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Synthesis and antiproliferative activity of α-branched α,β-unsaturated ketones

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ABSTRACT

A series of α-branched α,β-unsaturated ketones were prepared in a straightforward manner by the acid catalyzed coupling between arylalkynes and carbaldehydes. The method also allows producing as side product chalcone analogs bearing an additional α,β-unsaturated arylketone in the molecular scaffold. The evaluation of the antiproliferative activity in the human solid tumor cell lines HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast) and WiDr (colon) provided a structure–activity relationship. Overall, the compounds presented active against the resistant cancer cells T-47D. The resulting lead, displaying an unprecedented chalcone scaffold, showed GI_{50} values in the range 0.32 –0.53 μM against all cell lines tested. The methoxy group present in the lead might play an important role in the activity.

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1. Introduction

Chalcones (1,3-diaryl-2-propen-1-ones, **I**, Fig. 1) represent a class of flavonoids that occur naturally in fruits and vegetables. This class of natural products and their synthetic derivatives has shown interesting biological properties [1,2], among which, anticancer activity [3,4] is of particular interest to us. For the chalcones with various antitumor activities reported in the literature in the last decade, their mechanism of action could be organized into diverse categories including induction of apoptosis, antiangiogenesis, antimetastasis, antiinvasion, chemoprevention, cell signal transduction, regulation of cell cycle, NF-κB pathway, and redifferentiation [5]. In addition, some chalcone based compounds were not toxic to normal cells, while have shown in clinical trials reasonable plasma concentrations and did not cause toxicity [6]. Besides all these advantages, there is still room for exploding the pharmacological potential of chalcones by modifications on the molecular scaffold [7]. In this particular context, we have reported earlier that α-branched α,β-unsaturated ketones (**II**, Fig. 1) and β′-acyloxy-α,β-unsaturated ketones (**III**, Fig. 1) prepared *via* iron (III) catalyzed tandem processes, show remarkable biological activity towards human cancer cell lines, including cell cycle arrest and apoptosis induction [8,9].

Chemically, chalcones are defined as open chain flavonoids consisting of two aromatic rings joined by a three carbon α,β-unsaturated carbonyl system (**I**, Fig. 1). Although chalcones may exist in *Z* and *E* isomeric forms, the *E* form is thermodynamically favorable. A common synthetic approach toward the synthesis of α,β-unsubstituted chalcones is *via* the Claisen–Schmidt condensation between *acetophenones* and benzaldehydes in basic media [10,11]. Moreover, some modern synthetic protocols have been reported, such as the palladium-mediated Suzuki coupling between cinnamoyl chloride and phenyl boronic acids [12], the carbonylative Heck coupling with aryl halides and styrenes in the presence of carbon monoxide [13] and Meyer–Schuster rearrangement of propargylic alcohols [14] have been reported. For the synthesis of α-substituted chalcones the Knoevenagel [15], Aldol-Grob [16] type condensations as well as Horner-Wadsworth-Emmons olefination [17] reactions can be applied. Another useful alternative for the construction of the C=C bond is through an alkyne carbonyl metathesis. This transformation represents a completely atom-economical alternative to the use of stabilized Wittig reagents in carbonyl olefination reactions [18]. The metathesis reaction

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generally proceeds *via* a formal [2 + 2] cycloaddition and cycloreversion pathway and produces conjugated carbonyl compounds [19].

Having in mind that the chalcone scaffold and α-substituted α,β-unsaturated ketones are important pharmacophores, we explored the possibility of α-substituted chalcones as antitumor agents. Herein we report on the synthesis and biological activity of a series of functionalized α-substituted chalcones and structural analogs. The compounds were obtained by the Lewis acid catalyzed coupling of alkynes and aldehydes. As a model system to study the biological activity, the representative human solid tumor cells HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung cancer, NSCLC), T-47D (breast) and WiDr (colon cancer) were selected. A structure–activity relationship (SAR) is also discussed.

2. Chemistry

For the preparation of α-branched α,β-unsaturated ketones, we utilized the reaction between arylalkynes and carbaldehydes. First of all, we tested the reactivity of starting alkynes towards Lewis acid-catalyzed coupling reaction with aldehydes. Several Lewis acids such as $BF_3 \cdot Et_2O$, $FeCl_3$, $AgSbF_6$, SbF_5, BBr_3, TMSOTf, diverse solvents (DCM, DCE, CH_3CN, THF, CH_3NO_2) and different reaction temperatures were examined. After this brief searching of the most suitable reaction conditions we came to conclusion that 1 equivalent of $BF_3 \cdot Et_2O$ in dichloromethane at room temperature gave the best results. It should be noted that using nitromethane as a solvent resulted in smoother reactions; however side condensation of benzaldehydes with solvent occurs. Moreover, we found that the outcome of the reaction strongly depends on the structure of both starting materials and, in some cases together with main *E*-configuration enone **2**, smaller amounts of *Z*-isomer **3** or 2:1 adduct **4** formed (Scheme 1). The data of reactions between alkynes **1a**–**f** and various aldehydes under the optimal conditions are summarized in Table 1.

Thus, when phenylacetylene **1a** and (3-chloroprop-1-ynyl) benzene **1b** were used, in all cases a regioselective formation of enones **2** took place (Table 1, entries 1–6). However, during the reaction of 1,2-diphenylethyne **1c** and cyclohexylcarbaldehyde, two products – major *E* (**2**) and minor Z (**3**) were isolated (entry 7). On the other hand, during the reaction between 1,2-diphenylethyne **1c** and 2,4-dichlorobenzencarbaldehyde, *Z*-enone (**3**) was isolated as sole product (entry 8).

Results of the reactions between 3-arylprop-2-inylcarboxylates **1d**–**f** and carbaldehydes were much more intriguing. While in all cases when aliphatic carbaldehydes were used (entries 9, 10, 21, 24) the selective formation of *E*-configurated alkyne–carbonyl metathesis products **2** took place in low or moderate yields. Low overall yields can be explained by possible side self-condensation reaction between two aliphatic aldehydes molecules. However, the mixtures of *E* (**2**) and Z (**3**) isomers of the corresponding α,β-unsaturated ketones were formed during reaction of **1d**–**f** with aromatic aldehydes, especially those having an *ortho*-substituent (Table 1, entries 14, 15, 17–19, 22, 23, 26). The reaction of **1d** with 4-methoxybenzaldehyde was complicated and took longer times for the full conversion of the alkyne; and also a lot of tars were produced. After the work-up of the reaction mixture, 2:1 adduct **4dl** was isolated in poor yield as sole reaction product (entry 20). Moreover, the formation of 2:1 adducts **4** was observed in the case when plain benzaldehyde (entry 11) or halogenated benzaldehydes (entries 12, 13, 16, 25) were used.

3. Antiproliferative activity

From the set of 43 synthesized chalcone analogs, a total of 40 compounds were submitted for biological assays. The in vitro activity was assessed in HBL-100, HeLa, SW1573, T-47D and WiDr human solid tumor cells. The results expressed as GI_{50} were obtained using the SRB assay [21], and the results are given in Table 2. In addition, Fig. 2 shows the mean graph derived from the obtained dose–response data. The standard anticancer drugs cisplatin and etoposide were used as positive controls. Overall, the data on antiproliferative activity show that all tested compounds exhibited growth inhibition in at least two of the cell lines of the panel. For the most active compound of the series **4dl** the GI_{50} values were in the range 0.32–0.53 μM.

The analysis of the GI_{50} values allowed us to establish some SARs. A first comparison was done between *E* (**2**) and *Z* (**3**) isomers. In most cases, *E* isomers (**2ca**, **2di**, **2dj**, **2dk**, **2ec**, **2fc**) appear more active than the corresponding *Z* isomer (**3ca**, **3di**, **3dj**, **3dk**, **3ec**, **3fc**). However, *E* compounds **2dg**, **2eb** and **2fb** did not show a clear enhanced activity when compared to the corresponding *Z* analogs **3dg**, **3eb** and **3fb**, respectively. When considering the substituent at the β position of the unsaturated ketone, an alkyl side chain produces loss of activity (**2db**) when compared to *c*Hex (**2da**, **2fa**) or Ar (**2dc**, **2dd**, **2de**, **2dg**, **2dh**, **2di**, **2dj**, **2dk**, **2fb**, **2fc**). This result is consistent with our past observations [8]. In the same context, the presence of halogenated substituents on the aryl ring tend to ameliorate the antiproliferative activity (**2bd** > **2bc** > **2bb**; **2dd** > **2dc**) if they are allocated at the *para* position. In contrast, a substituent at the *ortho* position (**2dc** vs **2dg**, **2dh**) does not influence positively the antiproliferative effect. Next, the presence of chloromethyl (**2bb**, **2bc**, **2bd**), acetoxymetyl (**2dc**, **2dd**, **2di**, **2fb**, **2fc**), benzyloxymethyl (**2eb**, **2ec**) groups in α-position of chalcone moiety enhances the antiproliferative activity. Finally, a chlorine atom in *para* position of the phenyl ring next to the ketone does not produce a significant effect on the activity (**2da**, **2dd**, **2di** vs **2fa**, **2fb**, **2fc**; respectively). A direct comparison of the GI_{50} data of *E* (**2**) chalcones with the previously reported data for analog **II** (Fig. 1) [9] indicates that compounds **2dd**, **2fb** and **2fc** show an improved biological activity only in the most resistant cell line T-47D.

In addition to *E* (**2**) and *Z* (**3**) chalcones, our synthetic procedure produces adduct **4** under certain conditions as described above. From the five adducts obtained in our investigations, the best results of antiproliferative activity were obtained for adduct **4dl**, which showed as the most potent compound from the whole study. These adducts possess in their structure an additional α,β-unsaturated arylketone. When considering the GI_{50} data, adducts **4dc**, **4dd**, **4de**, **4dh** and **4fb** do not improve the results of their corresponding *E* (**2**) and *Z* (**3**) chalcones. However, analog **4dl**, the only compound of the series with a methoxy group in *para* position of the phenyl ring at the β position of the unsaturated ketone.

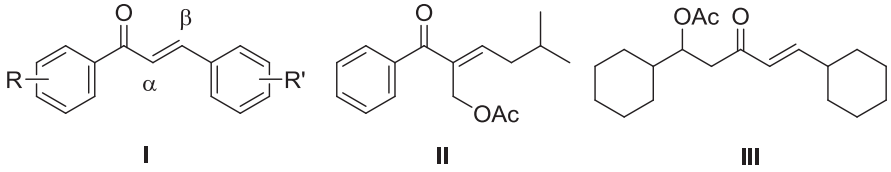

Fig. 1. General structure of chalcones (**I**) and previously described anticancer compounds **II** and **III**.

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