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Design, synthesis, characterization, and anticancer activity of a novel series of *O*-substituted chalcone derivatives

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ABSTRACT

A new series of *O*-substituted chalcone derivatives bearing an/a allyl-, prenyl- or propargyl-substituent at different positions of rings A and B and their derivatives as drug leads, was designed, synthesized, and characterized. The chalcone derivatives were synthesized *via* base catalyzed Claisen-Schmidt condensation in MeOH or EtOH solutions of appropriately substituted aromatic ketones with *O*-allyl, and *O*-propargylvanillin, respectively. The intermediates *O*-substituted phenylketone derivatives were firstly synthesized by nucleophilic substitution reaction. All the newly synthesized compounds were characterized by IR, NMR spectral data and elemental analyses. A preliminary cytotoxicity was performed with the compounds (**1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **5a-f**, **6a-d**, **7a-d**) and the positive control, doxorubicin towards CCRF-CEM leukemia cells. Amongst them, compounds **1a**, **2a**, **5b-d**, **6b**, **7a**, **7c** and doxorubicin displayed IC_{50} values below 20 μM while other compounds were less or not active at up to 50 μM. Remarkably interesting cytotoxic effects, with IC_{50} values below 1 μM were recorded with **5c** against HCT116 $p53^{-/-}$ colon adenocarcinoma cells, **5e** against CCRF-CEM cells and MDA-MB-231-*BCRP* breast adenocarcinoma cells, and **6b** against HCT116 $p53^{+/+}$ cells and HCT116 $p53^{-/-}$ cells.

Introduction

Cancer, occurring by abnormal division and spread of cells, is recognized as the main global health problem and is one of the major causes of death.[1,2] There are many methods used in the current cancer treatment such as chemotherapy, radiotherapy, surgery or their combinations.[3] Among these treatments, chemotherapy method is one of the most common and effective treatments used in many types of cancer. But, most antitumor agents used in chemotherapy suffer from serious side effects.[4] Therefore, the design, synthesis, and discovery of chemotherapeutic agents with high anticancer potential and selectivity is still a crucial need.

Chalcones and their derivatives are a major class of natural sources belonging to the flavonoid family.[5–8] Chalcones are usually found in fruits, vegetables, teas, and other plants.[9] Chalcones are also considered as the precursors of a panel of biologically important heterocycles such as isoflavonoids, flavones, flavanones, benzothiazepines, and pyrazolines.[10,11] Chemically, they consist of an α, β-unsaturated ketone moiety with two phenyl rings, and can act as Michael acceptors (Fig. 1).[12,13] This was recognized as the main and important pharmacophore for chalcones regarding their biological profiles, as removal of this functionality made them mostly inactive.[5] Over the last decades, chalcones have captured the interest of chemical and pharmacological researchers because of their simple chemical structure and various biological activities.[10] Attractively, chalcones are synthesized with good yields by Claisen-Schmidt acid- or base-catalyzed condensation.[14] Due to their simple chemistry and widespread applications in the medicinal, synthetic and material sciences, chalcones have incessantly been paid a huge attention.[15] Chalcone derivatives exhibited significantly photophysical and photochemical properties.[16] Chalconoids are widely used

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in optoelectronic fields such as nonlinear materials, chromophore sensors and DNA biosensor.[16] Therefore, chalcones as well as their synthetic analogues possess a remarkably wide spectrum of useful biological and pharmacological properties, including antioxidant,[17] antimicrobial,[18] antimalarial,[19] antibacterial,[20] anti-HIV,[21] anti-inflammatory,[22] anti-Alzheimer's,[23] antiulcer[24] properties. In addition, chalcones have exhibited excellent anticancer activity and attracted much attention in anticancer studies.[25,26] Isoliquiritigenin,[27] Butein,[28] Xanthohumol,[29] Xanthoangelol,[30] Isobavachalcone,[31] Licochalcone A[32] and Millepachine[33] isolated from natural products, have been reported to display potent cytotoxicity against a variety of human cancer cells (Figure 1). A good safety profile and possibility of oral administration[34] are the major factors contributing to the increasing interest of many researchers to isolate and elucidate them from nature and to develop efficient synthetic methods. Also, synthesized chalcones bearing propargylic substitutions were recently reported as potent antimalarial and antitubercular agents.[35] In addition, the substitution of ring B with electron-donating groups like methoxy or hydroxy group improves the antiproliferative activity against human colon HT-29 cancer cell line.[36] In this line, our research group has demonstrated that the substitution of the hydroxy group of ring B of chalcone with allyloxy substituent enhanced the *in vitro* cytotoxic activities with IC_{50} values below 100 μM against the five human cancer cell lines (THP-1 (4.76 μM), DU-145 (5.21 μM), HL60 (7.90 μM), Hep-G2 (10.12 μM) and MCF-7 (10.32 μM)).[37] All our synthesized allyloxychalcone derivatives have shown their ability to kill tumor cells *in vitro*.[37]

On the other hand, aromatic compounds containing the propargyl functional group are of considerable interest in the medicinal and analytical fields, and have long been recognized as mechanism-based inhibitors of CYPs.[38] Then, both Tremorine and Oxotremorine compounds have been reported to have potential value in Parkinson's disease.[39] Acetylenic derivatives are an important class of compounds due to their ability to exhibit anticancer properties.[40] They also function as a key pharmacophoric unit in acetylenic antibiotics, and these functional groups have been reported to contribute to enhancing lipophilicity.[35] This group is found in the structure of synthetic drugs as well as naturally occurring antitumor and anticancer drugs such as calicheamicin, esperamicin, dynemicin, and namenamicin which are the most potent anticancer agents identified up to the present.[40] The presence of the nucleophilic triple bond, coupled with fairly acidic terminal acetylenic hydrogen in many cases, make these propargylic compounds highly potential for a wide useful chemical transformations.[41] Altogether, alkynes are versatile building blocks for the synthesis of natural products and also hybrid structures with interesting biological activities. Most important of all of its applications is to use them as triazole intermediate.[42] Furthermore, chalcones holding a propargyl group are known as the key intermediate in the synthesis of various biologically important heterocyclic compounds. The acetylenic chalcones and their analogues are relatively rare as drug molecule models. However, the appearance of acetylenic groups in drugs is increasing, given the frequency of use and ease of the Sonogashira coupling reaction[43] that provides for a facile coupling of terminal alkynes to various aromatic systems. Otherwise, prenylation is a very interesting reaction because it increases the lipophilic character and biological activity compared to the unsubstituted chalcones.[44] However, synthetic chalcone derivatives containing *O*-propargyl and *O*-prenyl groups are less common and less attention has been focused on these compounds.[45]

In the present study, we reported on the synthesis and structural characterization of a new series of *O*-allylic, *O*-prenylic and *O*-propargylic chalcones and their derivatives as drug leads via two-steps reaction, and investigated their anticancer activities.

4-*O*-substituted phenylcarbonyl derivatives **1a-b** and **2a-b** were synthesized by nucleophilic substitution reaction of vanillin (**1**) or 4-acetyl-2-allylphenol (**2**) with the allyl-, prenyl- or propargyl bromide in the presence of K_2CO_3 in dry acetone at reflux (62–65 °C) under a nitrogen atmosphere.[37,46,47] The vanillin (**1**) and 4-acetyl-2-allylphenol (**2**), which were commercially available, became the key structures that allowed us to prepare 4-*O*-substituted phenylcarbonyl derivatives **1a-b** and **2a-b**.

Synthesis of key intermediates **2a-b** were reported here for the first time while the compounds **1a-b** were synthesized via a previously reported method (Schemes 1).[37,46] The synthetic methods of allylated, prenylated or propargylated chalcones **3a-b**, **4a**, **5a-f**, **6a-d** and **7a-d** are illustrated and summarized in Schemes 2–5. In order to obtain both 4-*O*-allyl-4′-O-prenyl and 4-*O*-allyl-4′-*O*-propargylchalcone derivatives **3a-b** and **4a**, respectively; we examined Claisen-Schmidt condensation reactions between 4-allyloxy-3-methoxybenzaldehyde (**1a**) and the *O*-substituted ketones **2a-b**.[48,49] As a result of these reactions, we obtained from the first reaction two chalcone isomers, the major *E* isomer **3a** with good yield (80%) and its minor *Z* isomer **3b** (20%) while the second reaction provides only a major *E* isomer **4a** with excellent yield (90%) (Scheme 2).

Similarly, chalcones **5a-f** were synthesized via the Claisen-Schimidt condensation of various appropriate substituted aromatic ketones **8a-f** with *O*-propargylvanillin (**1b**). The newly synthesized *O*-propargylchalcones **5a-f** were obtained in good yields of up to 96% (Schemes 3).

In order to further explore a biological profile of some chalcones containing a substituted heterocyclic moiety, we synthesized the novel compounds **6a-d** via the Claisen-Schimidt condensation from *O*-propargylvanillin **1b** (Scheme 4).

Surprisingly, during the Claisen-Schimidt condensation of *O*-

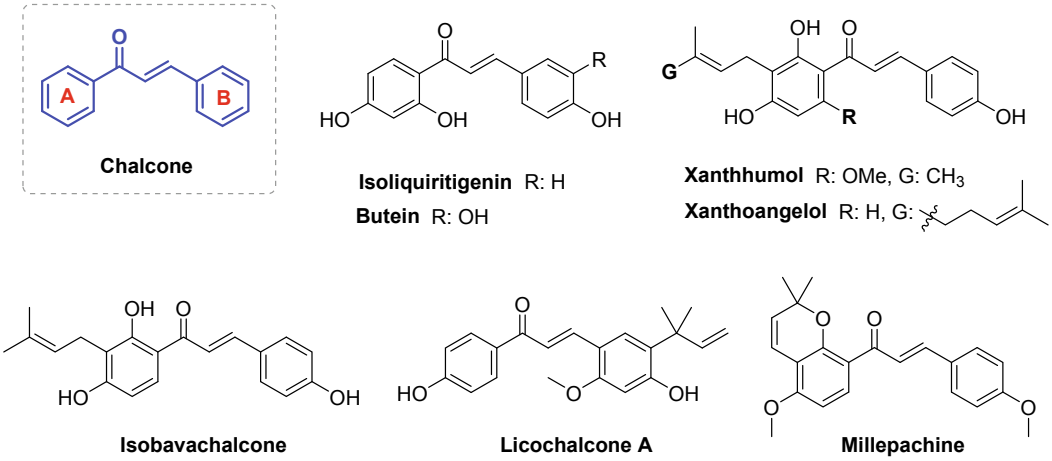
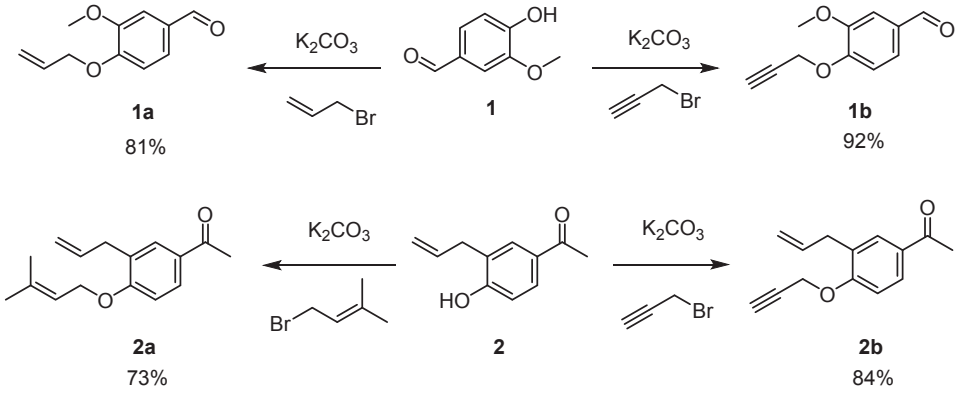
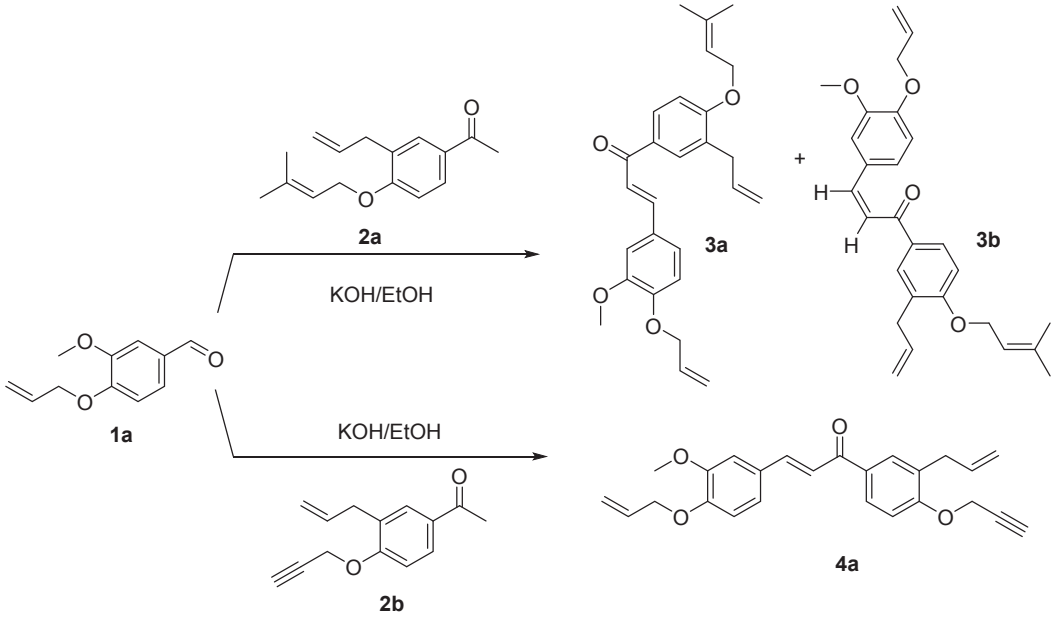


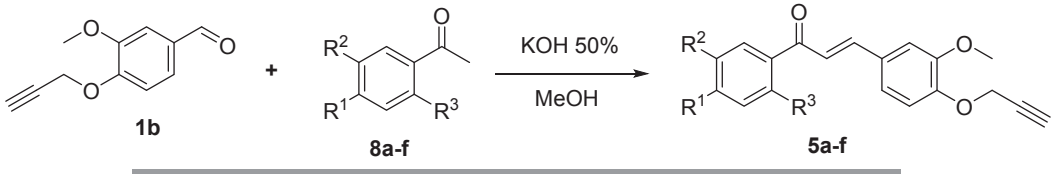
Fig. 1. Structures of simple chalcone, and some isolated natural chalcones.



Scheme 1. Synthesis of the key intermediate 4-*O*-substituted phenylcarbonyl derivatives **1a-b** and **2a-b**.



Scheme 2. Synthesis of novel *O*-allyl, *O*-prenyl and *O*-propargylchalcone derivatives **3a-b** and **4a** from **1a** and **2a-b**.



5a R^1: Prenyl, R^2: H, R^3: H (59%)

5b R^1: Isopropyl, R^2: H, R^3: H (68%)

5c R^1: OMe, R^2: OMe, R^3: H (76%)

5d R^1: H, R^2: OMe, R^3: H (56%)

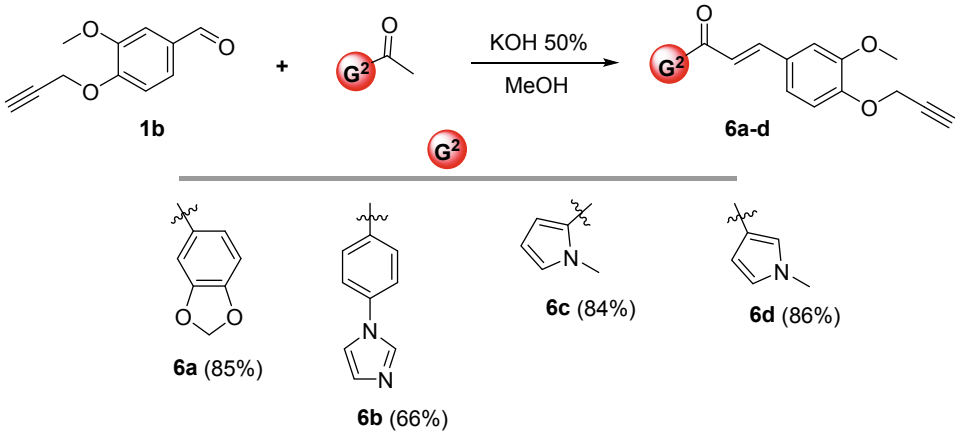
5e R^1: H, R^2: H, R^3: Me (85%)

5f R^1: Me, R^2: H, R^3: H (96%)

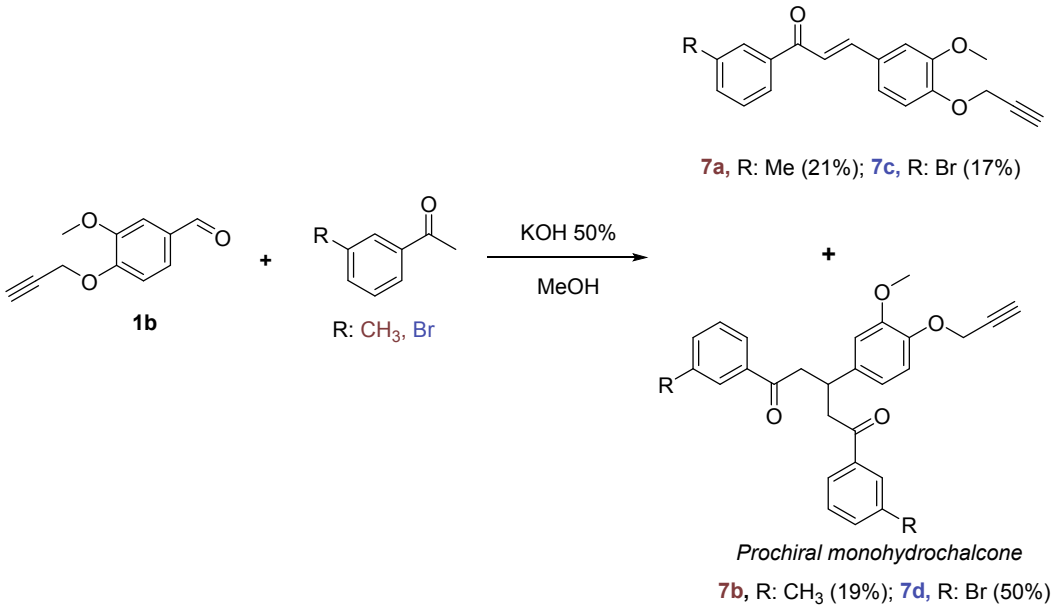
Scheme 3. Synthesis of novel *O*-propargylchalcone derivatives **5a-f** from *O*-propargylvanillin **1b**.

propargylvanillin (**1b**) with *m*-bromo or *m*-methylacetophenone in the presence of KOH 50% in methanol, the prochiral monohydrochalcone derivatives **7b**, and **7d** are obtained from moderate (19%) to good yield (50%) in both cases, respectively (Scheme 5). Otherwise, the lower temperature of reaction conditions of *m*-bromoacetophenone between 30 and 34 °C for 21 h under N_2 atm. is provided two products: **7c** (24%) and **7d** (43%) while at the high temperature (44–46 °C), the formation of prochiral product is more increased (50%) compared to the chalcone **7c** (17%). The difference observed in the formation of compounds **7c** and **7d** regarding their yields is more crucial for these reaction conditions and can also help on further to oriente the synthesis of major product.

Furthermore, the mechanism of formation of the newly synthesized compounds **7b** and **7d** can be explained via a Michael reaction which occurred 1,4-addition or a conjugate addition between the α, β-unsaturated ketones and nucleophiles (aromatic enolate ion) (Scheme 6). The



Scheme 4. Synthesis of novel *O*-propargylated chalcones (**6a-d**) containing a substituted heterocyclic moiety from *O*-propargylvanillin **1b**.

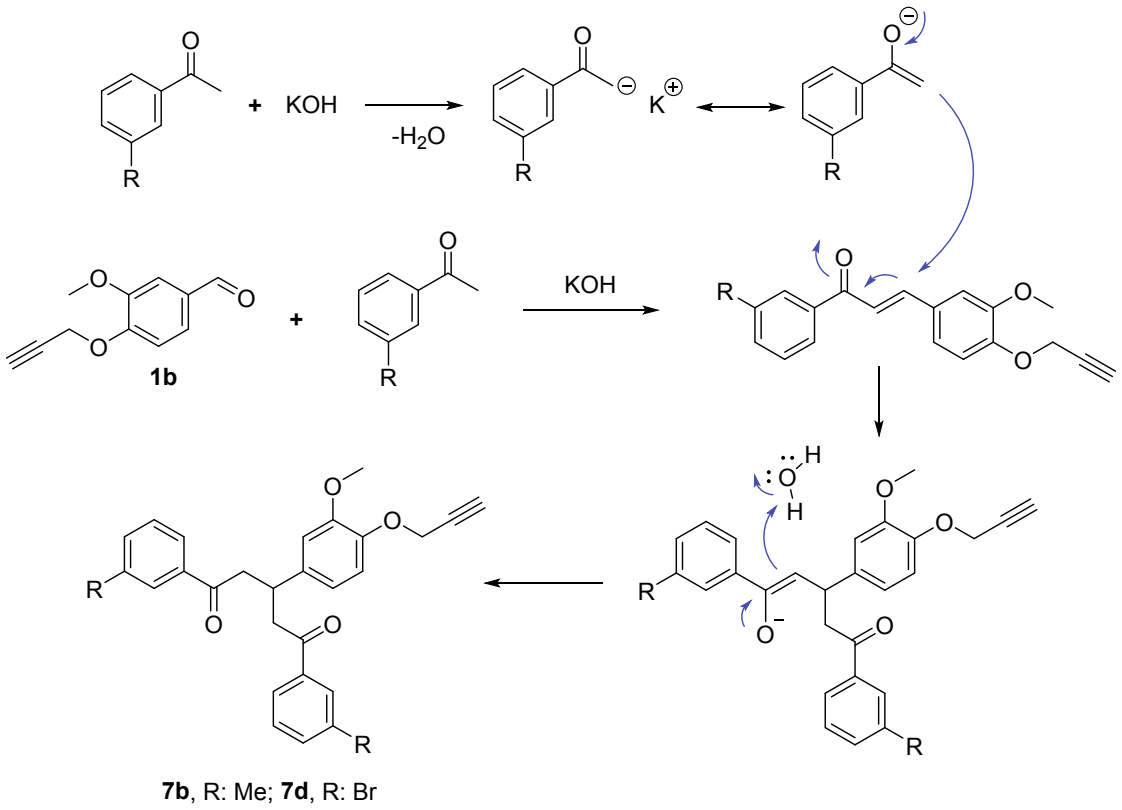


Scheme 5. Synthesis of novel *O*-propargylchalcone derivatives **7a-d** from *O*-propargylvanillin **1b** with formation of unusually prochiral monohydrochalcones **7b** and **7d**, respectively. Repeated reaction at low temperature: **7c** 24%, **7d** 43%.

resulting products of our approach, prochiral chalcones **7b** and **7d** were reported here for the first time via base-catalyzed condensation reaction.

Then, the method used is effective since it specifically generates more (*E*)-isomer. This is supported by the ^{1}H NMR spectra which indicates that chalcones **3a**, **4a, 5a-f, 6a-d, 7a, and 7c** were geometrically pure and with *E* configuration ($J_{H\alpha-H\beta}$ = 15.5–15.8 Hz). The configuration is also commonly found in naturally occurring chalcones.[50] All the synthesized compounds present characteristic signals of the two vinylic protons H_α and H_β of the propenone chain as two doublets at δ_H 7.14–7.41 (H_α) and δ_H 7.66–7.75 (H_β). The high coupling constant (*J* = 15.5–15.8 Hz) of the two doublets corresponding to protons H_α and H_β of the propenone chain indicates that the synthesized chalcones were obtained with *E* configuration.[51] Herein, the newly synthesized compounds offer a new template for the design and future development of Click chemistry for the valorization of heterocyclic chemistry. Additionally, the present study potentially also paves the way for the construction of novel chalcone for use of its derivatives in different applications.

A preliminary cytotoxicity was performed with the synthetized compounds (**1a, 1b, 2a, 2b, 3a, 3b, 4a, 5a-f, 6a-d, 7a-d**) and the positive control, doxorubicin towards CCRF-CEM cells (Table 1). Amongst them, compounds **1a, 2a, 5b-e, 6b, 7a, 7c** and doxorubicin displayed IC_{50} values below 20 μM, **2b** had an IC_{50} value of 38.20 μM meanwhile other compounds were not active at up to 50 μM (Table 1). The cytotoxicity of **1a, 2a, 5b-e, 6b, 7a, 7c** as well as doxorubicin were selected and tested towards a panel of 8 other cancer cell lines and a normal AML12 hepatocytes (Table 2). All selected compounds (**1a, 2a, 5b-e, 6b, 7a, 7c)** had cytotoxic effect in the 8 tested carcinoma cell lines with below 50 μM (Table 2). The accepted IC_{50} values for good cytotoxic compounds are below 10 μM.[52–54] In the present study, it was noted that compounds **1a, 5b, 5c, 5d, 5e, 6b, 7a** and **7c** had IC_{50} values below or around 10 μM on all selected cancer cell lines including drug-sensitive and multidrug resistant (MDR) phenotypes (Table 2). This is a clear indication that these compounds could offer good alternative to fight malignant diseases including refractory cancers. This hypothesis is confirmed by the fact that in most of the cases, the D.R. was below 1 as shown in Table 2. Collateral sensitivity (D.R. below 1) of MDR cells to phytochemicals combined to their good cytotoxicity could be better criteria to select substances for clinical studies, as they can be better candidate to reverse cancer drug resistance or to tackle MDR cancer cells.[55–56] Hence, compounds **1a**, **2a**, **5b**, **5c**, **5d**, **5e**, **6b**, **7a** and **7c** appear as good drug candidates to tackle the multidrug resistance of



Scheme 6. Proposed mechanism of the formation of prochiral monohydrochalcone derivatives **7b**, and **7d**.

Table 1
Preliminary cytotoxicity of compounds on the sensitive CCRF-CEM leukemia cells.

Tested compounds	IC_{50} values (in μM)
1a	14.04 ± 0.39
1b	–
2a	16.25 ± 0.44
2b	38.20 ± 2.13
3a	–
3b	–
4a	–
5a	–
5b	11.85 ± 1.27
5c	**8.65 ± 0.93**
5d	**5.59 ± 0.48**
5e	**6.95 ± 1.77**
5f	–
6a	–
6b	14.95 ± 3.63
6c	–
6d	–
7a	**8.82 ± 0.77**
7b	–
7c	15.16 ± 3.66
7d	–
Doxorubicin	**0.02 ± 0.00**

(-): IC_{50} value above 50 μM; In bold: significant cytotoxic effect.[52–54]

cancer cells. Remarkably interesting cytotoxic effects, with IC_{50} values below 1 μM were recorded with **5c** towards HCT116 *p53*$^{-/-}$ cells (IC_{50} value of 0.32 μM), **5e** towards CCRF-CEM cells and MDA-MB-231-*BCRP* cells (IC_{50} value of 0.92 μM and 0.99 μM, respectively), and **6b** towards HCT116 *p53*$^{+/+}$ cells and HCT116 *p53*$^{-/-}$ cells (IC_{50} value of 0.78 μM and 0.67 μM, respectively) (Table 2). It is noteworthy that contrary to other selected compounds, **5d, 5e, 6b, 7a** and doxorubicin had good selectivity to HepG2 hepatocarinoma cells compared to the normal AML12 hepatocytes (S.I. above 2), suggesting that they could be more appropriate for cancer chemotherapy. Interestingly, all the selected compounds had better cytotoxicity than doxorubicin towards the doxorubicin resistant CEM/ADR5000 cells (Table 2). Furthermore, better cytotoxic effects than that of doxorubicin (IC_{50} value of 1.78 μM) were also recorded with **5c, 5d, 5e, 6b** and **7a** against HCT116 *p53*$^{-/-}$ (IC_{50} value of 0.32 μM, 1.01, 1.06, 0.67 and 1.06, respectively) (Table 2).

Regarding the structure–activity relationship, it appears that the key intermediate 4-*O*-substituted phenylcarbonyl derivatives **1a-b** and **2a-b**, as well as allylated, prenylated or propargylated chalcones **3a-b**, **4a**, **5a-b**, **5f**, **6a-d**, and **7b-d** had poor or no cytotoxic effects (IC_{50} values above 10 μM (Table 1). In contrast, *O*-propargylated chalcones **5c-e** without as allyl, isopropyl or prenyl substituents, as well as the novel *O*-propargylchalcone derivatives **7d** has the best cytotoxic effect with IC_{50} values below 10 μM against many cancer cell lines(Tables 1 and 2). This is an indication that allyl, isopropyl or prenyl substituents decrease the activity of *O*-propargylchalcones. Within the *O*-propargylated chalcones, it was observed that the numbers and positions of both methoxy (**5c** and **5d**) and methyl (**5e** and **5f**) significantly influence the cytotoxic activity (Tables 1 and 2). The presence of Br substituent also significantly increases the activity *O*-propargylchalcones, as **7c** (with Br substituent), had good cytotoxicity contrary to **7a** (with methyl substituent) (Table 1). However, the prochiral monohydrochalcones **7d** also having a Br substituent was devoid of cytotoxic effect, suggesting that the additional aromatic cycle containing another Br rather cancelled the biological activity, probably due to the steric hindrance that might prevent the compound to reach its biological target.

In summary, seventeen new chalcone derivatives were designed and synthesized via the Claisen-Schmidt condensation, in basic media, with good yields 80–90%, and characterized. Anticancer activities of the obtained new compounds evaluated against a panel of 10 cancer cell lines including drug sensitive and MDR phenotypes. Compounds **1a, 5b,**

Table 2
Cytotoxicity of selected compounds and doxorubicin towards drug sensitive cell line, their resistant counterpart's and hepatocytes as determined by RRA after 72 h incubation.

Tested compound	Cell lines, IC_{50} values (in μM), D.R.* or S.I.** (in bracket)								
	CEM/ ADR5000	MDA-MB-231-*pcDNA*	MDA-MB-231 -*BCRP*	HCT116 $p53^{+/+}$	HCT116 $p53^{-/-}$	U87MG	U87MG. Δ*EGFR*	HepG2	AML12
1a	**3.48 ± 0.17** (0.25)	14.99 ± 1.67	**7.53 ± 0.75** (0.50)	**5.77 ± 0.39**	**8.02 ± 0.67** (1.39)	**7.50 ± 0.66**	**6.97 ± 0.47** (0.93)	10.46 ± 1.13	15.27 ± 1.28 (1.46)
2a	**5.25 ± 0.89** (0.32)	17.87 ± 2.01	11.92 ± 2.00 (0.67)	10.64 ± 0.94	13.95 ± 0.93 (1.31)	12.93 ± 1.21	12.20 ± 1.16 (0.94)	14.67 ± 1.28	18.08 ± 1.17 (1.23)
5b	**2.72 ± 0.31** (0.23)	**4.07 ± 0.33**	**2.93 ± 0.24** (0.72)	**3.70 ± 0.27**	**3.13 ± 0.40** (0.85)	**2.84 ± 0.18**	**2.12 ± 0.11** (0.75)	**6.31 ± 0.42**	**9.91 ± 0.10** (1.57)
5c	**1.44 ± 0.22** (0.17)	13.62 ± 1.49	**1.89 ± 0.14** (0.14)	**2.01 ± 0.33**	**0.32 ± 0.28** (0.16)	**2.86 ± 0.15**	**1.56 ± 0.18** (0.55)	**5.98 ± 0.61**	**6.75 ± 0.39** (1.13)
5d	**1.10 ± 0.17** (0.20)	13.76 ± 1.18	**1.23 ± 0.07** (0.09)	**1.92 ± 0.17**	**1.01 ± 0.19** (0.53)	**1.46 ± 0.12**	**1.33 ± 0.10** (0.91)	**5.54 ± 0.44**	11.38 ± 1.03 (2.05)
5e	**0.92 ± 0.06** (0.13)	14.78 ± 1.42	**0.99 ± 0.01** (0.07)	**1.66 ± 0.18**	**1.06 ± 0.07** (0.64)	**2.10 ± 0.30**	**1.21 ± 0.09** (0.58)	**2.64 ± 0.31**	**8.20 ± 0.77** (3.11)
6b	**1.00 ± 0.08** (0.07)	**2.03 ± 0.13**	**1.74 ± 0.10** (0.86)	**0.78 ± 0.05**	**0.67 ± 0.01** (0.86)	**1.41 ± 0.09**	**1.08 ± 0.06** (0.77)	**5.39 ± 0.56**	12.71 ± 1.06 (2.36)
7a	**1.38 ± 0.09** (0.16)	**2.03 ± 0.21**	**1.77 ± 0.18** (0.87)	**1.38 ± 0.11**	**1.06 ± 0.06** (0.77)	**1.80 ± 0.28**	**1.97 ± 0.20** (1.09)	**5.03 ± 0.47**	11.27 ± 0.97 (2.24)
7c	**2.28 ± 0.19** (0.15)	**3.50 ± 0.40**	**3.09 ± 0.21** (0.88)	**2.90 ± 0.38**	**1.90 ± 0.14** (0.66)	**2.59 ± 0.32**	**4.16 ± 0.29** (1.61)	10.10 ± 0.88	12.51 ± 1.12 (1.24)
Doxorubicin	122.96 ± 10.94 (6,683.00)	**0.13 ± 0.01**	**0.79 ± 0.08** (6.14)	**0.48 ± 0.06**	**1.78 ± 0.08** (3.73)	**0.26 ± 0.03**	**0.98 ± 0.07** (3.79)	**4.56 ± 0.48**	52.90 ± 4.09 (11.59)

(*): D.R.: the degree of resistance (D.R.) was determined as the ratio of IC_{50} value in the resistant divided by the IC_{50} in the sensitive cell line; CEM/ADR5000, MDA-MB-231-*BCRP,* HCT116 $p53^{-/-}$ and U87.MGΔ*EGFR* were used as the corresponding resistant counterpart for CCRF-CEM (Table 1), MDA-MB-231-*pcDNA*, HCT116 $p53^{+/+}$, U87.MG cell lines, respectively; (**): S.I.: the selectivity index (S.I.) was determined as the ratio of IC_{50} value in the normal AML12 hepacytes divided by the IC_{50} in HepG2 hepatocarcinoma cells; In bold: significant cytotoxic effect.[52–54]

5d, 5e, 6b, 7a and **7c** had good cytotoxic potential, with IC_{50} values below or around 10 μM on all selected cancer cell lines. The present study clearly shows that compounds **1a, 5b, 5d, 5e, 6b, 7a** and **7c** have a promising potential for the future development of active anticancer agents. These results make the newly synthesized chalcones and their derivatives interesting lead molecules for further intermediated synthetic and biological evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127827.

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