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ORIGINAL ARTICLE

# Tandem chalcone-sulfonamide hybridization, cyclization and further Claisen–Schmidt condensation: Tuning molecular diversity through reaction time and order and catalyst

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Claisen–Schmidt condensation

**Abstract** We here report the synthesis of novel chalcone-sulfonamide compounds based on the hybridization at 2′ position and nitro substitution at the side chalcone phenyl ring followed by tandem cyclization into quinolinone derivatives and then a further aldol condensation only as a function of the reaction time. Therefore, for the first time, we have controlled the sequential preparation of chalcone-sulfonamide hybrids, quinolinones and then (*E*)-3-ene-2,3-dihydroquinolinones simply stopping reaction over increasing time periods. Furthermore, a new molecular scaffold based on a chalcone-(bis)sulfonamide hybrid has been gotten through changing the sequence of coupling reactions and catalyst. This study means practical and useful ways of constructing in high yields new biologically active compounds bearing diversified molecular scaffolds.


## 1. Introduction

Molecular hybridization has been used for a long time in the medicinal chemistry as one of the main strategies to conceive new bioactive compounds (Bahia et al., 2016; Jeankumar et al., 2015; Viegas-Junior et al., 2007). It is based on the coupling of two or more molecular fragments of recognized biological profile, named pharmacophores, which can be

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powering their bioactivities or even giving rise to another different property that is not manifested by the parent molecules alone (Araujo et al., 2015; Raj et al., 2015). In this sense, many compound classes have been subject of molecular hybridization researches, such as bronchodilator, psychotropic, antimalarial, antileishmanial, anti-inflammatory, anticancer, among others (Jones et al., 2015; Valli et al., 2015; Piens et al., 2014; Vandekerckhove and D'hooghe, 2013; Sharma et al., 2013; Hernandes et al., 2012).

The hybridization of chalcone and arylsulfonamide scaffolds has been investigated nowadays (Winter et al., 2016; Mahapatra et al., 2015; Ghorab et al., 2015; Singh et al., 2014; Seo et al., 2005). These two classes are well known as rich sources of compounds owning many bioactivities, including anticancer profiles (Lu et al., 2016; Ghorab et al., 2016; Jeon et al., 2016; Mirzaei and Emami, 2016). One of their hybrids has recently shown strong anticancer profiles, being pointed out as drug candidate for treatment of hepatocarcinoma. This is 4′-(*p*-toluenesulfonylamide)-4-hydroxychalcone (TSAHC), a synthetic derivative accumulating several antitumor features, such as inhibition of tumor multilayer growth and invasion and inhibition of cytochrome P450 2J2 isoform responsible for the promotion of tumor growth and proliferation (Lee et al., 2011; Seo et al., 2010). Another contribution on synthetic approaches on chalcones concerns their uses as building blocks to prepare thiazole derivatives with pharmacological activities such as anticancer agents (Gomha et al., 2017). Besides, benzenesulfonamide and chalcone derivatives have been investigated lately due to their biological application as carbonic anhidrase inhibitors (Alp et al., 2012; Arslan et al., 2016a,b), where such compounds showed potent inhibitory activity against three carbonic anhydrase isozymes (CA I, CA II and CA III).

Based on the knowledge of TSAHC properties, we have prepared chalcone-sulfonamide derivatives hybridized at 4′ position of chalcone scaffold and evaluated their anticancer profiles (Castro et al., 2016, 2013). Compounds with nitro group at 4-position of chalcone pharmacophore have shown a noteworthy antitumor activity motivating us to continue searching other related nitro-substituted chalcone-sulfonamide hybrids. In this sense, we here report a novel chalcone-sulfonamide series based on the hybridization at 2′ position and nitro substitution at the side chalcone phenyl ring followed by cytotoxicity evaluation. However, besides getting the hybrids as expected, we have observed tandem cyclization into quinolinone derivatives followed by a further aldol condensation as a function of the reaction time. Even though these reactions cascade is already known (Wang et al., 2016; Cheng et al., 2014; Kim et al., 2009; Liu and Lu, 2010; Tokes et al., 1992), for the first time we have controlled the sequential preparation of chalcone-sulfonamide hybrids, quinolinone and then (*E*)-3-ene-2,3-dihydroquinolones simply stopping reaction over increasing time periods, which is highly desired for scaling-up purposes in chemical industry. Furthermore, a new molecular scaffold based on a chalcone-(bis)sulfonamide hybrid has been gotten through changing the sequence of coupling reactions and the catalyst. Therefore, this study means practical and useful ways of constructing new biologically active compounds bearing diversified molecular scaffolds.

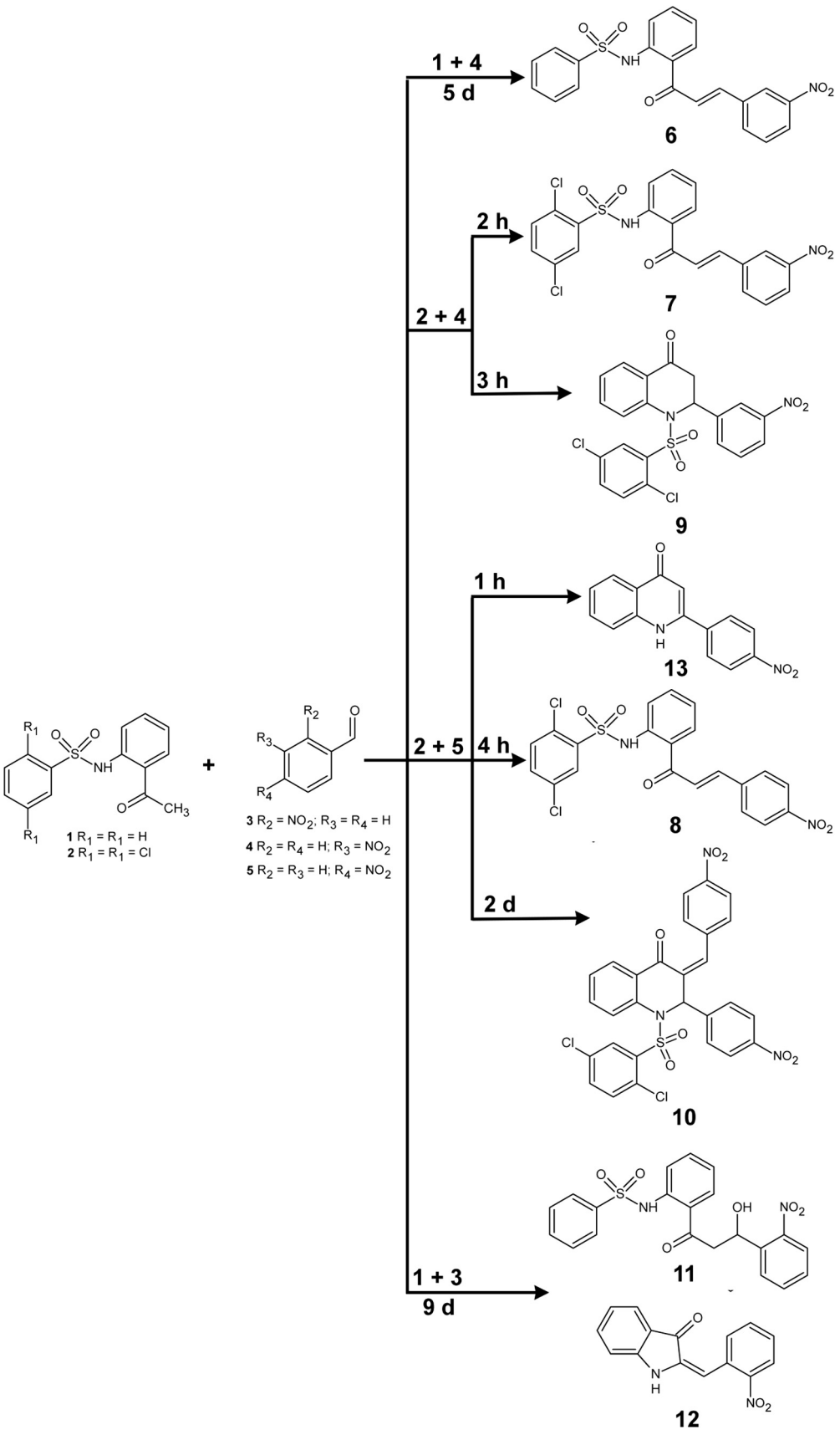
## 2. Experimental part

### 2.1. General procedure for synthesis and crystallization

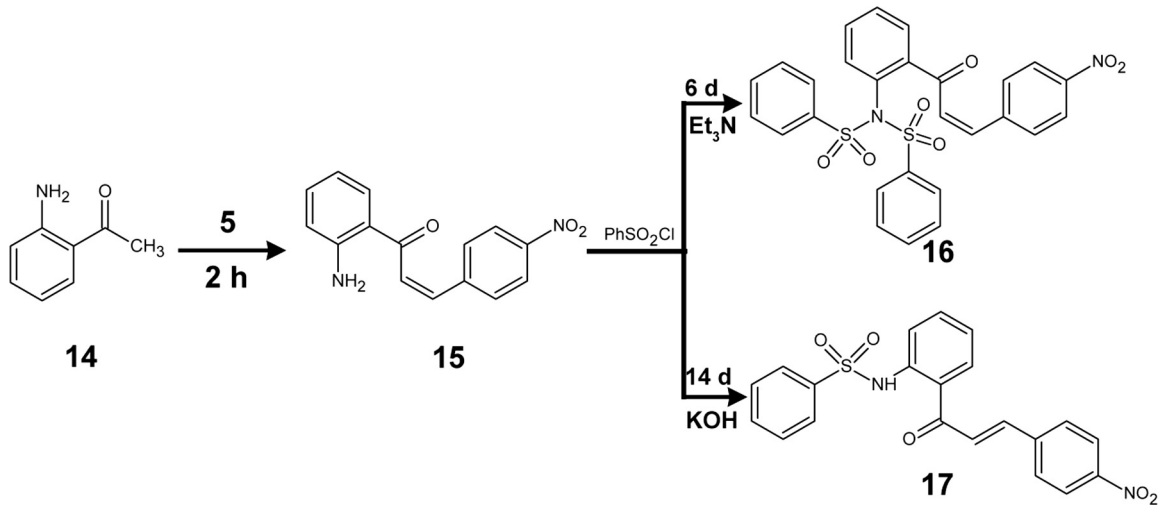
Except for compounds **16** and **17**, all compounds were synthesized by Claisen–Schmidt condensation using as reagents either *N*-(2-acetylphenyl)benzenesulfonamide or *N*-(2-acetylphenyl)-2,5-dichlorobenzenesulfonamide (1 mmol) and either benzaldehyde or nitrobenzaldehydes (3 mmol) (Scheme 1). Potassium hydroxide in ethanol (10 mL, 50% w/w) was used as catalyst, except for concomitant synthesis of compounds **11** and **12** in which triethylamine (2 mmol) was employed instead. This last reaction was conducted in dichloromethane (15 mL) at 273 K for the first 8 h, being next attained 298 K until completing 9 days, while all others were entirely performed at 298 K for periods ranging from 1 h to 14 days (Scheme 1). Compounds **16** and **17** were obtained in two steps. First, 2-aminoacetophenone (2 mmol) and *p*-nitrobenzaldehyde (4 mmol) were initially reacted (20 mL of 50% w/w $KOH_{(et.)}$, 298 K, 2 h), followed by isolation of the chalcone **15** and then reaction of 1 mmol with benzenosulfonyl chloride (2 mmol). Triethylamine (2 mmol, 15 mL of dichloromethane, 273 K during the first 8 h and then 298 K up to complete 6 d) and KOH (10 mL of 50% w/w ethanolic solution, 298 K, 14 d) were used as catalyst for synthesis of compounds **16** and **17**, respectively (Scheme 2). Regardless of the catalyst, all reactions were monitored by thin layer chromatography every hour in the first reaction day, and at each 4 h starting from the second reaction day until ending reactants. All KOH catalyzed reaction batches had their aliquots neutralized with 2 M HCl followed by addition of ice-cooled water (10 mL). These elaboration steps were enough to precipitate products which were isolated by filtration, which did not occur if triethylamine was used as catalyst. In these last cases, the aliquots were extracted with dichloromethane (10 mL) and then concentrated under reduced pressure in rotary evaporator. In all cases, the solid product was recrystallized from an acetone solution to obtain non-twinned single crystals larger enough to collect single-crystal X-ray diffraction intensities. Two compounds were additionally isolated as solid state polymorphs from ethyl alcohol solution (see below), as well as compound **16**. High yields (15–65%) were obtained in all cases, as can be viewed in the Supporting Information together with complete characterization data of all synthesized compounds. More synthetic details can be found in other related papers (Castro et al., 2016, 2013).

### 2.2. Single crystal X-ray diffraction

Single crystal X-ray diffraction data were measured using a Bruker-AXS Kappa Duo diffractometer with an APEX II CCD detector using Mo Kα radiation. Bruker programs SAINT and SADABS (Bruker, 2012) were used for cell refinement and data indexing, integration and reduction. Multi-scan absorption correction was performed for all dataset. Structure solution and refinements were performed using SHELX97 (Sheldrick, 2008) within the WinGX (Farrugia, 1999). Non-hydrogen and hydrogen atoms were refined anisotropically and isotropically, respectively. All NH and OH hydrogen atoms were firstly located on the difference Fourier map but


1 + 4
5 d
6
2 h
7
2 + 4
3 h
9
1 h
13
2 + 5
4 h
8
2 d
10
11
1 + 3
9 d
12
1 R1 = R1 = H
2 R1 = R1 = Cl
3 R2 = NO2; R3 = R4 = H
4 R2 = R4 = H; R3 = NO2
5 R2 = R3 = H; R4 = NO2

**Scheme 1**




**Scheme 2**

they then were constrained following a riding model with fixed bond lengths, valence angles and torsions. For hydrogens bonded to carbons/nitrogens and oxygen atoms, their isotropic thermal parameters were set to $1.2U_{iso}$(C/N) or $1.5U_{iso}$(O), respectively. All asymmetric units were present with just one crystallographically independent molecule, except that of compound **16** which was present with two of its molecules and half of one ethyl alcohol molecule crystallized together in the lattice. The methylene carbon from this solvent molecule is on an inversion centre, which is therefore inverted on itself to generate a full occupancy site which is shared with another half ethyl alcohol molecule generated by inversion symmetry. The X-ray diffraction dataset for all structures is available under CCDC number codes presented together with a summary of X-ray diffraction data collect and treatment in Table 1.

### *2.3. Cell line and cell culture*

All cytotoxicity evaluations were carried out in the Laboratório Nacional de Oncologia Experimental at Universidade Federal do Ceará (Fortaleza, CE, Brazil). The procedures to know the cytotoxicity of the chalcone-sulfonamide hybrids were as follows: cells gotten from National Cancer Institute (Bethesda, MD, USA) (Skehan et al., 1990) maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 U $mL^{-1}$ penicillin, and 100 µg $mL^{-1}$ streptomycin at 37 °C with 5% $CO_2$, culture for 24 h before testing with chalcone-sulfonamide hybrids through the colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tet razolium bromide (MTT) assay (Mosmann, 1983; Berridge et al., 1996) in a 96-well plates; chalcone-sulfonamide hybrids (0.078–5 µg $mL^{-1}$) dissolved in sterile DMSO prior to addition to each well, followed by incubation for 72 h. Next, plates were centrifuged and the supernatant was withdrawn. Each well was treated with 150 µL of MTT solution at 0.5 mg $mL^{-1}$, followed by incubation for 3 h at an atmosphere of 5% $CO_2$ at 37 °C. Doxorubicin (0.03–5 µg $mL^{-1}$) and sterile DMSO (0.05%) were used as positive and negative controls, respectively. Absorbance at 570 nm was measured and converted into a cell growth inhibition percentage (GI-%) by the following equation: GI-% = 100 − [(T/C) × 100%], wherein C is the absorbance for the negative control, and T was the absorbance in the presence of the tested compound. Next, their $IC_{50}$ values were determined using nonlinear regression (GraphPad Prism program, version 5.0). All experiments were performed in triplicate.

## 3. Results and discussion

Two synthetic pathways have been used for the synthesis of chalcone-sulfonamide hybrids in this study. Even though we expected the same product from both approaches, diversified molecular scaffolds were obtained. In the first approach, the Claisen–Schmidt condensation reaction between a sulfonamidoacetophenone [*N*-(2-acetylphenyl)benzenesulfonamide (**1**) or *N*-(2-acetylphenyl)-2,5-dichlorobenzenesulfonamide (**2**)] and a nitrobenzaldehyde (*ortho*, *meta* or *para*-nitrobenaldehyde, compounds **3**, **4** and **5**, respectively) was performed (Scheme 1). In the second setup, the 2′-aminochalcone was firstly synthesized through Claisen–Schmidt condensation between a nitrobenzaldeyde and 2-aminoacetophenone and then reacted with benzensulfonyl chloride (Scheme 2). Despite the reaction sequence differed for these two approaches, the same chalcone-sulfonamide hybrid bearing only three rings was predicted to be isolated from both pathways. However, four molecular scaffolds were obtained according to the pathway, reaction time, catalyst, nitro position at the benzaldehyde and the 2,5-dichloro substituents presence at the benzenesulfonamide.

In the first approach, the initial preparation of the sulfonamidoacetophenone increases the reactivity of amine group which is observed in the course of the reaction time. The reaction between **1** and **4** for 5 days resulted in the chalcone-sulfonamide product **6**, which has been already synthesized (Ganguly et al., 2003). However, no report of its crystal structure is available thus far (Fig. 1). Similarly, by reacting **2** with either **4** or **5**, the chalcone-hybrid product **7** or **8** is obtained within 2 h and 4 h, respectively. However, if the reaction between **2** and **4** is stopped only after 3 h from reaction beginning, the expected product is cyclized into the quinolinone **9** through addition of the sulfonamide amine group to the double-bonded carbons from the open-chain chalcone core.

**Table 1** Summary of crystal data and refinement statistics for compounds elucidated for first time in this study using MoKα radiation at 296 K.

| | **6** | **7** | **8** | **9-I** | **9-II** | **10-I** | **10-II** | **11** | **12** | **13** | **16** | **17** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Structural formula[a] | $C_{21}H_{16}N_2O_3S$ | $C_{21}H_{14}Cl_2N_2O_3S$ | $C_{21}H_{14}Cl_2N_2O_3S$ | $C_{21}H_{14}Cl_2N_2O_3S$ | $C_{21}H_{14}Cl_2N_2O_3S$ | $C_{28}H_{17}Cl_2N_3O_3S$ | $C_{28}H_{17}Cl_2N_3O_7S$ | $C_{21}H_{18}N_2O_6S$ | $C_{15}H_{10}N_2O_3$ | $C_{15}H_{10}N_2O_3$ | $(C_{27}H_{20}N_2O_7S_2)$ $(C_3H_6O)_{0.25}$ | $C_{21}H_{16}N_2O_3S$ |
| Space group | $P2_1/n$ | $P2_1/n$ | $P6_1$ | $P2_1cn$ | $P2_1/c$ | $P2_1/c$ | $P2_1/n$ | *P*-1 | $P2_1$ | $P2_1/c$ | $P2_1/c$ | *P*-1 |
| *a* (Å) | 13.9668(9) | 8.4997(6) | 8.2576(3) | 7.335(3) | 7.3044(16) | 9.6278(8) | 10.8996(8) | 8.018(2) | 3.897(6) | 8.6648(5) | 7.906(5) | 8.577(3) |
| *b* (Å) | 7.6342(4) | 17.0027(12) | 8.2576(3) | 14.914(5) | 14.915(4) | 22.274(2) | 14.2308(10) | 10.434(3) | 20.47(2) | 11.2242(7) | 47.59(3) | 8.736(3) |
| *c* (Å) | 18.3378(11) | 14.1764(10) | 51.6873(17) | 18.505(5) | 18.550(4) | 12.3422(11) | 17.0098(11) | 12.753(4) | 7.447(8) | 12.7144(12) | 13.864(9) | 14.724(6) |
| α (°) | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 108.053(16) | 90 | 90 | 90 | 79.829(18) |
| β(°) | 101.221(4) | 94.928(3) | 90 | 90 | 92.018(12) | 95.481(3) | 94.481(2) | 94.687(17) | 90.45(3) | 94.687(4) | 98.116(13) | 87.68(2) |
| γ(°) | 90 | 90 | 120 | 90 | 90 | 90 | 90 | 103.144(16) | 90 | 90 | 90 | 61.29(2) |
| V (Å)$^3$ | 1917.9(2) | 2041.2(2) | 3052.3(2) | 2024.3(12) | 2019.8(8) | 2634.7(4) | 2630.3(3) | 974.4(5) | 594.1(13) | 1232.41(16) | 5164(6) | 951.2(6) |
| Completeness to θ = 25°(%) | 99.9 | 96.5 | 97.8 | 99.9 | 96.7 | 99.9 | 98.0 | 94.0 | 97.6 | 97.2 | 96.2 | 99.6 |
| Final *R1* factor for $I > 2\sigma$ ($I$) | 0.0592 | 0.0317 | 0.0462 | 0.0671 | 0.0408 | 0.0514 | 0.0442 | 0.0665 | 0.0425 | 0.0757 | 0.0709 | 0.1954[b] |
| *wR2* factor for all data | 0.1751 | 0.0941 | 0.0809 | 0.1767 | 0.1165 | 0.1591 | 0.1220 | 0.2001 | 0.1144 | 0.2482 | 0.1997 | 0.5408[b] |
| Largest Δρ peaks ($e$/Å$^3$) | 0.314 /−0.458 | 0.367/−0.369 | 0.201/−0.215 | 0.664/−0.412 | 0.335/−0.389 | 0.315/−0.321 | 0.247/−0.365 | 0.352/−0.290 | 0.143/ −0.159 | 0.711/ −0.296 | 0.940/−0.429 | 1.175/ −0.816[b] |
| CCDC deposit number | 1,570,496 | 1,570,501 | 1,570,498 | 1,570,502 | 1,570,500 | 1,570,497 | 1,570,494 | 1,570,493 | 1,570,491 | 1,570,492 | 1,570,499 | 1,570,495 |

[a] All asymmetric units were composed with one structural formula defined in this table, except compound **16** which has two units of the structural formulae in the asymmetric unit.
[b] Bad refinement statistics were due to strong random twinning of that crystals. Twin law was applied to the structural refinement, but no improvement in refinement statistics was gotten.

A six-membered ring is formed in this cyclization since amine nitrogen binds to β-carbon from propenone. Otherwise, if the reaction time is extended up to 2 days for precursors **2** and **5**, a further *p*-nitrobenzaldehyde is attached to the quinolinone through an additional Claisen–Schmidt condensation step involving its methylene moiety formed in the former cyclization path. This gives rise to the (*E*)-3-ene-2,3-dihydroquinolinone derivative **10** resulted from two Claisen–Schmidt condensation reactions intercalated by a NH addition to the open chain unsaturated carbons.

Furthermore, compounds **9** and **10** exhibit polymorphism. Each one of them was isolated in the two different solid forms if crystallized from either acetone (labeled as form **I**) or ethyl alcohol (labeled as form **II**). In both crystal forms of **9**, molecular conformations are resembled (Figs. 1 and 2), but the growth direction of supramolecular chains differs between them (Fig. 3). In **10**, both the conformations and the intermolecular interaction patterns change for its polymorphs (Figs. 1–3). Relative to quinolinone mean plane, *p*-nitrophenyl moiety bonded to α-carbon is more bent in **10-II** than in **10-I**. Likewise, if **10-I** is taken as reference, the 2,5-dichlorobenzenesulfonamide group conformation is slightly rotated on the S—N bond axis in **10-II**.

A compound related to **10**, with *p*-toluenesulfonyl and *p*-hydroxyphenyl moieties in lieu of 2,5-dichlorobenzensulfonyl and *p*-nitrophenyl, has been synthesized previously (Kim et al., 2009). Its molecular conformation is similar to that of **10-I** (root-mean square deviation (RMSD) of 0.261 Å for their correspondent non-hydrogen atoms), including the formation of a π…π interaction between π-electrons rose from the second Claisen–Schmidt condensation and the phenyl ring bonded directly to sulfonamide. Such intramolecular interaction also occurs in **10-II**, but it is much weaker than in **10-I** (the centroids calculated between the α and β -carbons and among the six phenyl carbons from 2,5-dichlorobenzenesulfonamide are distanced by 3.7456(2) Å and 4.1244(2) Å in **10-I** and **10-II**, respectively). To the formation of this known compound similar to **10**, it was believed to occur simultaneously the reaction of two *p*-hydroxybenzaldehyde molecules with one 2′-*N*-(*p*-toluenesulfonyl)-aminoacetophenone through its amine and methyl groups, resulting in the formation of both chalcone and Schiff base functionalities into an intermediate which then undergoes cyclization lastly (Kim et al., 2009). Here, the isolation of quinolinone **9** suggests that one benzaldehyde does not react with sulfonamide amine moiety. Contrarily, cyclization succeeds the first Claisen–Schmidt condensation to get the expected chalcone-sulfonamide hybrid, ending with an additional Claisen–Schmidt condensation to the methylene group formed in the first one. The occurrence of such mechanism has been recently suggested in the formation of another **10**-like 5-methylated compound with *p*-toluenesulfonyl and *p*-bromophenyl moieties (Wang et al., 2016), which is also conformationally resembled to **10-I** (RMSD of 0.270 Å for their correspondent non-hydrogen atoms).

Furthermore, the cyclization step without benzaldehyde attaching at the amine group can be viewed in the side product of the reactions between **1** and **3** and between **2** and **5**. The first Claisen–Schmidt condensation occurs if reacting **1** and **3**, but there is not water elimination, and, therefore, a β-hydroxylated derivative **11** is formed without double bond between α- and β-carbons. Besides this main product, a side product (**12**) was also isolated. It is already known

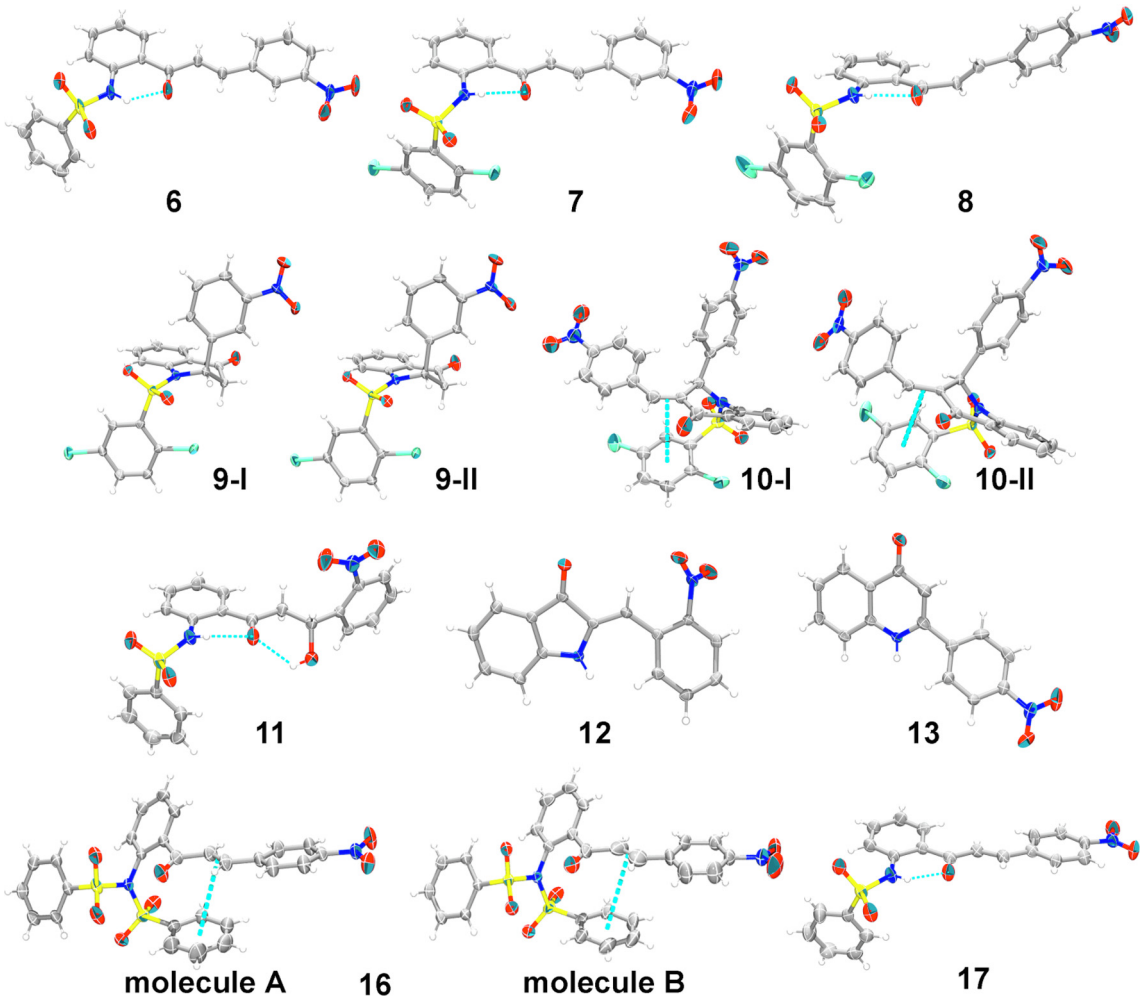



**Fig. 1** Projection of the molecules found in the crystallographic asymmetric units determined here. Non-hydrogen atoms are drawn with their 30% probability ellipsoid, while hydrogen atoms are arbitrary radius spheres. In the asymmetric unit of **16**, there is also one 50% occupancy ethyl alcohol molecule whose methylene carbon lies on an inversion centre (not shown for clarity).

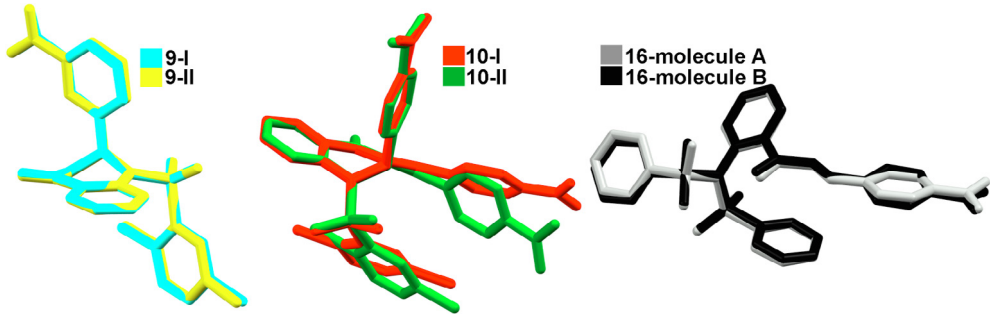



**Fig. 2** Molecular superimpositions for the polymorphic systems and for the two-crystallographically independent molecules of **16**.

(Katritzky et al., 1988) and is featured by benzenosulfonyl elimination and then cyclization through substitution on α -carbon. This gives rise to a 3-oxo-1,3-dihydro-2*H*-indol-2-ylidene derivative with a further five-membered ring and a remaining double-bond between α- and β-carbons, as also occurs in the 3-(*p*-nitrobenzylidene)-quinolinone **10**. It is important to state that this reaction was conducted using triethylamine as catalyst instead of KOH, which led to a non-separable complex mixture in trial reactions. It is important to mention that triethylamine dissolved better at 0 °C than at room temperature. After 1 h of beginning the reaction between **2** and **5**, the side product **13** is formed in a similar way of that

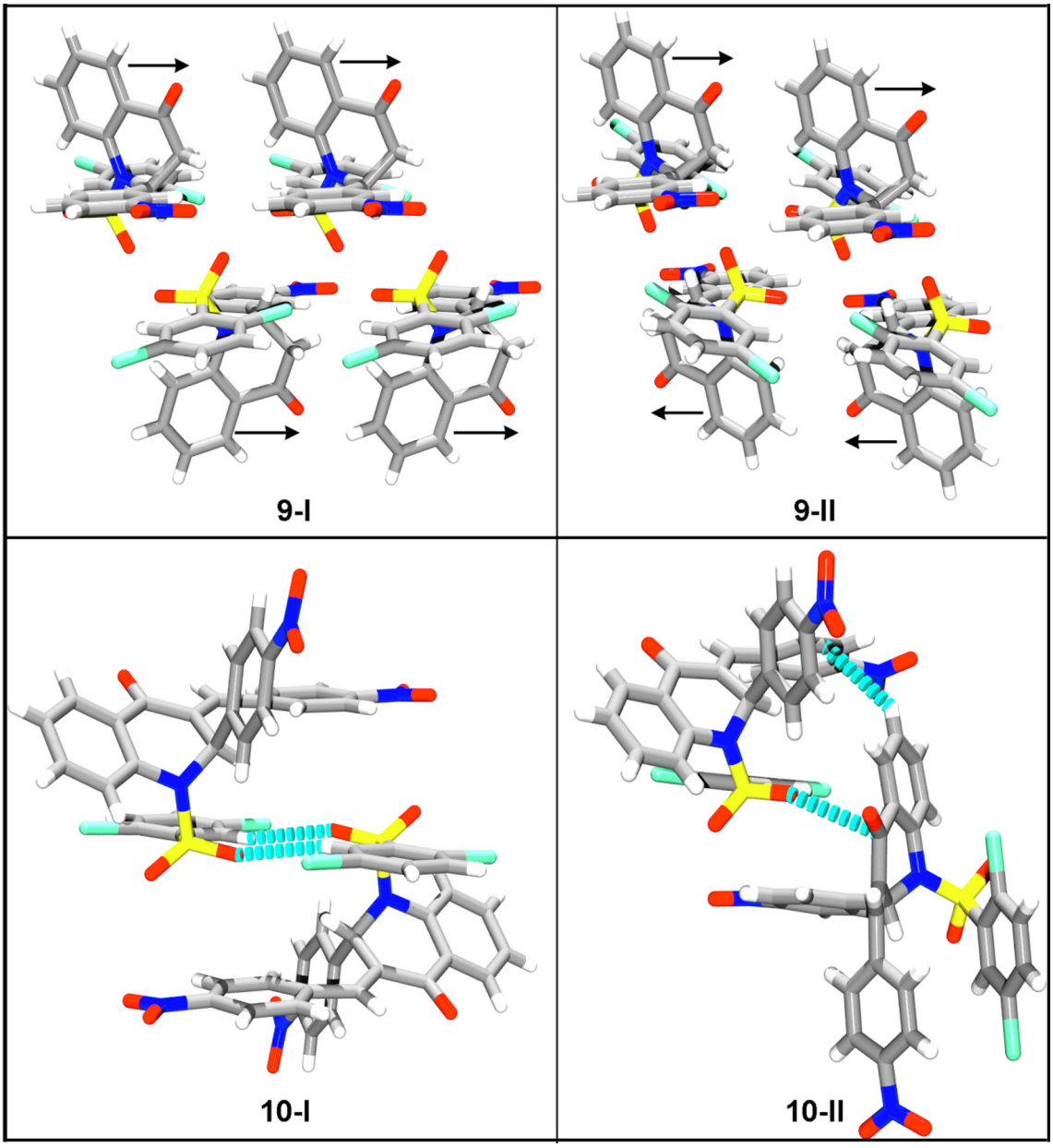



**Fig. 3** Crystal packing differences in the polymorphic systems. In **9**, arrows indicate the direction of quinolinone packing into one-dimensional chains, which are further packed on top of each other. In **10**, cyan dashed sticks draw some selected intermolecular interactions changing for the polymorphs.

found in the formation of **12**. Benzenosulfonyl elimination and cyclization through substitution on β-carbon occurs, giving rise to the known quinolinone **13** (Rocha et al., 2015; Li et al., 2009), but whose crystal structure is reported for the first time here.

If chalcone **15** is first synthesized through Claisen–Schmidt condensation between 2-aminoacetophenone (**14**) and *p*-nitrobenzaldehyde (**5**) and then reacted with benzenosulfonyl chloride, two products can be obtained according to catalyst. A new chalcone-(bis)sulfonamide hybrid is isolated out from the triethylamine catalyzed batch (Scheme 2). This procedure (Iqbal et al., 2014), contrary to all others in which the sulfonamidoacetophenone was first synthesized prior to Claisen–Schmidt condensation with nitrobenzaldehydes, resulted in the (bis)-sulfonamide derivative **16** with bonding of two benzenesulfonyl moieties to amine nitrogen. This chalcone-(bis)sulfonamide hybrid scaffold is new and can be a recipe of getting novel compounds with desired biological and technical properties, as well as simply controlling reaction time as exposed before. Based on the crystal structure of **16**, it is possible to see an intramolecular π...π interaction between the double-bonded carbons from propenone moiety and the phenyl ring from one of the two benzenosulfonyl groups. This interaction is found in the two crystallographically independent molecules of **16**, which, by the way, are conformationally similar (RMSD of 0.248 Å for all non-hydrogen atoms; Figs. 1

and 2), and is responsible to drive their conformation. This suggests a stabilizing role of this non-covalent intramolecular contact contributing to the entry of the further benzenesulfonyl moiety. Furthermore, the role of the catalyst in the molecular diversity of chalcone-sulfonamide hybrids can be realized if chalcone **15** is reacted with benzenosulfonyl chloride in the presence of KOH rather than triethylamine. The chalcone-sulfonamide hybrid **17** with just one benzenesulfonyl group is formed from this reaction, showing the catalyst controls the number of benzenesulfonyl groups bonded to nitrogen.

Through expanding reaction time, inverting the order of reactions, or changing catalyst, a wide range of new chalcone-sulfonamide hybrid based scaffolds and then new compounds can be designed and prepared for varied purposes. In medicinal chemistry, this is highly desired and can provide new drugs. In this sense, we have tested the chalcone-sulfonamide hybrids synthesized here against three cancer lines as well as the known side products **12** and **13** (Table 2). Among the compounds synthesized for the first time here, only the non-cyclized hybrid **7** and the chalcone-(bis)sulfonamide **16** were significantly active against all lineages tested. Literature compound **12** and chalcone-sulfonamide hybrid **6** were also well active against the three cancel cell types. Among these three most active compounds, the open-chain chalcone-sulfonamide **7** had the lowest $IC_{50}$ values (0.12–0.28 μmol $L^{-1}$) against the three cancer cell lines evaluated, being, therefore, the most promising new drug candidate synthesized here. Non-cyclized compounds **8**, **11** and **17** and cyclized compounds **9** and **10** were not active against them ($IC_{50}$ > 25 μmol $L^{-1}$). This reveals that formation of the further six-membered ring through N—C bond establishment depletes the cytotoxicity of the hybrids, which seems to depend on the presence of the NH group (probably to assemble hydrogen bonds with macromolecular targets). One could think that the loss of the α, β-unsaturated carbons in compound **9** would be responsible for anticancer profile decrease, but it is present in compound **10** which was also inactive here. Therefore, the free amine group can have provided the cytotoxic property of the tested compounds.

**Table 2** $IC_{50}$ Values for compounds **6**–**13**, **16** and **17**.[a]

| Compound | PC-3[b] | HCT-116 | SF-295 |
|---|---|---|---|
| **6** | 7.94 (7.30–8.64) | 5.57 (4.87–6.38) | 6.79 (6.09–7.57) |
| **7** | 0.28 (0.17–0.30) | 0.12 (0.09–0.17) | 0.24 (0.20–0.27) |
| **8** | > 25 | > 25 | > 25 |
| **9** | > 25 | > 25 | > 25 |
| **10** | > 25 | > 25 | > 25 |
| **11** | > 25 | > 25 | > 25 |
| **12** | 1.86 (1.58–2.18) | 0.53 (0.49–0.57) | 2.77 (2.52–3.05) |
| **13** | > 25 | > 25 | > 25 |
| **16** | 2.2 (1.97–2.45) | 0.92 (0.84–1.0) | 3.02 (2.83–3.23) |
| **17** | > 25 | > 25 | > 25 |

[a] $IC_{50}$ (CI 95%) [μmol $L^{-1}$]: 50% inhibitory concentration and 95% confidence interval in parenthesis.
[b] Cancer cell lines: PC-3, prostate cancer, HTC-116, colon cancer, and SF-295, central nervous system.

## 4. Conclusion

In summary, we have demonstrated here how to obtain different molecular scaffolds only tuning the time of reaction, order of reactions and catalyst. Seven new compounds were prepared and twelve crystal structures, including two polymorphic systems, were reported for the first time here. Open-chain chalcone-sulfonamide hybrids, whose molecular hybridization occurred at *ortho* position of chalcone benzoyl group through condensation of sulfonamidoacetophenone and nitrobenzaldehyde, can be obtained in shorter reaction times, while cyclization at β-carbon to form quinolinone derivatives and another sequential Claisen–Schmidt condensation to the α-carbon can be achieved if reaction is sequentially stopped later. Also, if chalcone is first synthesized and then reacted with benzenesulfonyl chloride, a compound bearing the new chalcone-(bis) sulfonamide framework was prepared under triethylamine catalysis. If this catalyst is changed by KOH, the corresponding chalcone-sulfonamide hybrid is synthesized instead. The control of the molecular diversity through time and reagents order and catalyst is highly desired to chemical engineering purposes and can be exploited to a broad range of relevant compounds belonging to this class.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arabjc.2017.11.005.

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