 129.2, 129.6, 129.9, 130.0, 130.2, 131.2, 131.2, 131.3, 132.1, 133.4, 134.7, 134.9, 135.0, 136.6, 136.7, 139.0, 139.0, 182.6; IR (ATR) ν / cm^{-1} 1674 (m), 1604 (m), 1474 (w), 1359 (m), 1294 (m), 1239 (m); HRMS calculated for $C_{28}H_{20}Cl_2NO_3S$ 520.0541, found 520.0458.

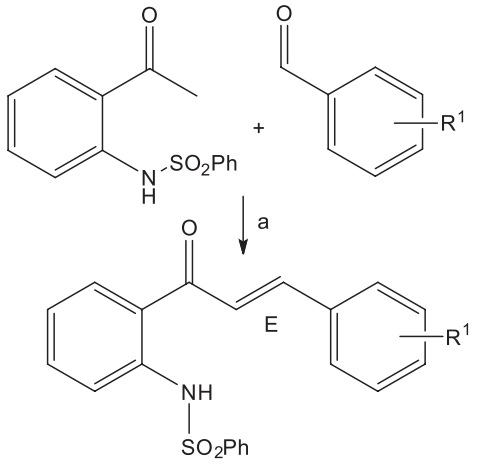
General procedure for antitumor tests

The cytotoxicity of the chalcones and chalcone-quinolinone compounds were evaluated against tumor cell line by the 3-(4,5-dimethyl-2-thiazole)-2,5-diphenyl-2-*H*-tetrazolium bromide (MTT) method. Human tumor cell line HCT-116 (colon) was used. The cells were given by the National Cancer Institute (USA) and cultured in Roswell Park Memorial Institute (RPMI) 1640 medium, supplemented with 10% fetal bovine serum and 1% antibiotic, kept in an oven at 37 °C and 5% CO_2 atmosphere. The samples were diluted in pure sterile dimethyl sulfoxide (DMSO) and were tested in a single concentration of 25 μg mL^{-1}. Tumor cells were plated at 0.7×10^5 cells mL^{-1} for HCT-116 lineage. After 24 h of incubation to adhere to the plate, the cells were treated with the test compounds at the single concentration of 25 μg mL^{-1} and incubated for 72 h in a 5% CO_2 oven at 37 °C. After this time, they were centrifuged, and the supernatant removed. Then 150 μL of 1% MTT solution (tetrazolium salt) was added, and the plates were incubated for 3 h. The absorbance was read after dissolution of the precipitate with 150 μL of pure DMSO in a plate spectrophotometer at 595 nm. The statistical analysis of the experiments was performed according to the mean and standard error of the mean (SEM) of the percentage of cell growth inhibition, using the program GraphPad Prism.[35] Compounds which showed a percentage of inhibition of tumor cell growth greater than 75% in the tumor line tested were tested again by serial dilution (dilution factor = 2), starting from the highest 25 μg mL^{-1} concentration for determination of concentration capable of inhibiting 50% of cell proliferation (IC_{50}). The experiments were analyzed by a non-linear regression curve for the calculation of IC_{50} using the GraphPad Prism program.[35] Doxorubicin was used as a positive control.[36]

Results and Discussion

Synthesis of chalcones **2** to **9**

2'*N*-Phenylsulfonyl-acetophenone (**1**) was synthesized by reaction between benzenesulfonyl chloride and 2-aminoacetophenone in dichloromethane.[29] After, eight 2'*N*-sulfonamide chalcones were synthesized (**2** to **9**) by Claisen-Schmidt condensation between the intermediate **1** and benzaldehyde derivative via basic catalysis in ethanolic medium,[29] as shown in Scheme 1.



2: R^1 = *o*-OCH_3 **6:** R^1 = *o*-Cl
3: R^1 = *o*-Br **7:** R^1 = *p*-Cl
4: R^1 = *p*-OCH_2CH_3 **8:** R^1 = *m*-NO_2
5: R^1 = *p*-OCH_3 **9:** R^1 = *p*-Br

Scheme 1. Claisen-Schmidt condensation for the synthesis of the chalcones **2** to **9**. (a) Ethanol, cat. KOH, room temperature.

The ^{1}H NMR spectra of compounds **2** to **9** show the presence of two doublets in the region between δ 7.18 and 8.06, with coupling constant of 15.5 Hz, which demonstrates the presence of a *trans* α-β carbonyl group. The singlet signals observed near δ 11.3, a chemical shift typical for sulfonamide hydrogens, corroborate the amino sulfonyl linkage. Intramolecular hydrogen bonding between carbonyl and NH groups, forming a six-member ring, justify this high chemical shift. Figure 2 highlights these assignments for compound **4**.

Synthesis of chalcone-quinolinone

One option for obtaining the target compounds might be synthesize a quinolinone compound, as those at upper right of Scheme 3, and react it by Claisen-Schimdt condensation with a second specie of aldehyde. The synthesis of such compound were made as described by Zheng *et al*.[37] However, the synthesis of the final product starting from these quinolinones, previously synthesized and purified, was not convenient, since in the homogenous basic ethanolic medium the quinolinone readily converted to the respective precursor chalcone after dissolution, with the reaction soon reaching a balance more favorable to chalcone. The synthesis of chalcone-quinolinones was then performed by reacting chalcone sufonamide (**2** to **9**) in a basic reaction medium with an aromatic aldehyde, with a configuration of ligands different from the aldehyde that led to the configuration of the ring B as shown on Scheme 2. The substitution on ring C would correspond to the substitution pattern of the second aldehyde. Scheme 2 shows the general conditions used to obtain the compounds from **10** to **41**.

The yields of the reactions were from 45 to 94%. Scheme 3 shows the proposed reaction mechanism that justifies obtaining the products. The sulfonamide nitrogen is added to the β-carbon of the α-β unsaturated ketone of the chalcone (conjugated addition). Two mechanism hypotheses can justify this step: the first supposes that the hydrogen of the sulfonamide is abstracted, and the nitrogen, with partial negative charge, is added to the β carbon; the second presumes that the nitrogen attacks the β-carbon directly, resulting in a nitrogen with four ligands, and therefore with partial positive charge, which then has the proton abstracted by the available hydroxide. Scheme 3 illustrates the first hypothesis. Subsequently, the enolate ion attacks the aldehyde and form a β-hydroxyketone. Finally, dehydration is favored by the conjugate system that can be formed.

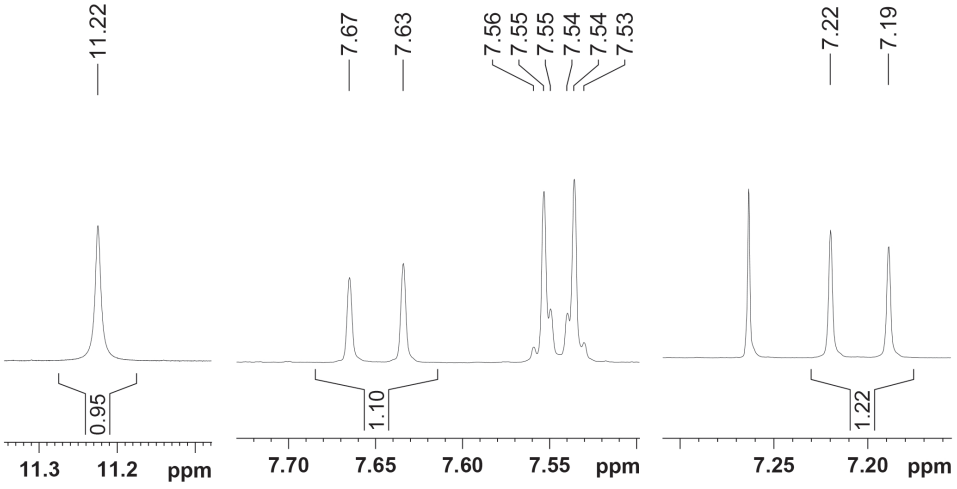
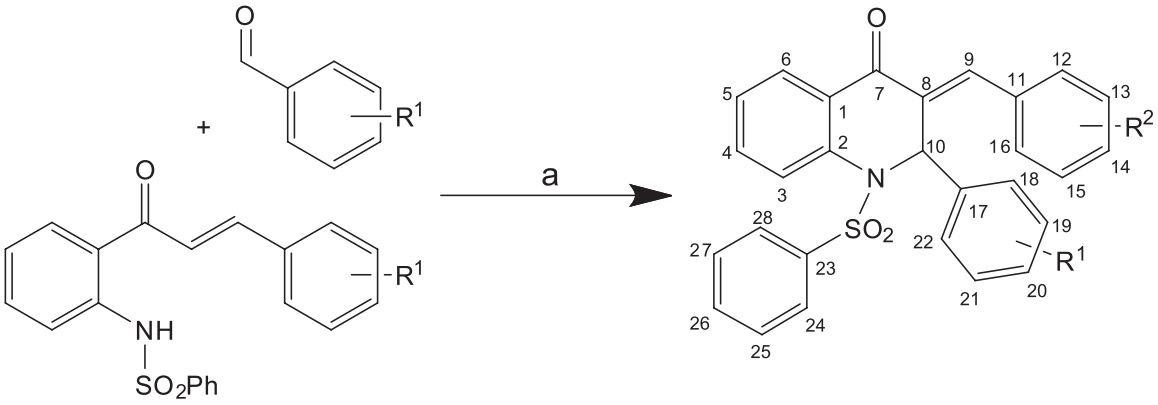


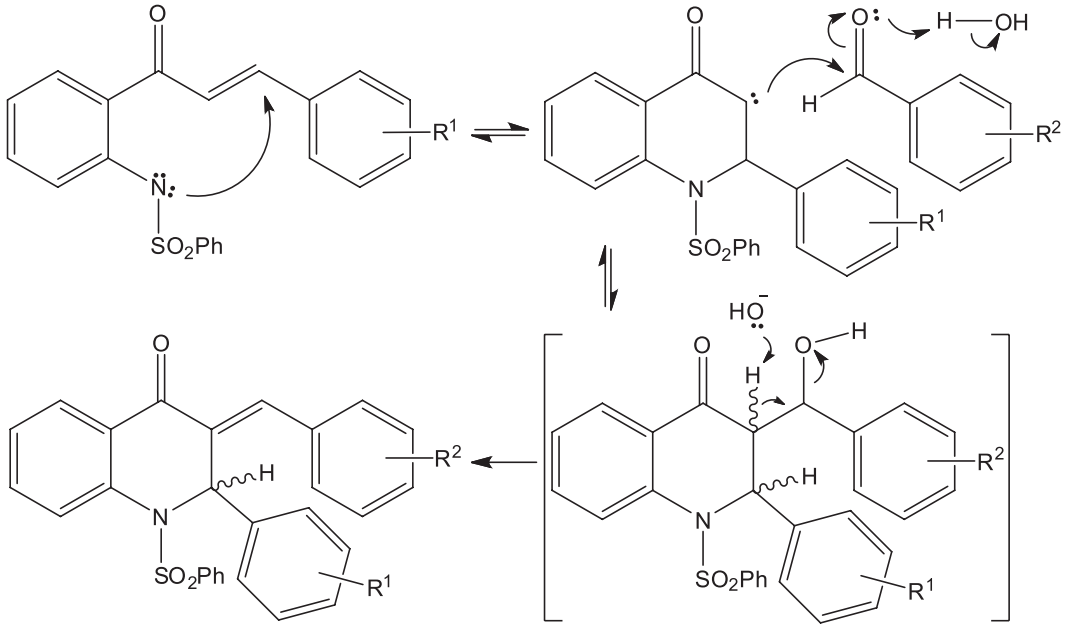
Figure 2. ^{1}H NMR spectrum for compound **4** (500 MHz, $CDCl_3$), highlighting the sulfonamide hydrogen (δ 11.2 ppm) and the doublets associated to *trans* α-β carbonyl group.



Chalcone-quinolinone hybrids:

10: R^1 = *p*-OC_2H_5; R^2 = *m*-NO_2
11: R^1 = *p*-OC_2H_5; R^2 = *p*-NO_2
12: R^1 = *p*-OC_2H_5; R^2 = *p*-Br
13: R^1 = *p*-OC_2H_5; R^2 = *p*-Cl
14: R^1 = *p*-OCH_3; R^2 = *m*-NO_2
15: R^1 = *p*-OCH_3; R^2 = *p*-NO_2
16: R^1 = *p*-OCH_3; R^2 = *p*-Br
17: R^1 = *p*-OCH_3; R^2 = *p*-Cl
18: R^1 = *p*-Cl; R^2 = *m*-NO_2
19: R^1 = *p*-Cl; R^2 = *p*-NO_2
20: R^1 = *p*-Cl; R^2 = *p*-Br
21: R^1 = *p*-Cl; R^2 = *p*-Cl
22: R^1 = *p*-Br; R^2 = *m*-NO_2
23: R^1 = *p*-Br; R^2 = *p*-NO_2
24: R^1 = *p*-Br; R^2 = *p*-Br
25: R^1 = *p*-Br; R^2 = *p*-Cl
26: R^1 = *o*-OCH_3; R^2 = *m*-NO_2
27: R^1 = *o*-OCH_3; R^2 = *p*-NO_2
28: R^1 = *o*-OCH_3; R^2 = *p*-Br
29: R^1 = *o*-OCH_3; R^2 = *p*-Cl
30: R^1 = *m*-NO_2; R^2 = *m*-NO_2
31: R^1 = *m*-NO_2; R^2 = *p*-NO_2
32: R^1 = *m*-NO_2; R^2 = *p*-Br
33: R^1 = *m*-NO_2; R^2 = *p*-Cl
34: R^1 = *o*-Br; R^2 = *m*-NO_2
35: R^1 = *o*-Br; R^2 = *p*-NO_2
36: R^1 = *o*-Br; R^2 = *p*-Br
37: R^1 = *o*-Br; R^2 = *p*-Cl
38: R^1 = *o*-Cl; R^2 = *m*-NO_2
39: R^1 = *o*-Cl; R^2 = *p*-NO_2
40: R^1 = *o*-Cl; R^2 = *p*-Br
41: R^1 = *o*-Cl; R^2 = *p*-Cl

Scheme 2. Established conditions for the synthesis of chalcone-quinolinone compounds starting from chalcone sulfonamide. (a) Ethanol, cat. KOH, room temperature.



Scheme 3. Proposed mechanism that explains the achievement of products under the conditions employed.

Scheme 2 shows the numbering system of the atoms of the common nucleus of the chalcone-quinolinone compounds for purposes of the following discussion. The B and C rings were numbered so that the substituents were at the lowest-numbered carbon possible. One piece of spectroscopic evidence of the formation of compounds **10** to **41** is the existence of two singlets corresponding to the two non-aromatic β carbonyl hydrogens observed

at δ 7.46 to 7.85 (H9) and at δ 6.47 to 6.96 (H10). The nonobservance of the signal from sulfonamide hydrogens in the δ 11.3 region, observed for chalcones **2** to **9** and 2'*N*-phenylsulfonyl-acetophenone **1**, reinforce the proposed compound structure. Figure 3 highlights these signals and absence of sulfonamide hydrogen for compound **22**.

Complete assignment of the multiplets for each hydrogen on the ^{1}H and ^{13}C NMR spectra, presented in Tables S1 to S9 (Supplementary Information (SI) section), were supported by COSY, HSQC and HMBC experiments (e.g. Figures 4 to 6, for compound **22**). The most deshielded carbon signal, near to δ 181, assigned to carbonyl carbon (C7), was a good starting point to complete assignment of NMR signals. The hydrogens H6, H9 and H10 were assigned based on cross-peak with C7 in the HMBC experiment ($^{3}J_{CH}$). Moreover, the correlations of

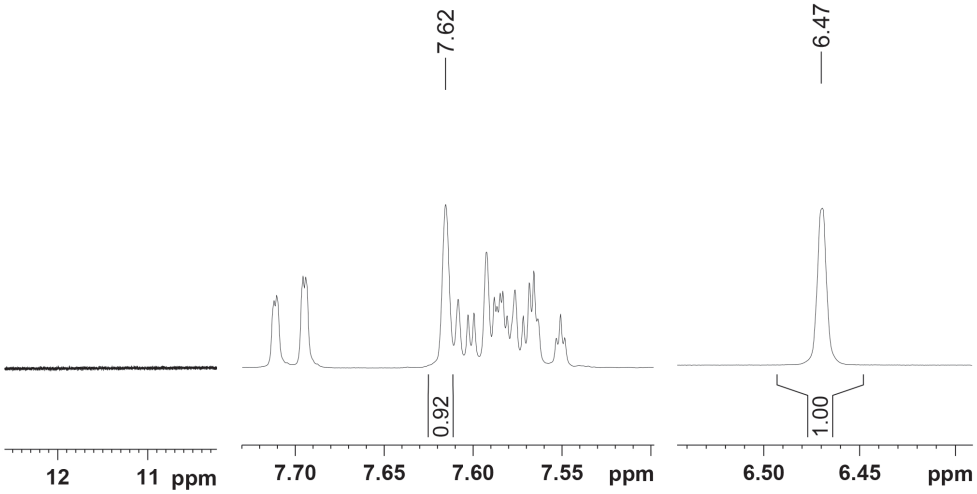


Figure 3. ^{1}H NMR spectrum for compound **22** (500 MHz, $CDCl_3$), highlighting the signals for H9 and H10, and absence of sulfonamide hydrogen in region near to δ 11.2 ppm.

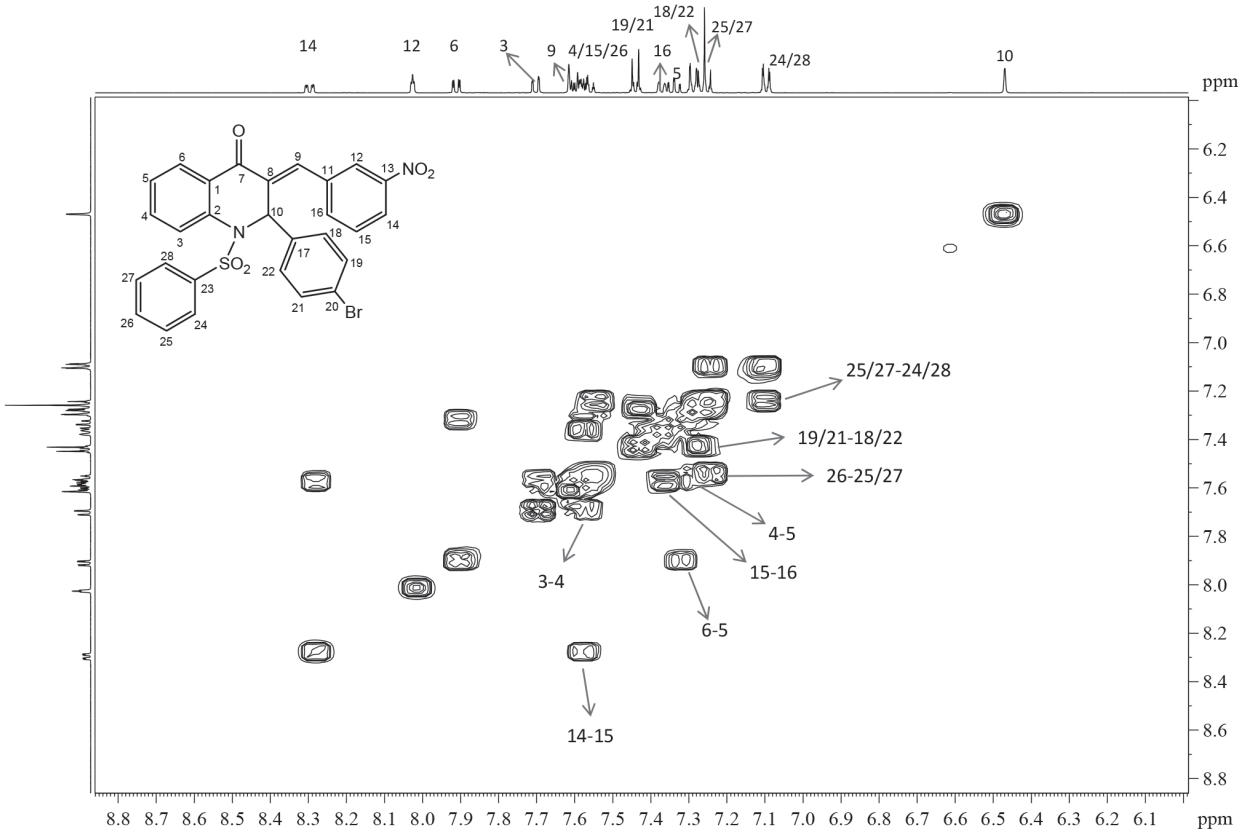


Figure 4. COSY correlation map of compound **22** (500 and 125 MHz, $CDCl_3$).

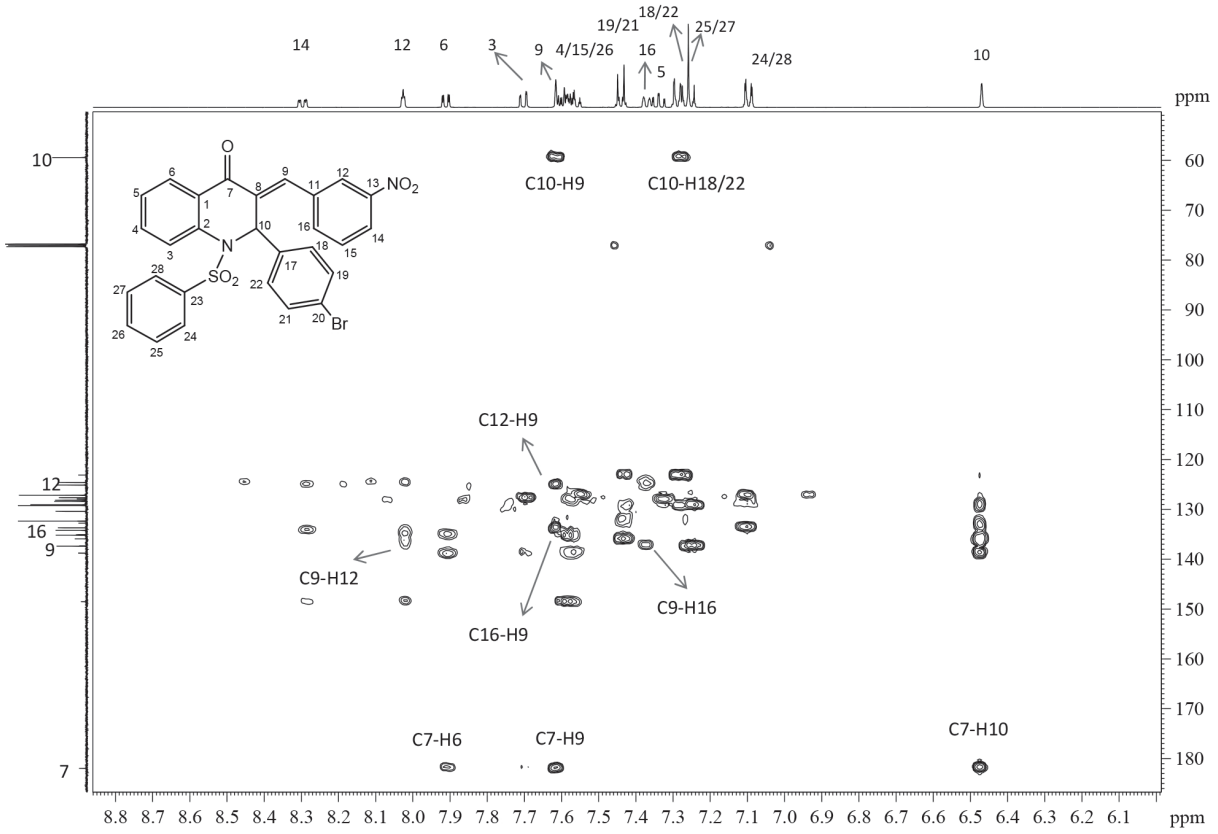


Figure 5. HMBC correlation map of compound **22** (500 and 125 MHz, $CDCl_3$).

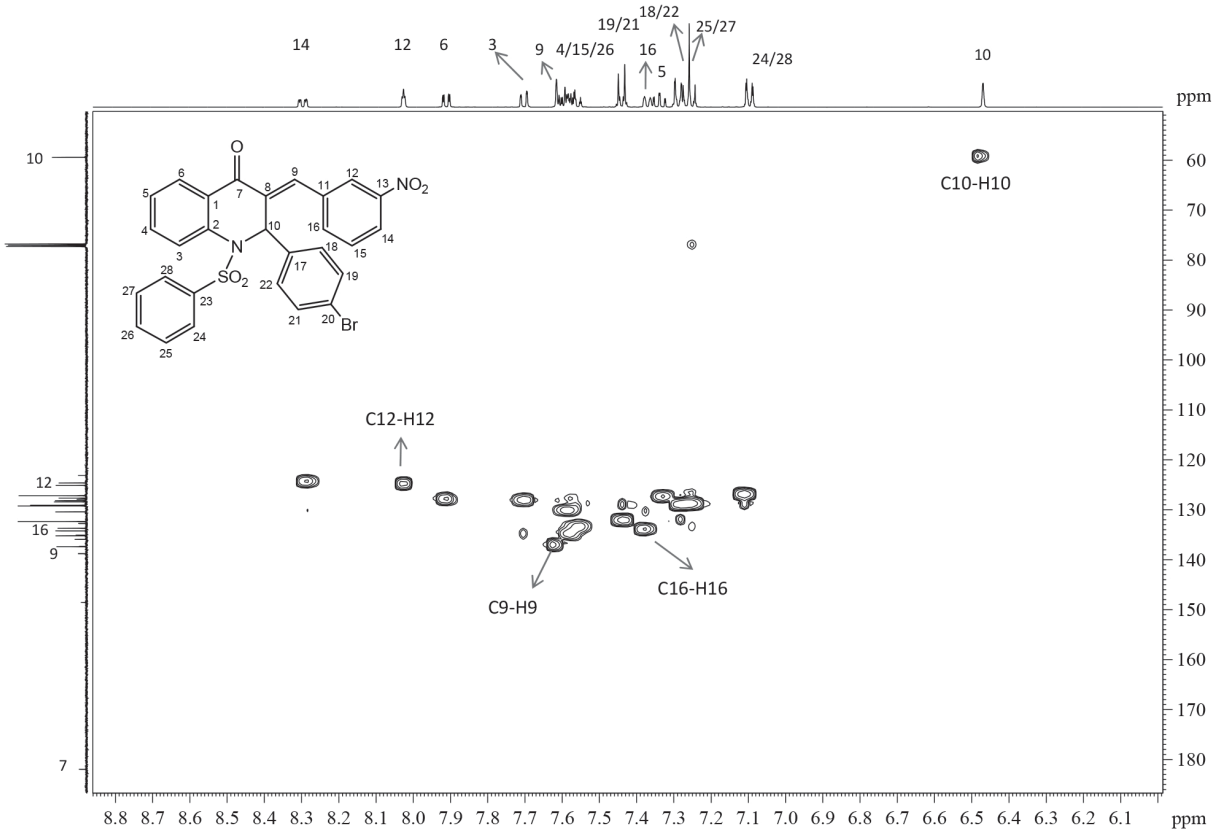


Figure 6. HSQC correlation map of compound **22** (500 and 125 MHz, $CDCl_3$).

these hydrogens with their respective carbons, by HSQC experiment ($^1J_{CH}$), enabled the assignment of the carbons C9 and C10. The H9, H18 and H22 hydrogens were assigned based on cross peak with C10 in HMBC. In the same way, H12 and H16 were attributed based on $^3J_{CH}$ with C9 in HMBC.

The H26 hydrogen was a good starting point for the assignments of aromatic H/C on the D ring. Its signal was a triple-triplet with signal area corresponding to one hydrogen and cross-peak with H25 and H27 in COSY. On the other hand, these last hydrogens present cross-peaks with H24 and H28. HSQC and HMBC experiments were used to corroborate these assignments. The same strategy was used for assignment of other aromatic hydrogens on rings A, B and C.

The complete hydrogen assignments of the ^{1}H NMR spectra for compounds **10** to **41** can be observed in Tables S1 to S8, in SI section. Table S9, also in SI section, shows the chemical shifts of C7, C9, C10, C12 and C16 carbons, important for the assignment of some hydrogens by means of the 2D experiments previously discussed. The HMBC, HSQC and COSY contour maps are also presented in the SI section.

The determination of the *E* configuration of the compounds, since these do not possess a pair of vinyl hydrogens, demanded a study of NOE (nuclear Overhauser effect) differential. In this experiment, the intense spatial interaction between H9 and H10 represents a *Z* configuration. On the other hand, an intense interaction between H10 and *ortho* hydrogens of the C ring (H12 or H16) represents *E*. Figure 7 shows the two isomers: on the left is the adaptation of the crystallography structure deposited by Kim *et al*.,[23] which has the *E* configuration (it possesses the same common nucleus as the compounds **10** to **41**, whose configuration we intend to determine); on the right it is illustrated what might be the *Z* configuration of the same compound, obtained by rotating the dihedral angle C10–C8–C9–H9 by 180°. This figure highlights how the relative distance of H10 to H9 and the distance of H10 to any hydrogen at the position 12 or 16 (H12 or H16) is expected to be different in each case (*E* or *Z* isomer). In the case of the *E* isomer, H10 is at 1.99 Å from H12/H16 (*ortho* to the C ring), and at 3.55 Å from H9. In the *Z* isomer, H10 is 2.40 Å from H9 and at least 4.49 Å from H12/H16. This last minimum value was obtained by pure geometric rotation of the C ring over the C9–C11 bond of the *Z* isomer.

The differential NOE spectra were obtained by irradiating H10. Table 1 shows the proportion of areas between the peaks related to H9, H10, the sum of H12 and H16, and the sum of H24 and H28 in the differential NOE experiments (Figure 8, for compound **22**). The sums of the signal areas of H12/H16 and H24/H28 were used because the rotational freedom presented by the aromatic ring in solution allows for an interaction between H10/H18 or H10/H22, for example. The results confirm that all compounds (**10** to **41**) were *E* isomers, since the proportion of the peak area related to H12 and/or H16 was much larger than that related to H9.

Antitumor tests

Cytotoxicity analysis by the MTT method is one of the methods used in the screening program of the National Cancer Institute of the United States (NCI), which tests more than 10,000 samples each year.[38] It is a quick, sensitive and inexpensive method. It was first described by Mosmann,[39] and has the ability to analyze the viability and the metabolic state of the cell. It is a colorimetric analysis based on the

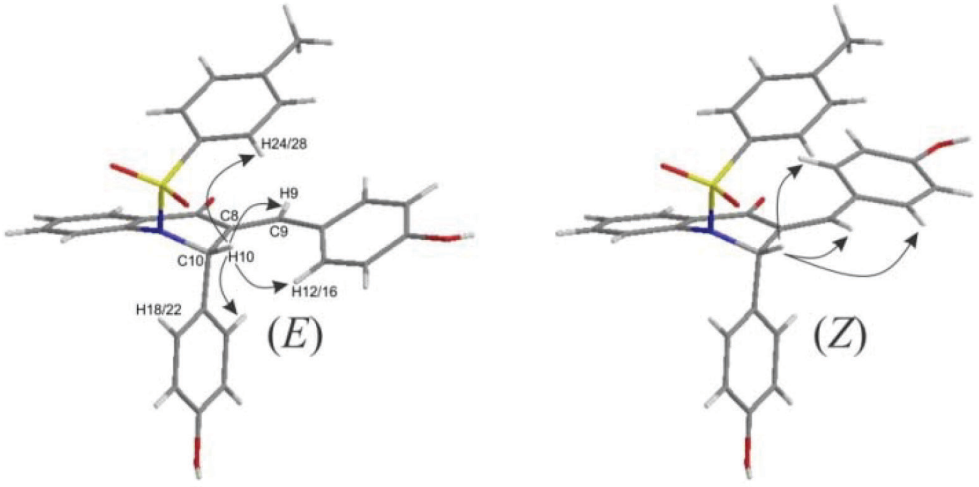


Figure 7. (Left) Adaptation of crystallographic structure deposited by Kim *et al*.,[23] (*E*) configuration; (right) (*Z*) configuration, obtained by rotating the dihedral angle C10–C8–C9–H9 by 180°.

Table 1. Signal area proportion for hydrogens 9, 12, 16, 18, 22, 24 and 28 in the NOE differential experiments of chalcone-quinolinones **10** to **41**

entry	H9	H12-16	H18-22	H24-28	entry	H9	H12-16	H18-22	H24-28
10	0.03	0.60	0.25	0.12	**26**	0.03	0.76	0.07	0.14
11	0.02	0.60	0.25	0.13	**27**	0.04	0.71	0.11	0.14
12	0.02	0.63	0.22	0.13	**28**	0.03	0.76	0.07	0.15
13	0.02	0.76[a]	0.22	–[a]	**29**	0.03	0.75	0.07	0.14
14	0.02	0.60	0.24	0.13	**30**	0.02	0.61	0.24	0.12
15	0.02	0.57	0.28	0.13	**31**	0.03	0.61	0.23	0.13
16	0.02	0.64	0.22	0.13	**32**	0.02	0.65	0.21	0.12
17	0.02	0.77[a]	0.21	–[a]	**33**	0.02	0.77[a]	0.21	–[a]
18	0.03	0.60	0.24	0.13	**34**	0.06	0.66	0.08	0.21
19	0.02	0.64	0.21	0.13	**35**	0.04	0.73	0.10	0.13
20	0.03	0.64	0.20	0.12	**36**	0.04	0.79	0.03	0.14
21	0.02	0.64	0.21	0.13	**37**	0.03	0.93[a]	0.04	–[a]
22	0.03	0.61	0.23	0.13	**38**	0.03	0.74	0.10	0.13
23	0.03	0.84[b]	–[b]	0.13	**39**	0.04	0.74	0.07	0.14
24	0.03	0.64	0.21	0.12	**40**	0.04	0.63	0.23	0.10
25	0.02	0.77[a]	0.21	–[a]	**41**	0.02	0.73[a]	0.25	–[a]

[a]The chemical shifts related to H12/H16 and H24/H28 were overlapped; [b]the chemical shifts related to H12/H16 and H18/H22 were overlapped.

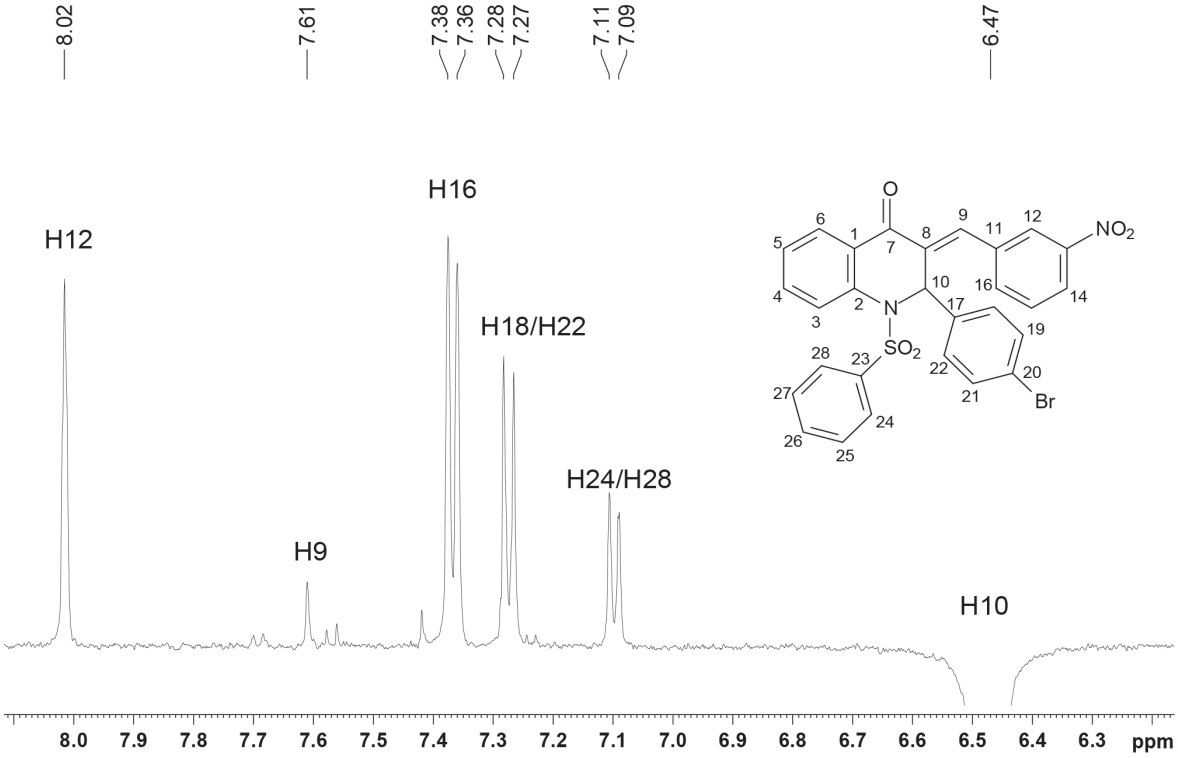


Figure 8. NOE differential spectrum for compound **22** (500 MHz, $CDCl_3$), irradiating H10.

conversion of the 3-(4,5-dimethyl-2-thiazole)-2,5-diphenyl-2-*H*-tetrazolium bromide (MTT) salt into formazan, by mitochondrial enzymes present only in metabolically active cells.[36] The cytotoxic study by the MTT method enables an easy definition of cytotoxicity, but not the mechanism of action.[40] Table 2 shows the results of cytotoxicity evaluation using chalcones, quinolinones and chalcone-quinolinones against HCT-116 (colon) human tumor cell lines.

Table 2. Percentage inhibition of tumor cell growth *in vitro* at a single concentration of 25 μg mL^{-1} against HCT-116 (colon) tumor cell line after 72 h of treatment determined by the MTT method

entry	HCT-116 / %	entry	HCT-116 / %	entry	HCT-116 / %	entry	HCT-116 / %
2	**76.2 ± 21.8**	**12**	20.4 ± 14.0	**22**	48.1 ± 3.3	**32**	72.9 ± 1.9
3	**83.6 ± 16.9**	**13**	35.4 ± 2.6	**23**	72.2 ± 0.5	**33**	68.5 ± 3.4
4	66.9 ± 3.9	**14**	3.2 ± 5.2	**24**	71.1 ± 1.0	**34**	65.3 ± 1.0
5	56.3 ± 16.7	**15**	31.5 ± 1.2	**25**	60.9 ± 2.9	**35**	42.5 ± 0.2
6	**100.0 ± 0.0**	**16**	49.8 ± 0.7	**26**	70.4 ± 0.4	**36**	33.8 ± 2.8
7	**78.8 ± 21.7**	**17**	44.7 ± 3.0	**27**	58.8 ± 1.7	**37**	46.6 ± 1.3
8	66.8 ± 0.9	**18**	53.0 ± 2.0	**28**	56.6 ± 3.8	**38**	72.8 ± 0.5
9	**100.0 ± 0.0**	**19**	56.9 ± 1.0	**29**	63.7 ± 3.0	**39**	**73.4 ± 2.4**
10	23.8 ± 0.2	**20**	69.0 ± 0.3	**30**	55.1 ± 6.0	**40**	55.5 ± 5.0
11	28.9 ± 3.3	**21**	68.2 ± 1.3	**31**	63.6 ± 3.1	**41**	66.6 ± 2.9

Among the tested compounds, only **2**, **3**, **6**, **7**, **9** and **39** (Table 2, in bold) were cytotoxic to the tumor cell line used for testing, with a percentage of inhibition of tumor cell growth greater than 75 ± 2%, and the values of IC_{50} were determined. Table 3 presents the results of the IC_{50} tests of these compounds.

Table 3. Determination of IC_{50} of synthetic chalcones, and the chalcone-quinolinone compound **39**, in tumor cell line after 72 h of treatment, as determined by the MTT method

entry	HCT-116 / (μg mL^{-1})
2	6.9 (6.2-7.7)
3	7.5 (6.8-8.3)
6	5.1 (4.8-5.4)
7	2.4 (2.1-2.6)
9	5.9 (5.2-6.9)
39	19.3 (13.7-27.2)
Doxorubicin	0.12 (0.09-0.17)

Although none of the samples tested had values close to those of the positive control, such values encourage the study of these compounds as possible candidates for anti-cancer drugs. Further studies must be done to test whether these compounds are mutagenic, and what happens in the cell cycle with the use of these compounds, among other considerations. It was not possible to identify a single trend relating the ring substitution of the chalcones **2** to **9** to the antitumor activity. In this sense, *ortho*-substituted chlorine and bromine chalcones (compounds **6** and **3**), showed, respectively, higher and lower inhibition results than the para-substituted chlorine and bromine chalcones (compounds **7** and **9**) (Table 3). In contrast, the inhibition results for *ortho*-substituted methoxy chalcone **2** was higher than the results of the *para*-substituted **5** (Table 2).

The type of chalcone moiety in chalcone-quinolinones (compounds **10** to **41**), i.e., the substitution in C ring of *m*-nitro, *p*-nitro, *p*-chlorine or *p*-bromine, did not have a demonstrable influence on the biological effect of these compounds. The average growth inhibition percentage for all the *p*-nitro, *m*-nitro, *p*-chlorine and *p*-bromine compounds were 49.1, 50.8, 51.1 and 56.2%, respectively.

The decrease in the tumor inhibition of chalcone-quinolinones relative to the precursor chalcones could be explained by the steric impediment or by the absence of the H at C8 of the α-β-unsaturated double bond, making the C9 more acid. α-β-Unsaturated compounds, such as chalcones, can be converted in conjugates with glutathione reduced (GSH) by nucleophilic attack of the sulfhydryl group by Michael reaction. This reaction leads to the reduction of GSH levels, which are related to cytotoxic effects, such as the activation of apotoses or to make the cells susceptible to oxidative damage.[32,33,39-41]

Conclusions

The results of the anti-tumor tests suggest that the classes of compounds studied have potentials for use in cancer research. The antitumor activities of the chalcone-quinolinone compounds were lower than those of the chalcone precursors. The type and orientation of the substituents in the chalcone moiety of the compounds influenced the activity of the precursor chalcones, but did not influence the activity of the chalcone-quinolinone compounds. The reaction conditions used for the synthesis of the chalcone-quinolinone compounds, focused on obtaining diferents patterns of substitution on rings B and C, allowed the formation of desired compounds in good yield, besides allowing the products of the reactions to be recovered by filtration. The synthetic procedure represents a case of

intramolecular 1-4 addition, thermodynamically induced by the subsequent formation of a conjugated system, a concept that can be adapted to circumstances in which the intermediate is not stable enough to be isolated. The second Claisen-Schmidt condensation can lead to the formation of a conjugated system, inducing the previously unfavorable cyclization. The results obtained by NMR analysis confirmed that all chalcone-quinolinone compounds were *E* isomers.

Supplementary Information

Supplementary information (^{1}H and ^{13}C NMR spectra of all compounds; complete hydrogen assignments of the ^{1}H NMR spectra for compounds **10** to **41** in Tables S1 to S8; chemical shifts of C7, C9, C10, C12 and C16 carbons in Table S9; HSQC and HMBC contour maps for compounds **2** and **10**; COSY contour map for compound **10**; spectra of NOE experiment of compouns **10** to **41**) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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