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Design and multi-step synthesis of chalcone-polyamine conjugates as potent antiproliferative agents

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ABSTRACT

The aim of this study is to synthesize chalcone-polyamine conjugates in order to enhance bioavailability and selectivity of chalcone core towards cancer cells, using polyamine-based vectors. 3-hydroxy-3′,4,4′,5′-tetramethoxychalcone (**1**) and 3′,4,4′,5′-tetramethoxychalcone (**2**) were selected as parent chalcones since they were found to be efficient anti-proliferative agents on various cancer cells. A series of ten chalcone-polyamine conjugates was obtained by reacting carboxychalcones with different polyamine tails. Chalcones **1** and **2** showed a strong cytotoxic activity against two prostatic cancer (PC-3 and DU-145) and two colorectal cancer (HT-29 and HCT-116) cell lines. Then, chalcone-spermine conjugates **7d** and **8d** were shown to be the most active of the series and could be considered as promising compounds for colon and prostatic cancer adjuvant therapy.

Chalcones constitute an important group of natural products belonging to the flavonoid family.[1] They are open-chain molecules in which two aromatic rings are joined by a three-carbon enone fragment. Chalcones and derivatives received significant attention due to their wide range of pharmacological activities, including anti-inflammatory,[2] anti-bacterial,[3] and anti-cancer properties.[4–6] More particularly, some of these compounds have been found to induce apoptosis in a variety of cell lines.[7–10] Considering structure-activity relationship, a trimethoxyphenyl ring is thought to be of great interest for anticancer activity of chalcones.[11–13] As reported by Ducki et al., 3-hydroxy-3′,4,4′,5′-tetramethoxychalcone (chalcone **1** in our study, Fig. 1), have shown an important antiproliferative activity against K562 cell line.[12] This chalcone, bearing the same aromatic substitution pattern as combretastatin A4 (CA-4) (Fig. 1), a highly cytotoxic natural product, also demonstrated an antiproliferative effect against various cancer cells and was further used as a lead compound of a series of anti-mitotic and pro-apoptotic agents.[14]

Besides, Qi et al. reported a series of CA-4 related chalcones[15]; among them, 3′,4,4′,5′-tetramethoxychalcone (chalcone **2** in our study, Fig. 1) was found to inhibit the proliferation of ovarian cancer cells. Considering these findings, we became interested in performing structural modifications of the chalcone core to improve both bioavailability and selectivity towards cancer cells. Our study focused on the derivatization of chalcones **1** and **2**.

An interesting approach for enhanced drug delivery is the use of polyamine-based vectors. Polyamines such as putrescine, spermidine or spermine, play an essential role as regulators of cell proliferation and differentiation.[16,17] It has been shown that many tumor cell lines are highly dependent on these growth factors.[18] Cancer cells are unable to biosynthesize enough polyamines to sustain their rapid growth rate. They consequently rely on exogenous polyamines, imported by the polyamine transport system (PTS) which is actually hyperactive in cancer cells. This system has been shown to display a relatively loose specificity[19]; accordingly, some polyamine-drug conjugates have been reported to be delivered into tumor cells expressing the PTS.[20–25]

The present work deals with the synthesis of chalcone-polyamine conjugates **7a-e**, **8a-e** (Fig. 2). Then, antiproliferative activities of these derivatives were evaluated against two colorectal (HT-29 and HCT-116) and two prostatic (PC-3 and DU-145) cancer cell lines, and compared with those of parent chalcones **1** and **2**.

Chalcones **1** and **2** were prepared using the Claisen-Schmidt condensation from building-blocks, namely 3,4,5-trimethoxyacetophenone and appropriate benzaldehydes.[10,15] ^{1}H NMR spectra showed that the (*E*)-stereoisomers were specifically generated since the coupling constant between the two ethylenic protons

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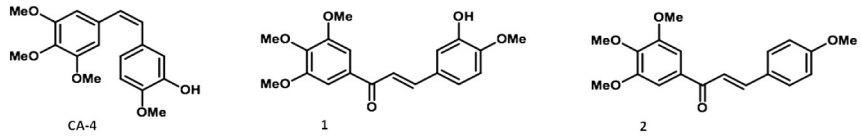


Fig. 1. Chemical structures of combretastatin A4 (CA-4), 3-hydroxy-3′,4,4′,5′-tetramethoxychalcone (**1**) and 3′,4,4′,5′-tetramethoxychalcone (**2**).

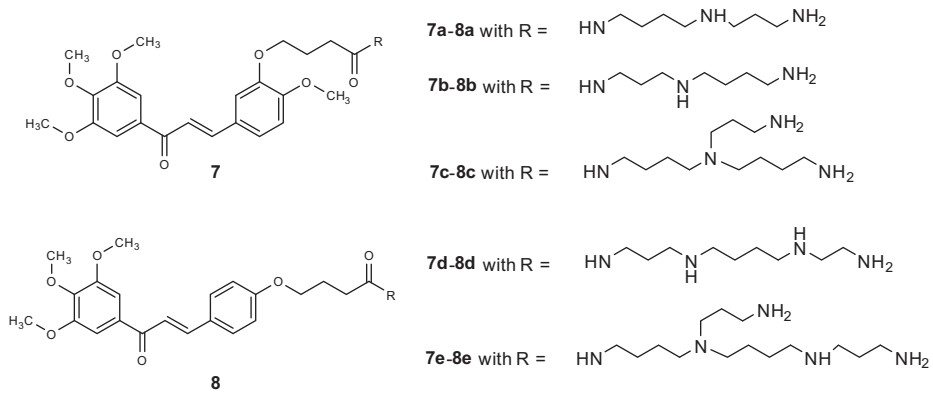


Fig. 2. Chemical structures of chalcone-polyamine conjugates.

was about 15–16 Hz. Chalcone **2** was obtained from 4-methoxybenzaldehyde in 51% yield while chalcone **1** was prepared in a good yield (69%) from 3-hydroxy-4-methoxybenzaldehyde.

Ten polyamine-chalcone conjugates (**7a-e**, **8a-e**) were synthesized, following a multistep strategy where chalcone core and polyamine tails were fused through an amide bond. The synthetic pathway involved the preparation of carboxy-chalcones **4** and **6** for the synthesis of the series **7** and **8** respectively. The preparation of carboxy-chalcone **4** first started with alkylation of the phenolic function of chalcone **1** by ethyl-4-bromobutyrate, to give **3** in a quantitative yield (Scheme 1A). Finally, the ester function was turned into a carboxylic acid in quantitative yield too, through the action of lithium hydroxide.

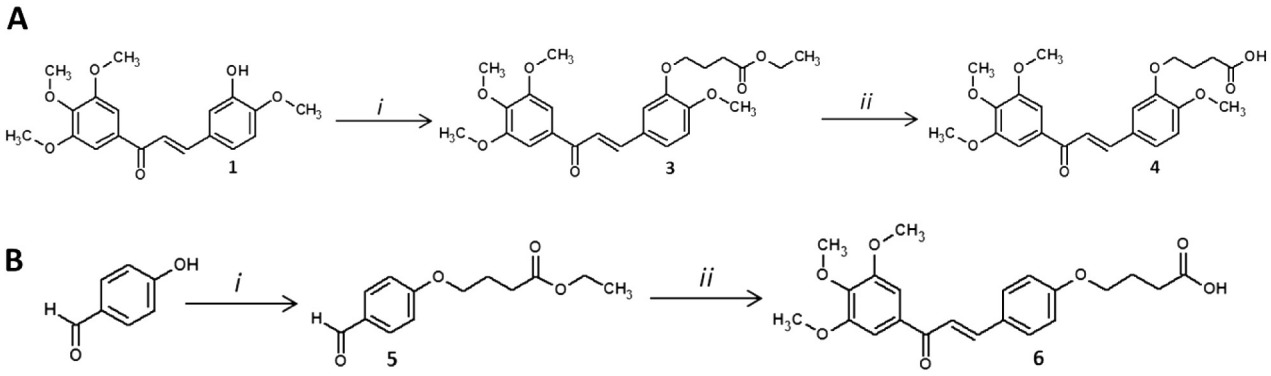
The synthesis of carboxy-chalcone **6** used a different synthetic pathway in order to avoid the multistep synthesis of the 4-hydroxy-3′,4′,5′-trimethoxychalcone as an intermediate. Indeed, the preparation of 4-hydroxychalcones involved a preliminary protection step of 4-hydroxy-benzaldehyde prior to the Claisen-Schmidt condensation. A new pathway consisted in the *O*-substitution of 4-hydroxy-benzaldehyde, by reaction with ethyl-4-bromobutyrate, followed by the Claisen-Schmidt condensation with 3′,4′,5′-trimethoxyacetophenone (Scheme 1B). Due to the alkaline conditions, condensation and saponification occurred during the same step, leading directly to compound **6**. This strategy only involved two steps with a 57% global yield.

Protected linear polyamines were purchased whereas ramified polyamines were prepared following the strategy developed in our laboratory and previously described.[23] Many ways for the selective protection of polyamines have been reported.[26] In our study, we chose the BOC-protective group that can be selectively removed with TFA or HCl.

The synthetic pathway of polyamine-chalcone conjugates through the formation of an amide bond was described in Scheme 2; it involved the coupling of the carboxylic acid function of chalcones **4** and **6**, with the primary amine function of the polyamine tails, in presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) as coupling agents.

Removal of the *tert*-butoxy-carbonyl (BOC) was performed using aqueous hydrochloric acid in ethanol at reflux. All the yields are reported in Table 1.

The coupling reaction between the carboxy-chalcones and polyamine tails, using DCC and HOBt as coupling agents, was really effi-



Scheme 1. A: Reagents and conditions for synthesis of compound **4**: (i) K_2CO_3 (20 eq), ethyl-4-bromobutyrate (10 eq), DMF, rt, 2 h, 98%; (ii) LiOH (5 eq), THF/H_2O (8/2), rt, 3 h, 94%. B: Reagents and conditions for synthesis of **6**: (i) K_2CO_3 (20 eq), ethyl-4-bromobutyrate (10 eq), DMF, rt, 1 h, 98%; (ii) 3,4,5-trimethoxyacetophenone (0.84 eq), NaOH (4.17 eq), MeOH, reflux, 1 h, 58%.