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Synthesis of novel quinoline-2-one based chalcones of potential anti-tumor activity

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ABSTRACT

Novel quinoline-2-one based chalcones were synthesized from a Claisen–Schmidt condensation by using the couple KOH/1,4-dioxane as reaction medium. A relatively stable aldol was isolated and identified as the intermediate species in the formation of the target chalcones. Nine of the obtained compounds were *in vitro* screened by the US National Cancer Institute (NCI) for their ability to inhibit 60 different human tumor cell lines. Products **16c**, **16d**, **16h** and **27** exhibited the highest activity, being compound **27** the most active, displaying remarkable activity against 50 human tumor cell lines, thirteen of them with GI_{50} values $\leq$1.0 μM, being the HCT-116 (*Colon*, GI_{50} = 0.131 μM) and LOX IMVI (*Melanoma*, GI_{50} = 0.134 μM) the most sensitive strains. Compound **27** was referred to *in vivo* acute toxicity and hollow fiber assay by the Biological Evaluation Committee of the NCI. The acute toxicity study indicated that compound **27** was well tolerated intraperitoneally (150 mg/kg/dose) by athymic nude mice. This compound may possibly be used as lead compound for developing new anticancer agents.

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1. Introduction

Cancer represents one of the most serious clinical problems in the world and its incidence is rising in developing as well as developed countries. Apart from the utility of surgical operations and irradiation, chemotherapy still remains an important option for the management of cancer [1]. Among the wide range of compounds tested as potential anticancer agents, derivatives comprising functionalities as α,β-unsaturated Michael acceptor have attracted reasonable attention. Previous evidences suggest that anticancer compounds such as alkylating agents bind directly to various cellular nucleophiles, thus lacking selectivity. Meanwhile, Michael acceptors can be structurally modified, so that they can react selectively with target nucleophiles [2]. A group of representative natural and synthetic cytotoxic compounds containing Michael acceptors are conjugated enones or enone-like compounds such as chalcones and *bis*-chalcones.

Chalcones **1** are synthetic or naturally occurring α,β-unsaturated diaryl ketones which have shown a wide spectra of biological activities, as antibacterial [3], antifungal [4], anti-tubercular [5], anti-inflammatory [6], antimalarial [7], and mainly as antitumor [8]. It has been found that their biological activities may be enhanced by the insertion of heterocyclic rings in their structures [9]. The presence of the indole ring in chalcones **2** (R, R^1, R^2 = OMe; R, R^2 = H, R^1 = $N(Me)_2$) increased significantly their anti-tumor activities [10]. Recently we found that the presence of the pyrazole ring in chalcones **3** was convenient for their anti-tumor activities displayed. Particularly substituents R = NO_2 and R^1 = Cl showed the highest activity [11] (Fig. 1).

Curcumin **4** is a naturally occurring β-diketonic yellow–orange dye isolated from the root of the *Curcuma longa Linn* (*zingiberaceae*). Its versatile biological properties as anti-inflammatory [12], antioxidant [13], antiviral [14] but mainly its chemopreventive and anti-carcinogenic activities [15], have inspired a growing number of scientist pursuing for the design, synthesis and anti-tumor studies of novel symmetric and unsymmetric curcumin mimic derivatives, based mainly in *bis*-arylideneketones. Structures **5**–**9** represent some of such examples [16] (Fig. 2). It has been postulated that the broad spectrum of anti-carcinogenic activity of curcumin and its curcuminoid relatives may be due in part to an angiogenesis inhibition mechanism [17], probably associated with their Michael acceptor character

Quinolines and their oxo-derivatives have attracted considerable interest for many years due to their presence in the skeleton of a large number of bioactive compounds and natural products [18]. Particularly the 3-substituted quinolin-2-one is an important

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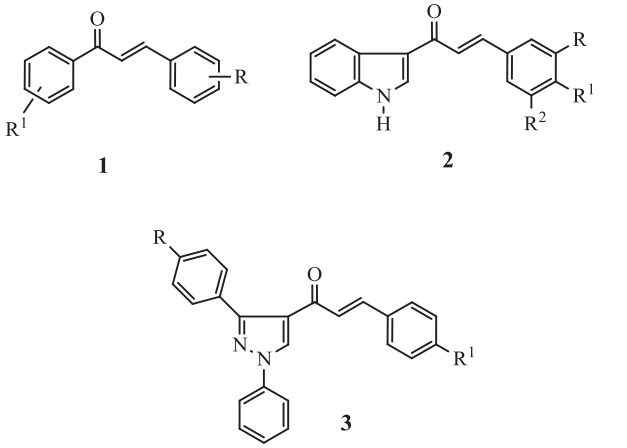


Fig. 1. Some chalcone derivatives of biological interest.

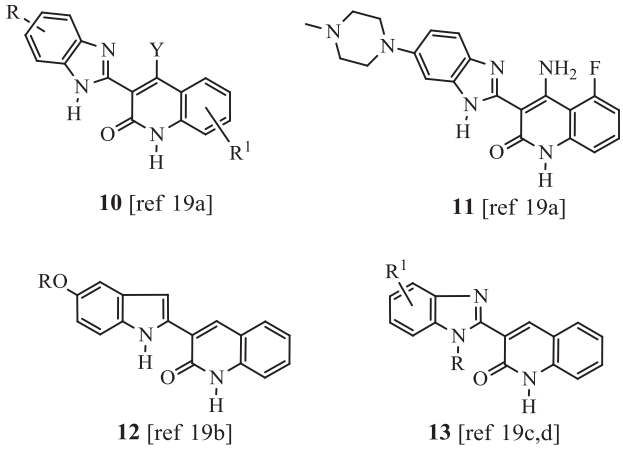


Fig. 3. Some quinoline-2-one based compounds with anti-tumor properties.

moiety which is found in a number of compounds with interesting anti-tumor activities. Tyrosine kinases are a class of enzymes that catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. They have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation. In this sense, several types of compounds have been developed as inhibitor of tyrosine kinase KDR receptors and currently are in clinical stage [19]. Between them, quinoline-2-one based compounds have recently merged as promising and effective leader structures for KDR kinase inhibition mechanism. Compounds **10**–**13** represent some examples of these quinoline-2-one based anti-tumor agents [20], including a series of benzimidazoloquinolin-2-ones **13** recently reported by us [20c,d] (Fig. 3).

Continuing with our current studies directed toward the synthesis of potential anti-tumor agents [11,20c,d], herein we visualized the possibility of combine the synergic anti-carcinogenic effects of the Michael acceptors and the quinoline-2-one moiety whiting a same structure, through the synthesis of the novel quinoline-2-one based chalcones **16**, pursuing for an improvement of their possibilities as anti-tumor agents, for such new compounds.

2. Results and discussion

2.1. Chemistry

The typical procedure for the synthesis of chalcones consists on a Claisen–Schmidt condensation of acetophenones and benzaldehydes in alcoholic solutions using alkali as catalyst [21]. Applying this procedure to 4-bromoacetophenone **14a** and 3-formylquinolin-2-one **15** as our model reaction, Table 1, initially, the stirring of an equimolar mixture of both compounds in ethanol, at ambient temperature, in the presence of 10% aq NaOH afforded, after 5 h of stirring, a white solid along with part of unreacted aldehyde **15**. This reaction proceeded in heterogeneous phase all time, being the low solubility of aldehyde **15** in ethanol the main limiting to allow the reaction reaches the completion. Nevertheless, the white solid was isolated and purified after several washes with warm ethanol. Surprisingly, after a complete spectroscopic analysis the structure of this solid corresponded to the respective aldol intermediate **17a** but not to the expected chalcone **16a**. Repeating this reaction with 4-nitroacetophenone **14b** also afforded to its corresponding aldol intermediate **17b** in similar manner, as a paled yellow solid.

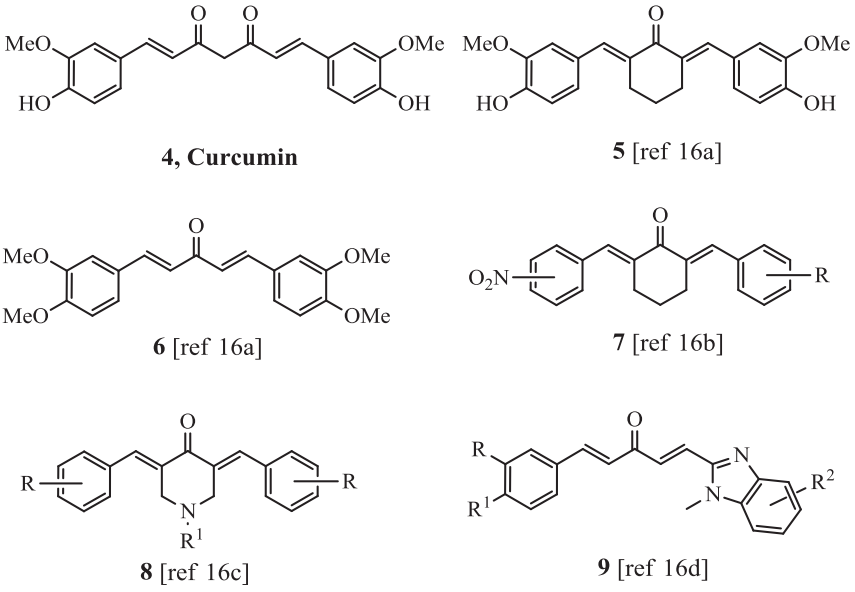
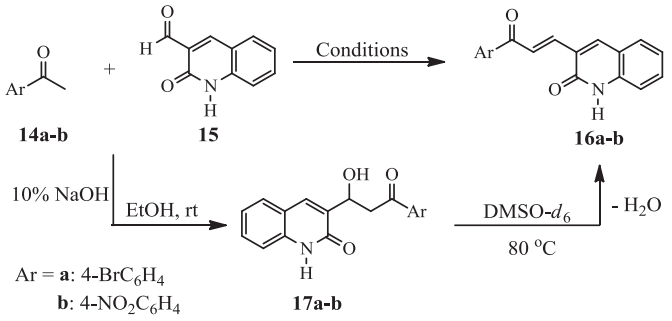


Fig. 2. Curcumin **4** and some curcumin mimic derivatives with anti-tumor properties.

Table 1
Optimization of reaction conditions for the synthesis of quinolinic chalcones **16a**,**b**.



Entry	Acetophenone	Reaction conditions	Time (h)	Product	Yield (%)
1	**14a**	10% NaOH, EtOH, rt	5	**17a**	76/white
2	**14b**	10% NaOH, EtOH, rt	5	**17b**	68/pale yellow
3	**14a**	20% NaOH, EtOH, 70 °C	60	**16a**	64/yellow
4	**14a**	20% w/w A-15, AcOH, 110 °C	30	**16a**	69/yellow
5	**14a**	KOH (1.6 mmol), 1,4-dioxane, rt	4	**16a**	92/yellow
6	**14a**	NaOH (1.6 mmol), 1,4-dioxane, rt	120	–[a]	–

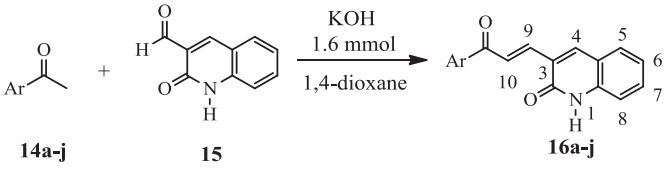
[a] A complex mixture of aldol **17a**, unreacted aldehyde **15**, small amount of **16a** and unknown products was obtained.

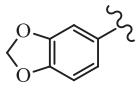
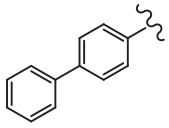
Trying to overcome the above drawback our model reaction was repeated in harder reaction conditions, by heating the solution at 70 °C and using 20% aq NaOH. The expected product **16a** was isolated in 64% yield just until 60 h of heating, along with some of unreacted aldehyde **15**. Although product **16a** was obtained directly without isolation of the aldol intermediate **17a**, the main limitation of this approach was the long reaction time. Aimed to improve the reaction yields of compound **16a** and trying to avoid the limitation of the low solubility of aldehyde **15** in ethanol, our model reaction was carried out in acidic media [22,23]. Thus, an equimolar mixture of acetophenone **14a** and aldehyde **15**, dissolved in AcOH, was heated at 110 °C in the presence of Amberlyst-15® (A-15) [23]. All starting aldehyde **15** and ketone **14a** dissolved and the reaction was completed after 30 h of heating (TLC control). After cooling product **16a** precipitated difficulting its separation from the Amberlyst-15®. Finally product **16a** could be mechanically isolated in 69% yield from the Amberlyst-15®. This time-consuming approach encourages us to continue exploring for a more efficient approach. Finally, the mixture of compounds **14a** and **15** was completely dissolved in 1,4-dioxane at ambient temperature, solid KOH (1.6 mmol) was added and the solution was stirred for 4 h until completion, (TLC) control. Then, solvent was removed under reduced pressure and the crude resultant was washed with water (2 × 3 mL), then with ethanol (2 × 3 mL) and dried under vacuum to afford the expected product **16a** in 92% isolated yield. This last approach turned optimal for our goals because of softer reaction conditions, easier work-up and higher reaction yields than the above. Repeating the same reaction but switching KOH by NaOH (entry 6), afforded to a complex mixture of products. Table 1 resumes all experiment carried out for finding the optimal reaction conditions for the synthesis of chalcone **16a**.

In order to explore the generality and scope of the approach described in entry 5, (Table 1), Claisen–Schmidt condensations of aldehyde **15** with various acetophenones **14b**–**j** were tested under the conditions found to be optimal for 4-bromoacetophenone **14a**. In all cases reactions proceeded with the same behavior, affording the expected chalcones **16b**–**j** in excellent yields (Table 2).

According to the scheme depicted in the Table 1, aldols **17** are proposed as intermediate for the formation of products **16**. The main ^{1}H NMR signal of aldols **17a**,**b** corresponded to a broad singlet at 5.43[5.23] ppm assigned to the OH functionality and the CH and CH_2 aliphatic protons appearing as a AMX system at 3.07[3.19] ppm (dd, *J*gem = 15.3[15.1] Hz, *J*vic = 9.3[9.5] Hz, 1H), 3.42[3.53] ppm (dd, *J*gem = 15.3[15.2] Hz, *J*vic = 2.8[1.5] Hz, 1H) and 5.24 [5.55] ppm (dd, *J*vic = 9.2[9.5] Hz, *J*vic = 2.6[1.2] Hz, 1H), respectively. Signals in brackets correspond to aldol **17b**. In order to confirm such intermediacy, after run the NMR spectra at ambient temperature and confirm the structures **17a**,**b**, subsequently, the probe of the NMR machine was heated at 80 °C with the samples **17a**,**b** inside, and after cooling the NMR experiments were repeated for the same two samples, to try to induce, *in situ*, the dehydration of **17a**,**b**. After three consecutive (heating–cooling) run the OH and the aliphatic CH and CH_2 signals disappeared completely in both samples, and the new ^{1}H , ^{13}C NMR spectra unambiguously matched with the structure of their corresponding chalcones **16a** and **16b**. The increasing of the intensity of the water signal in spectrum (b), Fig. 4, supports the dehydration process. The new AX system in the ^{1}H NMR spectra with two signals at 7.80[7.81] (d, *J* = 15.6[16.1] Hz, 1H) and 8.24[8.30] (d, *J* = 15.6[15.6] Hz, 1H) assigned to the new vinylic protons agrees with the proposed structure for **16a**,**b**. Signals in brackets correspond to chalcone **16b**. Fig. 4 shows the comparison of the ^{1}H NMR spectra of aldol **17a** before (a) and after (b) heating into the probe of the NMR machine. Furthermore, the melting points of aldols **17a** and **17b** were the same than those of chalcones **16a** and **16b** respectively, indicating their chemical transformations by thermal dehydration into the melting point apparatus. These finding also agree with the intermediate character of aldols **17a**,**b** in the Claisen–Schmidt condensation process.

Table 2
Synthesis and analytical data of the new quinoline-2-one based chalcones **16**.



Entry	Product **16**	Ar	Yield (%)[a]	Mp (°C)
1	**a**	*p*-BrC_6H_4	93	279–280
2	**b**	*p*-$NO_2C_6H_4$	95	304–305
3	**c**	*p*-ClC_6H_4	91	277–278
4	**d**	*p*-$CH_3OC_6H_4$	93	260–261
5	**e**	C_6H_5	93	273–274
6	**f**	*p*-FC_6H_4	85	294–295
7	**g**		85	269–270
8	**h**	*p*-HOC_6H_4	87	329–330
9	**i**	*p*-$CH_3C_6H_4$	91	266–267
10	**j**		95	316–317

[a] Isolated yield.

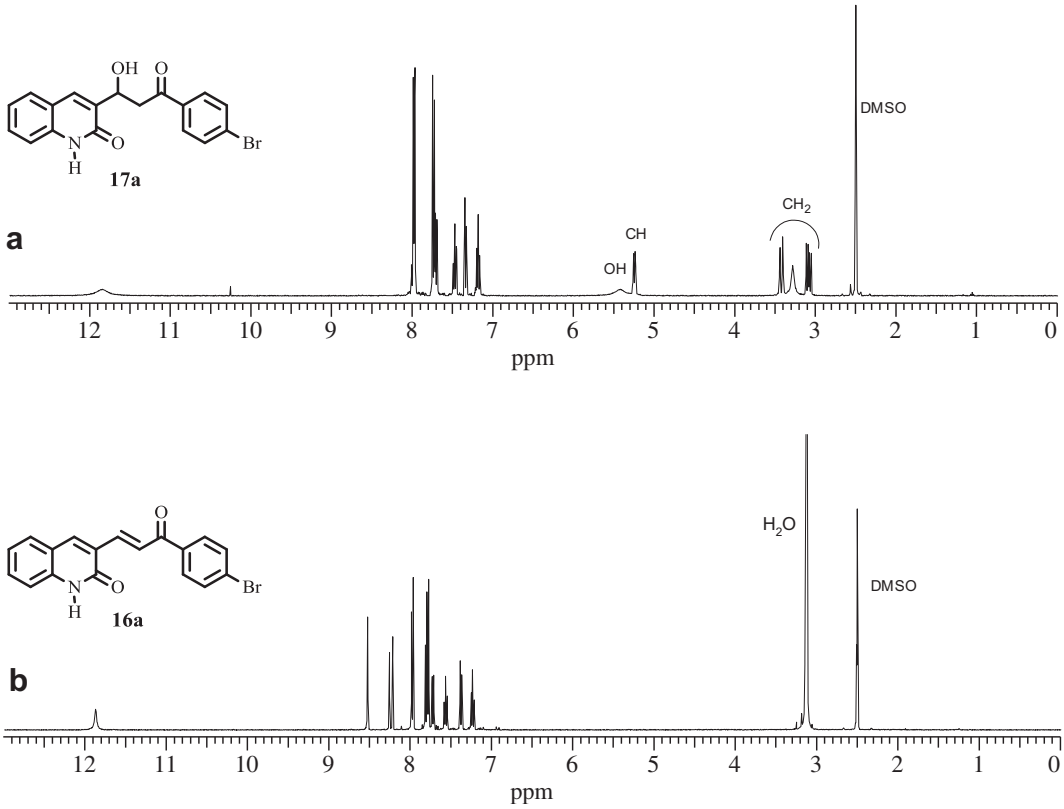


Fig. 4. Comparison of the ^{1}H NMR spectra of aldol **17a** (a) before heating into the probe of the NMR machine and (b) after heating.

A particularity of aldols **17** was their marked stabilities in solid state at ambient temperature. This fact should be explained in terms of their abilities to form intra-molecular hydrogen bonding, as shown in Fig. 5. Although some aldols **19**, originated from aldol condensations, have been isolated and identified [24]; certainly this fact is usually rare because of their low chemical stabilities. Both species **17** and **19** could form intra-molecular hydrogen bonding through their ketonic carbonyl functionalities, but probably aldols **17** are more stable than **19** due to their capabilities to form a second hydrogen bonding by the presence of the quinoline-amidic carbonyl group in their structures, through species **18**.

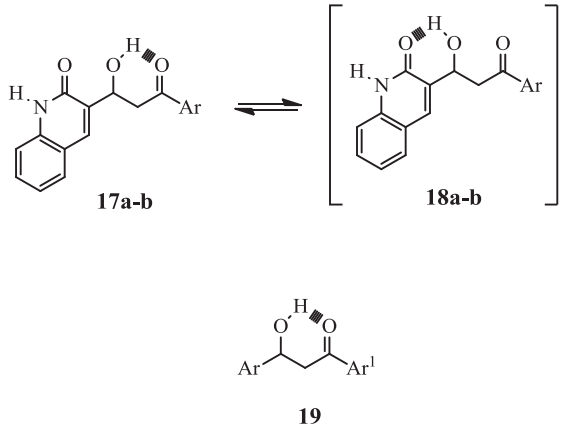


Fig. 5. Structure of aldol **17** showing its ketonic carbonyl and quinoline-amidic carbonyl intramolecular hydrogen bonds.

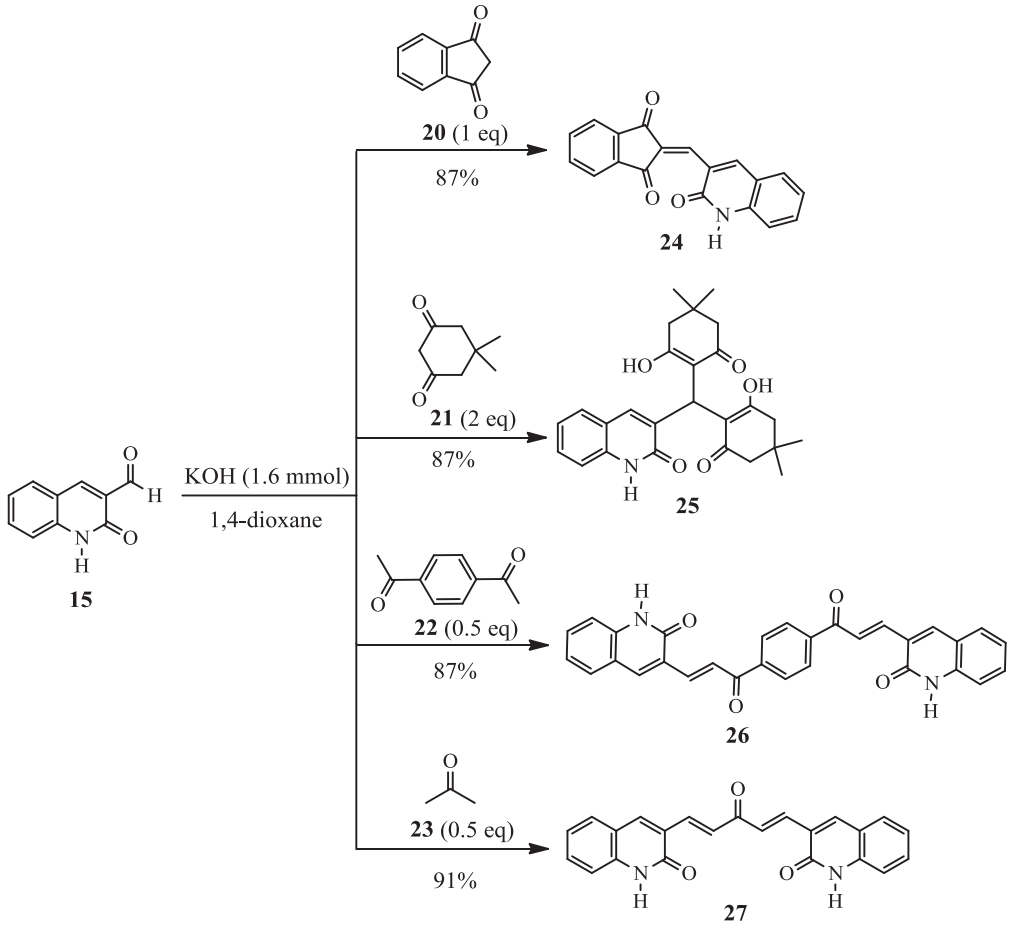
In order to expand the scope of our optimized protocol, the synthesis of indandione-chalcone **24** and the *bis*-arylideneketones **26** and **27** was planned. All three products were readily obtained in 82%, 87% and 91% yields, from the reaction of one and two equivalents of aldehyde **15** with indandione **20**, 1,4-diacetylbenzene **22** and acetone **23** respectively. In the case of compound **25**, two equivalents of dimedone **21** reacted with one of aldehyde **15** affording the 1:2 adduct **25** even when the reaction was performed with an equimolar mixture of **15** and **21**. In this experiment adduct **25** was obtained along with unreacted aldehyde **15**. The impossibility of isolate the 1:1 adduct indicates that a second molecule of dimedone **21** rapidly effected a Michael addition over the 1:1 adduct as soon as it was formed. The optimized 1:2 ratio of **15** and **21** afforded compound **25** in 88% yield (Scheme 1).

Products **16a**–**j** and **24**–**27**, also were characterized by analytical and spectroscopic methods (elemental analyses, FT-IR, ^{1}H , ^{13}C 1D and 2D NMR and EIMS) as summarized in experimental section. The most relevant feature in the MS spectra of compounds **16a**–**j** and **24**–**27** corresponded to a common base peak of 170 u.m.a, assigned to the particularly stable furanic species **28** depicted in Scheme 2.

3. Pharmacology

3.1. In vitro anticancer activity

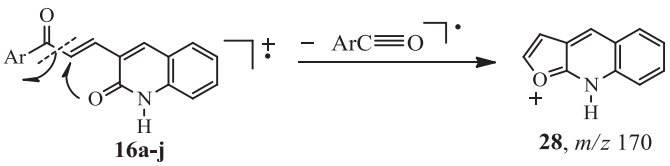
The two-stage screening process started with a primary *in vitro* evaluation of nine of the obtained compounds (i.e. **16c** (NSC: 752191), **16d** (NSC: 752192), **16g** (NSC: 755788), **16h** (NSC: 755790), **16j** (NSC: 755789), **24** (NSC: 759499), **25** (NSC: 756788), **26** (NSC: 755791) and **27** (NSC: 752193)) selected by the Drug Evaluation Branch of National Cancer Institute (NCI), Bethesda, MD, against 60



Scheme 1. Synthesis of novel quinoline-2-one derivatives **24**–**27** following the same procedure developed for chalcones **16**.

human tumor cell lines at a single dose of 10 μM. The 60 cell panel is derived from nine different cancer types: Leukemia, lung, melanoma, colon, CNS, ovary, renal, breast and prostate cancers. The output from the single dose screen was reported as a mean graph available for analysis by the COMPARE program [25]. Results of this primary assay, after a threshold inhibition criteria, suggested that compounds **16c**, **16d**, **16h** and **27** (Table 2 and Scheme 1), were declared as active.

Subsequently, due to compounds **16c**, **16d**, **16h** and **27** displayed considerable antiproliferative activity, they were selected for an advanced assay against the full 60 cell panel at five concentrations at 10-fold dilution (i.e. 100, 10, 1.0, 0.1 and 0.001 μM). The human tumor cell lines of the cancer screening panel were grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells were inoculated into 96 well microtiter plates in 100 μL at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates were incubated at 37 °C, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drug was solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μg/mL gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 μL of these different drug dilutions are added to the appropriate microtiter wells already containing 100 μL of medium, resulting in the required final drug concentrations. More details of this evaluation method and the complementary information which is encoded by the activity pattern over all cell lines have been published elsewhere [26].



Scheme 2. Main fragmentation pattern of chalcones **16** and their analogs **24**–**27** observed from their mass spectra.

The testing results were expressed according to the following three dose response parameters: Growth inhibition of 50% (GI_{50}), which is the molar drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation, the molar drug concentration resulting in total growth inhibition (TGI), and the molar concentration of drug resulting in a 50% reduction in the measured protein (LC_{50}), at the end of the drug treatment as compared to that at the beginning [27]. Furthermore, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an averaged activity parameter over all cell lines. For the calculation of the

MG_MID, insensitive cell lines are included with the highest concentration tested. Selectivity of the compounds with respect to one or more cell lines of the screen is characterized by a high deviation (Δ) of the particular cell line parameter compared to the MG_MID value.

Table 3 shows that compound **16c** displayed good activity against 57 human tumor cell lines, being SR (*Leukemia*, GI_{50} = 1.71 μM), OVCAR-4 (*Ovarian*, GI_{50} = 1.67 μM) and CAKI-1 (*Renal*, GI_{50} = 1.60 μM) the most sensitive strains, and compound **16d** displayed good activity against 53 human tumor cell lines, being LOX IMVI (*Melanoma*, GI_{50} = 1.85 μM) and CAKI-1 (*Renal*, GI_{50} = 1.78 μM) the most sensitive strains. Table 4 shows that compound **16h** displayed good activity against 57 human tumor cell lines, being SR (*Leukemia*, GI_{50} = 1.66 μM), NCI-H522 (*Non-small cell lung cancer*, GI_{50} = 1.70 μM); HCT-116, KM12 and SW-620 (*Colon*, GI_{50} = 1.94, 1.89 and 1.89 μM, respectively), RXF 393 (*Renal*, GI_{50} = 1.65 μM) and BT-549 (*Breast*, GI_{50} = 1.95 μM) the most sensitive strains. Likewise, compound **27** displayed the most remarkable activity against 50 human tumor cell lines, thirteen of them with GI_{50} values ≤1.0 μM. The HCT-116 (*Colon*, GI_{50} = 0.131 μM) and LOX IMVI (*Melanoma*, GI_{50} = 0.134 μM) were the most sensitive strains. The cytotoxic effects associated with compounds **16c**, **16d**, **16h** and **27** were measured as LC_{50} displaying values greater than 100 μM for most of the cell lines evaluated, indicating a low toxicity of these compounds for normal human cell lines, as required for development of potential antitumor agents.

3.2. In vivo evaluations

Owing to the remarkable activity displayed by compound **27**, it was subjected to two repetition tests and after that it was referred to the Biological Evaluation Committee of the NCI, for *in vivo* acute toxicity and hollow fiber assays.

3.2.1. Acute toxicity description

Generally, MTD determinations are done in a way that conserves compound and limits the number of animals used to the barest minimum possible. Thus, a single athymic nude mouse is given a single injection intraperitoneally (IP) of 400 mg/kg; a second mouse receives a dose of 200 mg/kg and a third mouse receives a single dose of 100 mg/kg. Dose volumes are generally 0.1 mL/10 g body weight and the mice are allowed *ad libitum* feed and water. The mice are observed for a period of 2 weeks. They are sacrificed if they lose more than 20% of their body weight or if there are other signs of significant toxicity. If all 3 mice must be sacrificed, then the next 3 dose levels (50, 25, 12.5 mg/kg) are tested in a similar way. This process is repeated until a tolerated dose is found. This dose is then designated the maximum tolerated dose (MTD) and is used to calculate the amount of material given to experimental mice during anti-tumor testing. Assays showed that the highest dose resulted in no body weight loss or lethality, indicating that compound **27** was well tolerated.

3.2.2. Hollow fiber assay

Advancement of potential anticancer agents from identification in the *in vitro* screen to preclinical development is enhanced with demonstration of *in vivo* efficacy in one or more animal models of neoplastic disease. Most such models require considerable materials in terms of laboratory animals and test compound as well as substantial amounts of time and cost to determine whether a given experimental agent or series of agents have even minimal antitumor activity. The hollow fiber assay has demonstrated the ability to provide quantitative indices of drug efficacy with minimum expenditures of time and materials and is currently being utilized as the initial *in vivo* experience for agents found to have reproducible activity in the *in vitro* anticancer drug screen.

3.2.3. Methodology of the hollow fiber assay

A standard panel of 12 tumor cell lines is used for the routine hollow fiber screening of the *in vitro* active compounds. These include NCI-H23, NCI-H522, MDA-MB-231, MDA-MB-435, SW-620, COLO 205, LOX, UACC-62, OVCAR-3, OVCAR-5, U251 and SF-295. In addition, alternate lines can be used for specialized testing of compounds on a nonroutine basis. The cell lines are cultivated in RPMI-1640 containing 10% FBS and 2 mM glutamine. On the day preceeding hollow fiber preparation, the cells are given a supplementation of fresh medium to maintain log phase growth. For fiber preparation, the cells are harvested by standard trypsinization technique and resuspended at the desired cell density ($2–10 \times 10^6$ cells/mL). The cell suspension is flushed into 1 mm (internal diameter) polyvinylidene fluoride hollow fibers with a molecular weight exclusion of 500,000 Da. The hollow fibers are heat-sealed at 2 cm intervals and the samples generated from these seals are placed into tissue culture medium and incubated at 37 °C in 5% CO_2 for 24–48 h prior to implantation. A total of 3 different tumor lines are prepared for each experiment so that each mouse receives 3 intraperitoneal implants (1 of each tumor line) and 3 subcutaneous implants (1 of each tumor line). On the day of implantation, samples of each tumor cell line preparation are quantitated for viable cell mass by a stable endpoint MTT assay so that the time zero cell mass is known. Mice are treated with experimental agents starting on day 3 or 4 following fiber implantation and continuing daily for 4 days. Each agent is administered by intraperitoneal injection at 2 dose levels. The doses are based on the maximum tolerated dose (MTD) determined during prior acute toxicity testing. The fibers are collected from the mice on the day following the fourth compound treatment and subjected to the stable endpoint MTT assay. The optical density of each sample is determined spectrophotometrically at 540 nm and the mean of each treatment group is calculated. The percent net growth for each cell line in each treatment group is calculated and compared to the percent net growth in the vehicle treated controls. A 50% or greater reduction in percent net growth in the treated samples compared to the vehicle control samples is considered a positive result. Each positive result is given a score of 2 and all of the scores are totaled for a given compound. The maximum possible score for an agent is 96 (12 cell lines × 2 sites × 2 dose levels × 2 [score]). A compound is considered for xenograft testing if it has a combined ip + sc score of 20 or greater, a sc score of 8 or greater, or produces cell kill of any cell line at either dose level evaluated. Then, compound **27** was tested against the following disease types and cell lines as shown in Table 5.

Although not further *in vivo* assays were programmed by the Biological Committee of the NCI, it is worth mentioning that the remarkable *in vitro* antitumor activity displayed by the *bis*-arylideneketone **27** could be related to its closely structural relationship with its curcumin mimic analogs depicted in Fig. 2. An angiogenesis inhibition mechanism associated with its Michael acceptor character, probably is the responsible of such activity [17].

According to literature [28], pyrazolic derivatives of chalcones have also displayed high anticancer activity. For that reason we decided to obtain the pyrazolo-derivatives **29c**,**d** by treatment of the active chalcones **16c**,**d** with thiosemicarbazide, following a previously reported procedure [29] (Scheme 3), aimed to increase their activities through their pyrazolic derivatives **29**. Both compounds **29c** (NSC: 755793) and **29d** (NSC: 755792) were evaluated *in vitro* by the NCI. After assays activities of compounds **29c**,**d** were lower than their starting chalcones **16c**,**d** and were declared inactives. Probably the presence of the α,β-unsaturated moiety is

Table 3
In vitro testing expressed as growth inhibition of cancer cells by compounds **16c** and **16d**.

Panel/cell line	Compounds[a]					
	16c			**16d**		
	GI_{50}[b] (μM)	TGI (μM)	LC_{50}[c] (μM)	GI_{50}[b] (μM)	TGI (μM)	LC_{50}[c] (μM)
Leukemia						
RPMI-8226	2.23	16.1	>100	2.79	>100	>100
SR	1.71	19.1	>100	2.83	>100	>100
CCRF-CEM	3.50	>100	>100	4.04	>100	>100
HL-60 (TB)	2.47	>100	>100	3.36	>100	>100
MOLT-4	3.11	>100	>100	3.39	>100	>100
Non-small cell lung cancer						
EKVX	4.92	>100	>100	4.40	83.8	>100
HOP-62	7.43	44.2	>100	3.68	11.6	59.0
NCI-H226	11.6	38.9	>100	5.57	>100	>100
NCI-H23	5.37	93.3	>100	2.90	14.9	>100
NCI-H460	3.99	18.9	>100	2.75	8.34	66.8
NCI-H522	2.23	6.58	47.2	2.12	6.13	>100
HOP-92	5.74	50.5	>100	2.97	8.76	80.9
NCI-H322M	13.4	79.0	>100	–	–	–
A549/ATCC	7.24	>100	>100	3.21	>100	>100
Colon						
COLO 205	10.1	51.3	>100	3.66	13.4	77.6
HCT-116	3.26	14.8	66.5	2.31	5.70	31.6
HCT-15	3.18	20.2	>100	3.18	21.1	>100
HT29	3.84	22.5	>100	3.67	>100	>100
KM12	3.23	16.3	98.9	2.85	7.81	26.9
SW-620	3.38	12.1	56.6	3.41	8.89	40.2
HCC-2998	6.55	22.3	59.6	2.5	6.49	29.0
CNS						
SF-295	4.57	38.3	>100	3.98	18.6	80.8
SF-539	2.07	8.02	74.2	2.76	7.49	45.5
U251	2.52	11.4	39.7	2.70	10.9	>100
SF-268	7.15	63.1	>100	2.85	9.77	40.7
SNB-19	5.11	>100	>100	4.20	19.1	75.8
SNB-75	6.21	48.8	>100	2.29	10.1	47.2
Melanoma						
LOX IMVI	3.26	22.1	>100	1.85	5.54	33.3
MALME-3M	9.42	35.3	>100	–	–	–
MDA-MB-435	2.83	13.1	>100	3.92	17.4	91.6
SK-MEL-5	18.9	>100	>100	5.73	18.1	45.0
UACC-257	7.78	46.9	>100	4.90	18.0	65.5
UACC-62	5.71	54.3	>100	4.38	19.3	60.2
SK-MEL-2	8.55	25.7	72.6	3.91	40.1	>100
M14	7.54	39.7	>100	4.06	22.5	>100
SK-MEL-28	17.7	72.5	>100	7.59	30.6	>100
Ovarian						
IGROV1	3.71	14.7	50.7	–	–	–
OVCAR-3	5.90	30.9	>100	2.49	6.72	29.8
OVCAR-4	1.67	>100	>100	2.94	>100	>100
NCI/ADR-RES	4.00	23.6	>100	2.63	8.44	>100
OVCAR-8	4.93	21.2	88.4	3.57	>100	>100
OVCAR-5	12.7	97.0	>100	3.60	18.4	>100
SK-OV-3	19.7	>100	>100	4.44	>100	>100
Renal						
ACHN	7.27	27.4	90.6	3.93	16.7	57.0
CAKI-1	1.60	3.3	6.8	1.78	3.51	6.90
RXF 393	4.32	29.9	>100	3.41	8.53	33.5
SN12C	8.16	>100	>100	3.17	>100	>100
TK-10	5.05	20.8	75.8	3.54	55.8	>100
UO-31	5.27	>100	>100	–	–	–
786-0	13.8	>100	>100	3.52	>100	>100
Prostate						
DU-145	4.08	48.9	>100	3.14	11.2	35.8
Breast						
MCF7	2.41	>100	>100	2.86	88.7	>100
MDA-MB-231/ATCC	6.16	28.3	>100	3.29	17.9	>100
BT-549	3.86	17.1	97.6	2.70	7.90	46.3
T-47D	7.31	>100	>100	3.55	>100	>100
MDA-MB-468	2.96	9.88	53.2	2.38	5.98	39.8
HS 578T	11.1	>100	>100	3.30	>100	>100

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cell lines screen [27].
[b] GI_{50} was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation, determined at five concentration levels (100, 10, 1.0, 0.1 and 0.001 μM).
[c] LC_{50} is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells.

Table 4
In vitro testing expressed as growth inhibition of cancer cells by compounds **16h** and **27**.

Panel/cell line	Compounds[a]					
	16h			**27**		
	GI_{50}[b] (μM)	TGI (μM)	LC_{50}[c] (μM)	GI_{50}[b] (μM)	TGI (μM)	LC_{50}[c] (μM)
Leukemia						
RPMI-8226	3.20	24.8	>100	0.341	>100	>100
SR	1.66	–	>100	1.14	>100	>100
CCRF-CEM	2.38	>100	>100	0.697	>100	>100
HL-60 (TB)	2.66	6.86	>100	3.38	>100	>100
K-562	3.89	>100	>100	–	–	–
MOLT-4	3.04	9.91	>100	2.27	>100	>100
Non-small cell lung cancer						
EKVX	13.4	27.2	55.2	2.61	>100	>100
HOP-62	2.62	8.17	85.2	3.65	>100	>100
NCI-H226	3.29	10.9	34.5	2.77	8.01	>100
NCI-H23	3.18	20.0	>100	2.42	87.7	>100
NCI-H460	2.39	6.87	>100	4.63	>100	>100
NCI-H522	1.70	3.29	6.36	2.52	–	>100
HOP-92	3.26	23.2	>100	>100	>100	>100
NCI-H322M	3.98	16.8	55.5	–	–	–
A549/ATCC	2.73	11.8	89.9	0.764	–	>100
Colon						
COLO 205	4.05	19.7	76.8	2.89	>100	>100
HCT-116	1.94	4.38	9.91	0.131	0.299	>100
HCT-15	2.71	12.8	>100	2.02	>100	>100
HT29	3.61	12.1	41.4	0.483	1.78	–
KM12	1.89	4.50	15.4	0.494	1.83	5.12
SW-620	1.89	4.45	>100	1.00	3.92	>100
HCC-2998	4.13	22.3	59.6	0.839	2.22	5.25
CNS						
SF-295	7.04	44.0	>100	2.64	–	>100
SF-539	2.55	8.64	61.674.2	2.13	>100	>100
U251	2.60	10.9	45.3	0.372	2.10	>100
SF-268	3.76	23.3	>100	3.75	>100	>100
SNB-19	4.59	18.0	50.6	5.12	>100	>100
SNB-75	9.30	23.0	55.0	–	–	–
Melanoma						
LOX IMVI	2.47	12.7	>100	0.134	0.352	–
MALME-3M	10.4	33.6	>100	–	–	–
MDA-MB-435	2.94	16.8	>100	0.258	0.81	–
SK-MEL-5	3.98	13.3	37.3	5.63	>100	>100
UACC-257	3.87	16.0	47.9	1.98	4.79	>100
UACC-62	2.88	8.73	39.6	4.61	>100	>100
SK-MEL-2	4.13	13.6	48.3	>100	>100	>100
M14	2.60	6.57	>100	0.393	–	>100
SK-MEL-28	5.11	19.5	66.3	4.96	>100	>100
Ovarian						
IGROV1	4.35	45.1	>100	–	–	–
OVCAR-3	3.22	11.8	35.0	4.20	>100	>100
OVCAR-4	–	–	–	2.06	>100	>100
NCI/ADR-RES	2.90	>100	>100	>100	>100	>100
OVCAR-8	3.23	21.1	>100	2.60	>100	>100
OVCAR-5	3.20	12.8	44.4	–	–	–
SK-OV-3	–	–	–	18.1	>100	>100
Renal						
A498	8.44	21.3	47.8	–	–	–
ACHN	2.67	8.86	34.0	2.49	>100	>100
CAKI-1	4.71	>100	>100	2.36	>100	>100
RXF 393	1.65	3.23	6.33	1.79	3.73	7.73
SN12C	3.48	16.0	>100	2.66	>100	>100
TK-10	3.81	11.8	34.6	4.60	>100	>100
UO-31	4.38	26.6	>100	–	–	–
786-0	–	–	–	2.75	6.82	>100
Prostate						
DU-145	4.02	14.3	38.0	4.18	>100	>100
PC-3	5.39	55.3	>100	–	–	–
Breast						
MCF7	3.49	16.8	82.9	0.327	>100	>100
MDA-MB-231/ATCC	2.31	15.0	>100	3.49	>100	>100
BT-549	1.95	5.35	>100	1.90	6.15	>100
T-47D	4.19	20.4	79.6	3.27	>100	>100
MDA-MB-468	2.12	5.30	19.8	1.58	4.39	>100
HS 578T	6.15	>100	>100	–	–	–

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cell lines screen [27].
[b] GI_{50} was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Determined at five concentration levels (100, 10, 1.0, 0.1 and 0.001 μM).
[c] LC_{50} is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells.

Table 5
In vivo hollow fiber testing expressed as growth inhibition of cancer cells by compound **27**.[a]

Panel name	Cell line name	Panel name	Cell line name
Experiment 1		*Experiment* 3	
Breast cancer	MDA-MB-231	Non-small cell lung cancer	NCI-H522
Non-small cell lung cancer	NCI-H23	CNS cancer	U251
Colon cancer	SW-620	Melanoma	UACC-62
Experiment 2		*Experiment* 4	
Colon cancer	COLO 205	Melanoma	MDA-MB-435
Melanoma	LOX IMVI	Ovarian cancer	OVCAR-5
Ovarian cancer	OVCAR-3	CNS cancer	SF-295

[a] Conditions for each experiment: schedule (QD × 4), route (IP), high dose (150 mg/kg/dose).

indispensable for the activity of these type of compounds in agreement with the angiogenesis inhibition mechanism as mentioned previously [17].

4. Conclusion

The synthesis of novel quinoline-2-one based chalcones **16a**–**j** and **24**–**27** was performed. The best reaction condition for this goal was achieved by using the couple KOH/1,4-dioxane as reaction media. Results showed that the formation of such compounds is mediated by a particularly stable aldol intermediate type **17**. All obtained compounds were completely characterized by spectroscopic data and elemental analyses. The *in vitro* antitumor assays showed that, among the eleven samples selected and evaluated by the NCI, compounds **16c**, **16d**, **16h** and **27** exhibited the higher activity. Particularly compound **27** displayed the most remarkable activity against 50 human tumor cell lines, thirteen of them with GI_{50} values $\leq$1.0 μM, being the HCT-116 (*Colon*, GI_{50} = 0.131 μM) and LOX IMVI (*Melanoma*, GI_{50} = 0.134 μM) the most sensitive strains. For that reason compound **27** was subjected to *in vivo* acute toxicity and hollow fiber assay by the Biological Evaluation Committee of the NCI. It is presumable that the remarkable *in vitro* antitumor activity displayed by the *bis*-arylideneketone **27** could be related to its closely structural relationship with the naturally occurring curcumin.

5. Experimental

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer in KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 400 MHz and 100 MHz respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. Mass spectra were run on a SHIMADZU-GCMS 2010-DI-2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Microanalyses were performed on an Agilent elemental analyzer and the values are within ±0.4% of the theoretical values. Silica gel aluminum plates (Merck 60 F_{254}) were used for analytical TLC. All chemicals including the starting acetophenones **14a**–**j** and ketones **20**–**23** were purchased from Aldrich, Fluka and Acros (analytical reagent grades) and were used without further purification. The key precursor 3-formylquinoline-2-one **15** was obtained from 2-chloroquinoline 3-carbaldehyde according to a procedure previously described by us [20d].

5.1. Synthesis of aldols (*16a*,*b*)

To a mixture of equimolar amounts of acetophenones **14a** (or **b**) (1 mmol) and 3-formylquinolin-2-one **15** was added ethanol (10 mL). Then aq 10% NaOH (10 drops) was added and the mixture was stirred for 5 h. The solid formed was filtered under reduced pressure, washed repeatedly with warm ethanol and finally recrystallized from ethanol.

5.1.1. 3-(3-(4-Bromophenyl)-1-hydroxy-3-oxopropyl)quinolin-2(1H)-one (*17a*)

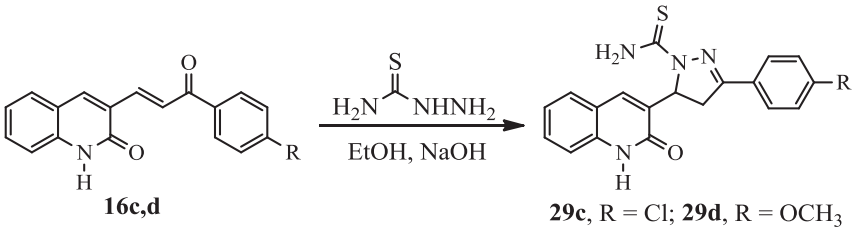
White solid. Mp 279–280 °C; FTIR (KBr) ν (cm^{-1}): 3265, 3237 (OH, NH), 3058, 2902, 1681 (C=O), 1648 (C=O), 1611, 1575 (C=C), 1183 (C–O); ^{1}H NMR (DMSO-d_6) δ 3.07 (dd, *J*gem = 15.3 Hz, *J*vic = 9.3 Hz, 1H), 3.42 (dd, *J*gem = 15.3 Hz, *J*vic = 2.8 Hz, 1H), 5.24 (dd, *J*vic = 9.2 Hz, *J*vic = 2.6 Hz, 1H), 5.43 (bs, 1H, OH), 7.19 (t, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.48 (t, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.98 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 2H), 11.85 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 45.9 (CH_2), 65.4 (CH), 115.3, 119.7 (Cq), 122.3, 127.6 (Cq), 128.2, 130.1, 130.7, 132.2, 134.7, 136.4 (Cq), 136.9 (Cq), 138.3 (Cq), 161.5 (HNC=O), 198.1 (C=O) ppm. Anal. Calcd. for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.95; H, 3.85; N, 3.59.

5.1.2. 3-[(3-(4-Nitrophenyl)-1-hydroxy-3-oxopropyl)]quinolin-2(1H)-one (*17b*)

Pale yellow solid. Mp 304–305 °C; FTIR (KBr) ν (cm^{-1}): 3274, 3243 (OH, NH), 1685 (C=O), 1647 (C=O), 1607, 1575 (C=C), 1523, 1344 (NO_2), 1190 (C–O); ^{1}H NMR (DMSO-d_6) δ 3.19 (dd, *J*gem = 15.1 Hz, *J*vic = 9.5 Hz, 1H), 3.53 (dd, *J*gem = 15.2 Hz, *J*vic = 1.5 Hz, 1H), 5.55 (dd, *J*vic = 9.5 Hz, *J*vic = 1.2 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.97 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 2H), 8.36 (d, *J* = 8.4 Hz, 2H), 11.89 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 46.5 (CH_2), 65.3 (CH), 115.3, 119.7 (Cq), 122.4, 124.3, 128.5, 129.3, 130.1, 134.8, 136.7 (Cq), 138.3 (Cq), 142.1 (Cq), 150.3 (Cq), 161.5 (HNC=O), 198.2 (C=O) ppm. Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 64.00; H, 4.02; N, 8.35.

5.2. General procedure for the synthesis of oxo-quinoline chalcones (*16*) and (*24*–*27*)

A mixture of 3-formylquinolin-2-one **15** (1 mmol), the corresponding acetophenone **14** (1.2 mmol), 1,4-dioxane (5 mL) and solid KOH (1.6 mmol) was stirred at ambient temperature for 4–8 h. The



Scheme 3. Synthesis of the pyrazolo derivatives **29c**,**d** from chalcones **16c**,**d**.

reaction progress was monitored by TLC and after complete disappearance of the starting aldehyde **15** the solvent was removed under reduced pressure and the solid formed was washed with water (2 × 3 mL), then with ethanol (2 × 3 mL) and dried under reduced pressure to afford compounds **16**. The same procedure was followed for the synthesis of compounds **24**–**27**. In the case of compound **24** indandione **20** was used as ketone. For the synthesis of compound **25**, 2 eq of dimedone **21** was necessary. For the synthesis of *bis*-arylideneketones **26** and **27**, 0.5 eq of 1,4-diacetylbenzene **22** and acetone **23** were used respectively, for each mmol of aldehyde **15**.

*5.2.1. (E)-3-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one (**16a**)*

Yellow solid. FTIR ν (cm^{-1}): 3154 (NH) w, 1668 br (C=O), 1586 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 7.8 Hz, 1H, H-6), 7.38 (d, J = 8.3 Hz, 1H, H-8), 7.57 (t, J = 8.3 Hz, 1H, H-7), 7.73 (d, J = 7.0 Hz, 1H, H-5), 7.79 (d, J = 8.5 Hz, 2H, Ar–H), 7.80 (d, J = 15.6 Hz, 1H, H-9), 7.98 (d, J = 8.5 Hz, 2H, Ar–H), 8.24 (d, J = 15.6 Hz, 1H, H-10), 8.53 (s, 1H, H-4), 11.88 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.6, 119.6 (Cq), 122.7, 124.6, 126.5 (Cq), 127.5 (Cq), 129.2, 132.4, 132.2, 133.4, 137.4 (Cq), 139.6 (Cq), 140.0, 141.9, 161.3 (HNC=O), 189.6 (C=O) ppm; MS (EI) m/z (%): 353/355 (M^+, 0.70/0.65), 170 (100). Anal. Calcd. for $C_{18}H_{12}BrNO_2$: C, 61.04; H, 3.41; N, 3.95. Found: C, 60.88; H, 3.53; N, 4.06.

*5.2.2. (E)-3-(3-(4-Nitrophenyl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one (**16b**)*

Yellow solid. FTIR ν (cm^{-1}): 3121 (NH) w, 1671 (C=O) br, 1583, 1548 (C=C), 1520, 1346 (NO_2); ^{1}H NMR (DMSO-d_6) δ 7.25 (t, J = 8.0 Hz, 1H, H-6), 7.36 (d, J = 8.3 Hz, 1H, H-8), 7.59 (t, J = 8.3 Hz, 1H, H-7), 7.73 (d, J = 7.0 Hz, 1H, H-5), 7.81 (d, J = 8.5 Hz, 2H, Ar–H), 7.83 (d, J = 16.1 Hz, 1H, H-9), 8.01 (d, J = 8.5 Hz, 2H, Ar–H), 8.28 (d, J = 15.6 Hz, 1H, H-10), 8.62 (s, 1H, H-4), 12.08 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.6, 119.7 (Cq), 122.7, 125.0, 126.7 (Cq), 127.3 (Cq), 129.1, 130.6, 132.1, 132.3, 137.6 (Cq), 139.7 (Cq), 140.0, 141.7, 161.3 (HNC=O), 189.8 (C=O) ppm; MS (EI) m/z (%): 320 (M^+, 1), 170 (100). Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.66; H, 3.84; N, 8.68.

*5.2.3. (E)-3-(3-(4-Chlorophenyl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one (**16c**)*

Yellow solid. FTIR ν (cm^{-1}): 3150 (NH) w, 1683 (C=O) br, 1621, 1552 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.25 (t, J = 7.3 Hz, 1H, H-6), 7.36 (d, J = 8.3 Hz, 1H, H-8), 7.58 (t, J = 8.0 Hz, 1H, H-7), 7.67 (d, J = 8.5 Hz, 2H, Ar–H), 7.72 (d, J = 7.8 Hz, 1H, H-5), 7.83 (d, J = 15.6 Hz, 1H, H-9), 8.05 (d, J = 8.3 Hz, 2H, Ar–H), 8.31 (d, J = 15.6 Hz, 1H, H-10), 8.62 (s, 1H, H-4), 12.10 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.7, 119.6 (Cq), 122.7, 124.8, 126.6 (Cq), 129.1, 129.4, 130.6, 132.1, 137.1 (Cq), 138.4 (Cq), 139.7 (Cq), 140.0, 141.8, 161.3 (HNC=O), 189.4 (C=O) ppm; MS (EI) m/z (%): (M^+) is missing, 170 (100). Anal. Calcd. for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.91; H, 3.83; N, 4.42.

*5.2.4. (E)-3-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one (**16d**)*

Yellow solid. FTIR ν (cm^{-1}): 3143 (NH) w, 1666 (C=O) br, 1592, 1552 (C=C), 1258, 1161 (C–O); ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H, OCH_3), 7.09 (d, J = 8.8 Hz, 2H, Ar–H), 7.22 (t, J = 7.0 Hz, 1H, H-6), 7.38 (d, J = 8.0 Hz, 1H, H-8), 7.54 (t, J = 7.3 Hz, 1H, H-7), 7.71 (d, J = 8.5 Hz, 1H, H-5), 7.74 (d, J = 15.6 Hz, 1H, H-9), 8.04 (d, J = 8.8 Hz, 2H, Ar–H), 8.23 (d, J = 15.6 Hz, 1H, H-10), 8.43 (s, 1H, H-4), 11.67 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 56.1 (OCH_3), 114.7, 115.6, 119.7 (Cq), 122.6, 125.4, 127.0 (Cq), 129.0, 131.0, 131.5 (Cq), 131.8, 138.5, 139.5 (Cq), 141.1, 161.4 (HNC=O), 163.81 (Cq), 188.8 (C=O) ppm. MS (EI) m/z (%): 305 (M^+, 0.89), 170 (100). Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.80; H, 5.00; N, 4.47.

*5.2.5. (E)-3-(3-Oxo-3-phenylprop-1-en-1-yl)quinolin-2(1H)-one (**16e**)*

Yellow solid. FTIR ν (cm^{-1}): 3110 (NH) w, 1672 (C=O) br, 1584, 1554 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.26 (t, J = 7.3 Hz, 1H, H-6), 7.36 (d, J = 8.3 Hz, 1H, H-8), 7.58 (t, J = 8.3 Hz, 1H, Ar–H), 7.61 (d, J = 7.9 Hz, 2H, Ar–H), 7.69 (t, J = 7.3 Hz, 1H, H-7), 7.73 (d, J = 8.5 Hz, 1H, H-5), 7.82 (d, J = 15.6 Hz, 1H, H-9), 8.07 (d, J = 7.5, 2H, Ar–H), 8.32 (d, J = 15.6 Hz, 1H, H-10), 8.61 (s, 1H, H-4), 12.06 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.7, 119.7 (Cq), 122.8, 124.5, 126.4 (Cq), 128.8, 129.2, 129.4, 132.3, 133.6, 138.2 (Cq), 139.5 (Cq), 139.6, 141.8, 161.4 (HNC=O), 189.8 (C=O) ppm. MS (EI) m/z (%): 275 (M^+, 1.70), 170 (100). Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.62; H, 4.55; N, 5.00.

*5.2.6. (E)-3-(3-(4-Fluorophenyl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one (**16f**)*

Yellow solid. FTIR ν (cm^{-1}): 3125 (NH) w, 1667 (C=O) br, 1591, 1554 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 7.5 Hz, 1H, H-6), 7.36 (d, J = 8.3 Hz, 1H, H-8), 7.43 (bt, J = 8.8 Hz, 2H, Ar–H), 7.58 (t, J = 7.6 Hz, 1H, H-7), 7.72 (d, J = 7.8 Hz, 1H, H-5), 7.83 (d, J = 15.6 Hz, 1H, H-9), 8.17 (dd, J = 8.7 Hz, J = 5.5 Hz, 2H, Ar–H), 8.32 (d, J = 15.6 Hz, 1H, H-10), 8.62 (s, 1H, H-4), 12.04 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.6, 115.9 (d, J_{C-F} = 22.0 Hz), 119.7 (Cq), 122.7, 125.6, 125.2 (Cq), 129.2, 129.1, 131.6 (d, J_{C-F} = 9.5 Hz), 132.6 (d, J_{C-F} = 3.7 Hz, Cq), 139.6, 141.6, 146.4 (Cq), 146.0 (d, J_{C-F} = 195.0 Hz, Cq-F), 161.3 (HNC=O), 185.8 (C=O) ppm. MS (EI) m/z (%): 293 (M^+, 1.3), 170 (100). Anal. Calcd. for $C_{18}H_{12}FNO_2$: C, 73.71; H, 4.12; N, 4.78. Found: C, 73.85; H, 4.00; N, 4.65.

*5.2.7. (E)-3-(3-(Benzo[d][1,3]dioxol-5-yl)-3-oxoprop-1-en-1-yl) quinolin-2(1H)-one (**16g**)*

Yellow solid. FTIR ν (cm^{-1}): 3120 (NH) w, 1676 (C=O) br, 1589, 1557 (C=C), 1262, 1029 (C–O); ^{1}H NMR (DMSO-d_6) δ 6.18 (s, 2H, CH_2), 7.13 (d, J = 8.3 Hz, 1H, Ar–H), 7.23 (t, J = 7.0 Hz, 1H, H-6), 7.35 (d, J = 8.3 Hz, 1H, H-8), 7.56 (t, J = 8.5 Hz, 1H, H-7), 7.57 (d, J = 1.8 Hz, 1H, Ar–H), 7.71 (d, J = 7.4 Hz, 1H, H-5), 7.77 (dd, J = 8.3 Hz, J = 1.8 Hz, 1H, Ar–H), 7.81 (d, J = 15.6 Hz, 1H, H-9), 8.29 (d, J = 15.6 Hz, 1H, H-10), 8.61 (s, 1H, H-4), 12.01 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 102.4 (CH_2), 108.2, 108.6, 115.1, 119.8 (Cq), 121.8, 125.1, 126.9 (Cq), 127.7, 129.0, 129.7, 131.8 (Cq), 137.2, 138.9 (Cq), 140.9, 148.6 (Cq), 151.6 (Cq), 162.0 (HNC=O), 188.4 (C=O) ppm. MS (EI) m/z (%): 319 (M^+, 1.98), 170 (100). Anal. Calcd. for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.56; H, 3.98; N, 4.60.

*5.2.8. (E)-3-(3-(4-Hydroxyphenyl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one (**16h**)*

Yellow solid. FTIR ν (cm^{-1}): 3143 (OH, NH) br, 1664 (C=O) br, 1605, 1574, 1554 (C=C), 1254 (C–O); ^{1}H NMR (DMSO-d_6) δ 6.93 (d, J = 8.5 Hz, 2H, Ar–H), 7.25 (t, J = 7.5 Hz, 1H, H-6), 7.36 (d, J = 8.3 Hz, 1H, H-8), 7.57 (t, J = 8.0 Hz, 1H, H-7), 7.72 (d, J = 7.8 Hz, 1H, H-5), 7.76 (d, J = 15.6 Hz, 1H, H-9), 8.00 (d, J = 8.8 Hz, 2H, Ar–H), 8.31 (d, J = 15.6 Hz, 1H, H-10), 8.58 (s, 1H, H-4), 10.43 (bs, 1H, OH), 12.06 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.6, 116.0, 119.6 (Cq), 122.8, 124.6, 126.6 (Cq), 129.1, 129.7 (Cq), 131.4, 132.1, 138.2, 139.4 (Cq), 141.2, 161.5 (HNC=O), 162.7 (Cq), 187.9 (C=O) ppm. MS (EI) m/z (%): 291 (M^+, 1.2), 170 (100). Anal. Calcd. for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.10; H, 4.68; N, 4.94.

*5.2.9. (E)-3-(3-Oxo-3-(p-tolyl)prop-1-en-1-yl)quinolin-2(1H)-one (**16i**)*

Yellow solid. FTIR ν (cm^{-1}): 3110 (NH) w, 1663 (C=O) br, 1585, 1553 (C=C); ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H, CH_3), 7.24 (t, J = 7.3 Hz, 1H, H-6), 7.36 (d, J = 8.0 Hz, 1H, H-8), 7.40 (d, J = 8.0 Hz, 2H, Ar–H), 7.57 (t, J = 7.9 Hz, 1H, H-7), 7.72 (d, J = 7.8 Hz, 1H, H-5), 7.81 (d, J = 15.8 Hz, 1H, H-9), 8.00 (d, J = 8.3 Hz, 2H, Ar–H), 8.32 (d,

J = 15.6 Hz, 1H, H-10), 8.61 (s, 1H, H-4), 12.06 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 21.7 (CH_3), 115.8, 119.8 (Cq), 122.7, 124.4, 125.6 (Cq), 127.8 (Cq), 128.9, 129.2, 129.9, 132.2, 137.4 (Cq), 139.0 (Cq), 139.3, 141.6, 161.8 (HNC=O), 188.5 (C=O) ppm. MS (EI) m/z (%): 289 (M^+, 1.6), 170 (100). Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 79.01; H, 5.12; N, 4.98.

*5.2.10. (E)-3-(3-([1,1′-Biphenyl]-4-yl)-3-oxoprop-1-en-1-yl) quinolin-2(1H)-one (**16j**)*

Yellow solid. FTIR ν (cm^{-1}): 3131 (NH) w, 1667 (C=O) br, 1585, 1552 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 7.8 Hz, 1H, H-6), 7.39 (d, J = 8.3 Hz, 1H, Ar–H), 7.44 (t, J = 7.5 Hz, 1H, H-8), 7.52 (t, J = 8.3 Hz, 2H, Ar–H), 7.56 (t, J = 8.0 Hz, 1H, H-7), 7.73–7.80 (m, 3H), 7.82 (d, J = 15.6 Hz, 1H, H-9), 7.86 (d, J = 8.3 Hz, 2H, Ar–H), 8.13 (d, J = 8.3 Hz, 2H, Ar–H), 8.30 (d, J = 15.6 Hz, 1H, H-10), 8.50 (s, 1H, H-4), 11.78 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.6, 119.7 (Cq), 122.7, 125.3, 126.8 (Cq), 127.4, 127.5 (×2), 128.7, 129.1, 129.4, 129.5, 132.0, 137.3 (Cq), 139.4, 139.6 (Cq), 141.5, 145.0 (Cq), 161.4 (HNC=O), 190.0 (C=O) ppm. MS (EI) m/z (%): 351 (M^+, 1.3), 170 (100). Anal. Calcd. for $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88; N, 3.99. Found: C, 81.85; H, 5.01; N, 4.12.

*5.2.11. 2-(2-Oxo-1,2-dihydroquinolin-3-ylmethylene)-indan-1,3-dione (**24**)*

Orange solid. 82% yield, mp 339–340 °C, FTIR (KBr) ν (cm^{-1}): 1726, 1689 (C=O), 1543 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.29 (t, J = 7.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.82 (d, J = 7.0 Hz, 1H), 7.97–8.03 (m, 4H), 8.22 (s, 1H), 9.79 (s, 1H), 12.25 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 116.0, 119.2 (Cq), 123.2, 123.5, 123.6, 124.7 (Cq), 130.4, 130.9 (Cq), 133.8, 136.3, 136.4, 139.3, 140.2 (Cq), 141.4 (Cq), 142.5 (Cq), 146.2. 161.3 (HNC=O), 189.3 (C=O), 189.4 (C=O) ppm. MS (EI) m/z (%): 301 (M^+, 100), 245 (88), 216 (50), 189 (15). Anal. Calcd. for $C_{19}H_{11}NO_3$: C, 75.74; H, 3.68; N, 4.65. Found: C, 75.63; H, 3.81; N, 4.80.

*5.2.12. 2,2′-((2-Oxo-1,2-dihydroquinolin-3-yl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**25**)*

White solid. 88% yield, mp >350 °C, FTIR (KBr) ν (cm^{-1}): 3448 br (OH, NH), 2961, 2873, 1662 br (C=O), 1627, 1569 (C=C), 1362, 1199 (C–O); ^{1}H NMR (DMSO-d_6) δ 0.97 (s, 6H, CH_3), 1.06 (s, 6H, CH_3), 2.07 (d, J = 16.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 2H), 2.43 (d, J = 17.56 Hz, 2H), 2.53 (d, J = 17.6 Hz, 2H), 4.61 (s, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.76 (s,1H), 11.10 (s, 1H, NH) ppm, OH signals are missing; ^{13}C NMR (DMSO-d_6) δ 27.0 (CH_3) 29.3 (CH_3), 30.8 (CH), 32.1 (Cq), 40.8 (CH_2), 51.1 (CH_2), 112.0 (Cq), 114.9, 119.8 (Cq), 121.8, 128.0, 129.7, 132.8 (Cq), 138.8 (Cq), 139.2, 161.0 (HNC=O), 164.5 (=C–OH), 196.4 (C=O) ppm. Anal. Calcd. for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.85; H, 6.50; N, 3.41.

*5.2.13. 3,3′-(1E,1′E)-1,4-Phenylenebis(3-oxoprop-1-ene-3,1-diyl) bis(quinolin-2-(1H)-one) (**26**)*

Yellow solid. FTIR ν (cm^{-1}): 3110 (NH) w, 1662 (C=O) br, 1584 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.25 (t, J = 7.0, 2H, H-6), 7.40 (d, J = 8.5 Hz, 2H, H-8), 7.58 (t, J = 8.5 Hz, 2H, H-7), 7.74 (d, J = 7.8 Hz, 2H, H-5), 7.84 (d, J = 15.6 Hz, 2H, H-9), 8.20 (s, 4H, Ar–H). 8.30 (d, J = 15.6, 2H, H-10), 8.55 (s, 2H, H-4), 11.85 (s, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.7. 119.7 (Cq), 122.7, 125.3, 126.6 (Cq), 129.0, 129.2, 132.2, 139.7 (Cq), 140.3, 141.6 (Cq), 142.0, 161.3 (HNC=O), 190.5 (C=O), ppm. MS (EI) m/z (%): M^+ is missing, 170 (100). Anal. Calcd. for $C_{30}H_{20}N_2O_4$: C, 76.26; H, 4.27; N, 5.93. Found: C, 76.11; H, 4.46; N, 6.05.

*5.2.14. 3,3′-((1E,4E)-3-Oxopenta-1,4-diene-1,5-diyl)bis(quinolin-2(1H)-one) (**27**)*

Yellow solid. FTIR ν (cm^{-1}): 3151 (NH), 1655 (C=O) br, 1548, 1522 (C=C); ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 7.8 Hz, 2H, H-6), 7.36 (d, J = 8.3 Hz, 2H, H-8), 7.58 (t, J = 7.3 Hz, 2H, H-7), 7.74 (d, J = 8.0 Hz, 2H, H-5), 7.77 (d, J = 15.6 Hz, 2H, H-9), 7.80 (d, J = 15.6 Hz, 2H, H-10), 8.52 (s, 2H, H-4), 12.10 (s, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 115.6, 119.7 (Cq), 122.6, 126.9 (Cq), 128.8, 129.1, 131.9, 138.0, 139.6 (Cq), 141.2, 161.3 (HNC=O), 189.8 (C=O) ppm. MS (EI) m/z (%): M^+ is missing, 170 (100). Anal. Calcd. for $C_{23}H_{16}N_2O_3$: C, 74.99; H, 4.38; N, 7.60. Found: C, 75.11; H, 4.23; N, 7.77.

*5.3. Synthesis of carbothioamides (**29c**,**d**)*

A mixture of chalcone **16c** (or **d**) (1.0 mmol), thiosemicarbazide (1.2 mmol), solid NaOH (1.5 mmol) and ethanol (5 mL) was stirred to reflux for 5 h (TLC control). After cooling the solid formed was filtered under reduced pressure and purified by washings with ethanol (3 × 1 mL).

*5.3.1. 3-(4-Chlorophenyl)-5-(2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrazolo-1-carbothioamide (**29b**)*

White solid. 75% yield, mp 299–300 °C, FTIR (KBr) ν (cm^{-1}): 3428, 3267 (NH_2), 166O (C=O), 1572 (C=C, C=N); ^{1}H NMR (DMSO-d_6) δ 3.48 (dd, Jgem = 18.1 Hz, Jvic = 11.5 Hz, 1H), 3.84 (dd, Jgem = 18.1 Hz, Jvic = 4.5 Hz, 1H), 5.98 (dd, Jvic = 11.5 Hz, Jvic = 4.3 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.22 (bs, 1H, NH_2), 7.34 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.43 (t, J = 7.3 Hz, 1H), 7. 48 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.66 (bs, 1H, NH_2), 7.86 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6) δ 40.8 (CH_2), 60.2 (CH), 115.5, 119.5 (Cq), 122.2, 128.2, 129.1 (×2), 129.2, 130.2, 130.6 (Cq), 132.8 (Cq), 134.5 (Cq), 138.8 (Cq), 155.3 (Cq), 161.3 (C=O), 177.6 (C=S) ppm. Anal. Calcd. for $C_{19}H_{15}ClN_4OS$: C, 59.60; H, 3.95; N, 14.63. Found: C, 59.82; H, 4.06; N, 14.48.

*5.3.2. 3-(4-Methoxyphenyl)-5-(2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrazolo-1-carbothioamide (**29d**)*

White solid. 84% yield, mp 289–290 °C, FTIR (KBr) ν (cm^{-1}): 3435, 3273 (NH_2), 1664 (C=O), 1584 (C=C, C=N), 1280, 1150 (OCH_3); ^{1}H NMR (DMSO-d_6) δ 3.13 (dd, Jgem = 18.0 Hz, Jvic = 11.8 Hz, 1H), 3.80 (s, 1H, OCH_3), 3.81 (dd, Jgem = 17.8 Hz, Jvic = 3.6 Hz, 1H), 5.90 (dd, Jvic = 11.4 Hz, Jvic = 3.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.34 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.87 (bs, 1H, NH_2), 8.01 (bs, 1H, NH_2) ppm; ^{13}C NMR (DMSO-d_6) δ 40.8 (CH_2), 55.8 (OCH_3), 59.3 (CH), 114.6, 115.4, 119.3 (Cq), 122.4, 123.8 (Cq), 128.3, 129.4, 130.3, 133.0 (Cq), 133.6, 138.5 (Cq), 155.2 (Cq), 161.2 (Cq), 161.6 (C=O), 176.1 (C=S) ppm. Anal. Calcd. for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80. Found: C, 63.55; H, 4.56; N, 14.93.

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