Cytotoxic Activity Evaluation and QSAR Study of Chromene-based Chalcones

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Chalcone and chromene motifs are synthetic or naturally occurring scaffolds with significant cytotoxic profile. Two types of novel regioisomeric chromene-chalcone hybrids, namely 1-(6-chloro or 6-methoxy-2H-chromen-3-yl)-3-phenylprop-2-en-1-one (Type A) and 3-(6-chloro or 6-methoxy-2H-chromen-3-yl)-1-phenylprop-2-en-1-one (Type B), both with different substituents on the phenyl ring attached to propenone linkage, have been evaluated for their cytotoxic activity against breast cancer cell lines (MCF-7 and MDA-MB-231). The results indicate that type A of chromene-chalcones demonstrated better cytotoxic profile than type B especially in MDA-MB-231 cell line. In addition, the growth inhibitory activity of most of the target compounds is higher than Etoposide as a reference drug. QSAR analysis of these novel compounds demonstrated that topological and geometrical parameters are among the important descriptors that influence the cytotoxic activity profile of compounds.

Key words: Chromene, Chalcones, Cytotoxic activity, QSAR

INTRODUCTION

Chalcones are synthetic or naturally occurring substructures in many plants as a precursor of flavonoids and isoflavonoids. The chemical structure of chalcone consists of two aromatic rings joined by a three carbon, α,β-unsaturated carbonyl system (1,3-diphenyl-2-propen-1-one) (Akihisa et al., 2006; Zhang et al., 2006; Nowakowska, 2007; Patil et al., 2009) (Fig. 1).

Chalcones have displayed widespread pharmacological activities, including anti-inflammatory (Rojas et al., 2002), antibacterial (Sivakumar et al., 2009), antileishmanial (Liu et al., 2003), antioxidant (Yayli et al., 2004), cytotoxic, antitumor and Pgp inhibitory properties (Bois et al., 1999; Go et al., 2005; Liu et al., 2008; Reddy et al., 2008; Sashidhara et al., 2010a). Recent studies demonstrated that chalcones inhibit cell proliferation in cancer cell lines and also induce apoptosis in different cancerous cell types with various proposed mechanisms such as depletion of tubulin assembly (Lawrence et al., 2000, 2005; Hadfield et al., 2003; Rozmer et al., 2006), tyrosine kinase inhibition (Nakatani et al., 2005), trigger of apoptosis signaling pathway and etc. (Dimmock et al., 1998, 1999; Nakatani et al., 2005; Reddy et al., 2011). The major advantage of chalcone derivatives as cytotoxic agents is their low propensity to interact with DNA, and such propensity...
eliminates the risk of mutagenesity as the common side effect of current chemotherapeutic agents (Dimmock et al., 1999).

Recently, several researchers developed the potent anticancer hybrid molecules of the chalcone type through the introduction of some cytotoxic heterocyclic pharmacophores such as coumarin and stilbene derivatives (Belluti et al., 2010; Sashidhara et al., 2010a). These heterocycle-chalcone hybrids have found much attention and demonstrated promising antitumor effects (Reddy et al., 2008; Belluti et al., 2010; Sashidhara et al., 2010a). On the other hand, Chromene (2H-1-benzopyran) derivatives have been widely employed as important intermediates in the synthesis of many natural products and medicinal agents. This important class of compounds received profound attention as a potent anticancer and apoptosis-inducing scaffold with different proposed mechanisms (Zhou et al., 2007; Huang et al., 2009; Mayur et al., 2009; Heo et al., 2011). The chemical structures of some naturally occurring chromene derivatives such as acronicine (Hughes et al., 1948) and phaseollidin (Gunatilaka et al., 1994) are demonstrated in Fig. 2.

According to these findings and in continuation of our work on chalcone derivatives (Foroumadi et al., 2010; Nazarian et al., 2010), herein we focused our attention on two types of regioisomeric chromene-chalcones hybrids (type A and type B) as novel cytotoxic agents. We have previously reported the antileishmanial activity of some of these compounds (Foroumadi et al., 2010; Nazarian et al., 2010); however, according to our interest in the design of potent cytotoxic agents (Alizadeh et al., 2010; Mahmoodi et al., 2010; Akbarzadeh et al., 2012) and the cytotoxic activity potential of chromene and chalcone derivatives, we have further investigated the cytotoxic activity of these derivatives. As breast cancer is one of the most commonly diagnosed cancer and the leading cause of cancer deaths in women worldwide today (Sharma et al., 2010), many molecules based on the chromene ring system including coumarins have been synthesized and found to be useful in antiproliferative activity against breast cancer (Mao et al., 2009; Sashidhara et al., 2010b). Accordingly, we also expect to incorporate a chromene ring instead of aryl moieties of chalcones to investigate their primary biological activity against MCF-7 (estrogen receptor-positive) and MDA-MB-231 (estrogen receptor-negative) breast cancer cell lines.

Thus, the synthesis of some new compounds and in vitro cytotoxic activity of both regioisomeric chromene-based chalcones are investigated in this article. We also examined the effects of structural parameters on the cell proliferation inhibitory activity of designed compounds in each cell line by means of linear quantitative structure-activity relationship (QSAR) models.

**MATERIALS AND METHODS**

**Chemistry**

All chemicals and solvents used in this study were purchased from Merck Chemical. The general procedures for synthesis of type A and type B of chromene-chalcone hybrids are illustrated in Scheme 1. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disks). 1H-NMR spectra were recorded using a Bruker 500 spectrometer and chemical shifts are reported in parts per million (ppm) relative to TMS as the internal standard. Elemental analyses were carried out on CHN-O rapid elemental analyzer (GmbH) for C, H and N, and the results are within ± 0.4% of the theoretical values. Merck silica gel F254 plates were used for analytical TLC. Column chromatography was performed on Merck silica gel (70–230 mesh). Yields were calculated for purified products and were not optimized. The intermediates 2 and 3 were prepared according to the literature methods (Foroumadi et al., 2010; Nazarian et al., 2010). The physicochemical pro-