European Journal of Medicinal Chemistry 85 (2014) 758–777

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Invited review

Recent developments in biological activities of chalcones: A mini review

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ARTICLE INFO

Article history:
Received 10 July 2014
Received in revised form
7 August 2014
Accepted 8 August 2014
Available online 12 August 2014

Keywords:
Chalcones
Anticancer agents
Antimalarials
Antimicrobials
Antiprotozal
Anti-HIV

ABSTRACT

Chalcones represent key structural motif in the plethora of biologically active molecules including synthetic and natural products. Synthetic manipulations of chalcones or their isolation from natural sources are being investigated worldwide for the development of more potent and efficient drugs for the treatment of several dreadful diseases such as cancer, diabetes, HIV, tuberculosis, malaria etc. Over the past few years, a large volume of research papers and review articles highlighting the significance of chalcone derivatives has been compiled in the literature. The present review article focuses on the recent developments (2010–2014) on various pharmacological and medicinal aspects of chalcones and their analogues.

1. Introduction

Chalcones, also known as α-β-unsaturated ketones (**A**, Fig. 1), are not only important precursors for synthetic manipulations but also form a major component of the natural products. Chalcones as well as their synthetic analogues (Fig. 1) display enormous number of biological activities [1].

The presence of double bond in conjugation with carbonyl functionality is believed to be responsible for the biological activities of chalcones, as removal of this functionality make them inactive. They have the tendency to exist both in *cis*- and *trans*-forms, and can easily be cyclized to form flavanones *via* Michael addition. A number of synthetic routes have been reported for synthesis of chalcones while their general synthesis involve Claisen–Schmidt condensation under homogeneous conditions in the presence of acid or base [2–5]. Traditionally, strong alkaline media including natural phosphates, $Ba(OH)_2$, KOH, NaOH, LiHMDS etc. have been employed for their synthesis [6–11]. The use of several lewis acids (*p*-toluene sulfonic acid, B_2O_3, $RuCl_3$, $AlCl_3$, BF_3 and dry HCl) in has also been demonstrated [12–17]. Numerous reports highlighting the synthesis and medicinal significance of chalcone derivatives have already been documented in the literature [18–24] while in this mini-review article, emphasis is given on diverse biological activities of chalcones and structurally related chalcones published in the last five years (2010–2014). Moreover, their structure activity relationship (SAR) and mechanism of action are also discussed.

2. Biological activities of chalcones

2.1. Anti-cancer agents

Cancer is one of the major causes of death worldwide. The number of patients diagnosed with different types of cancer has almost doubled in last three decades, and is expected to rise even higher in coming years if new efficient treatment methods are not developed [25–28]. Although, a number of cancer treatments are available nowadays, their associated limitations and side-effects are still prompting the researchers to develop more safe, potent and selective anti-cancer agents. The presence of chalcone derivatives as a main component, or a substituent or as a side-chain in different biologically active compounds has encouraged the synthetic organic chemists to synthesize new compounds bearing this moiety. Different newly synthesized chalcones with their anti-cancer activities are discussed in this section.

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http://dx.doi.org/10.1016/j.ejmech.2014.08.033
0223-5234/

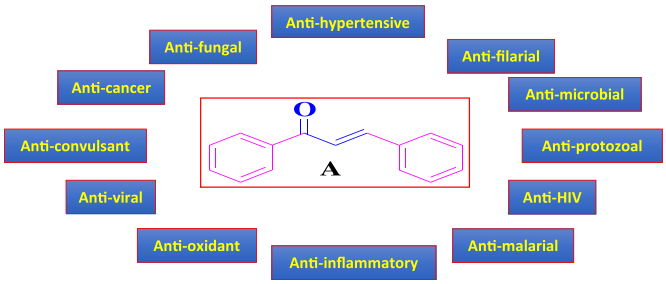

Fig. 1. Different biological activities displayed by chalcone analogues.

The molecules containing more than one pharmacophores have been reported to be useful for the cancer treatment [29,30]. Accordingly, the synthesis of a series of chalcone-coumarin hybrids *viz.* **1**–**5** and their *in vitro* evaluation against a panel of four human cancer cell lines, KB (oral squamous cell carcinoma), C33A (cervical carcinoma), MCF-7 (breast adenocarcinoma), A549 (lung) and one normal fibroblasts (NIH3T3) has been performed by Sashidhara and co-workers [31] (Fig. 2).

Compounds **1**–**3** were found to be inactive against all cancer lines studied. Although, compounds *viz.* **4**–**5** exhibited activity against all cancer lines, the compounds were most active against C33A with IC_{50s} ranging between 3.59 μM and 8.12 μM. Compound **5** with $-CH_3$ group at A-ring was found to be the most active against C33A (IC_{50} = 3.59 μM), followed by KB (IC_{50} = 17.97 μM), A549 (IC_{50} = 32.80 μM) and MCF7 (IC_{50} = 81.10 μM) with no activity against NIH3T3 cell line. The presence of ester functionality, especially methyl ester at position 3 and coumarin ring were thought to be crucial for the anti-cancer activity of these compounds.

Based on modelling predictions, two sets of chalcones, **6**–**8** (type I) and **9** (type II) having structural features of colchicine were synthesized and screened for their tubulin assembly inhibition and cytotoxicities on L1210 (murine acute lymphoblastic leukaemia cells) [32] as depicted in Fig. 3.

It was observed that the compound containing tri-methoxy phenyl ring adjacent to the carbonyl group (**7b**) was the most active in both assays, whereas the presence of similar functionality on the B-ring (**8**) did not significantly enhance cytotoxicity potency. Additionally, the *in vitro* studies of the most active compounds on human acute lymphoblastic leukaemia (REH and JURKAT), human umbilical vein endothelial cells (HUVEC), and NIHT3 further revealed their selectivity against cancer cell lines. Compound **9** having 4-$(CH_3)_2$N-phenyl group showed the highest activity in the type II category with IC_{50} values of 30 μM against L-1210, 1.5 μM (REH), 1.20 μM (JURKAT), 66 μM (NIH3T3), >100 μM (HUVEC), 92.5 μM (PBMC) and 2.8 μM (tubulin assembly).

Ratković et al. reported the synthesis of ferrocenyl pyrazole substituted chalcone derivatives **10** and their anti-proliferative studies against three cell lines including cervix adenocarcinoma HeLa, melanoma Fem-x and myelogenous leukaemia K562 [33] (Fig. 4).

The most significant cytotoxicity was observed for compound bearing 3-pyridyl moiety against all cancer lines, even better (IC_{50} = 5.42 μg/mL) than *cis*-platin (IC_{50} = 5.90 μg/mL) against K562 cell lines. For the remaining compounds, the calculated IC_{50} values range between 24.2 μg/mL to >100 μg/mL for HeLa, 9.15 μg/mL to >100 μg/mL for Fem-x and 9.0 μg/mL to >100 μg/mL in case of K562.

The analogues of chalcones bearing imine and anthraquinone functionalities were synthesized by Kolundzija et al. [34], and were screened against HeLa human colon carcinoma (LS174) and non-small cell lung carcinoma (A549) cancer lines under *in vitro* conditions (Fig. 5).

Compound **11** bearing furan ring linked to imino group was found to be most potent against all tested cell lines with IC_{50} values ranging from 1.76 μM to 6.11 μM. The presence of electron-withdrawing substituents (−Cl, $-CF_3$) especially at meta positions were found to be important for their cytotoxicity activity against HeLa cells, whereas the presence of electron-donating groups did not improve their cytotoxicity. Similar compounds tested against normal human foetal lung fibroblast cell line (MRC5) further revealed that compound **11** bearing 3-chlorophenyl group had the stronger anti-angiogenic effect with IC_{50} 16.7 μM.

Synthesis of twelve novel chalcones **12** and their biological evaluation against seven human cancer cell lines including prostate cancer (PC-3), breast cancer (MCF-7), human leukaemia (HL-60), pancreatic cancers (MIAPaCa-2 and AsPC), melanoma (MDA-MB-431) and colon (Caco-2) has been reported by Murthy and co-workers [35]. Majority of the compounds exhibited cytotoxicity against all types of cancer in micromolar (μM) concentrations (Fig. 6).

Three compounds bearing electron withdrawing groups (3-NO_2, 4-NO_2 and 4-CN) on the B-ring of chalcones were highly potent for HL-60 cancer cell line with IC_{50} values in the range between 6 and 15 μM. Same compounds also displayed >90% cell proliferation inhibition for Caco-2 at 50 μM concentration.

Reddy et al. reported the synthesis of *bis*-chalcones analogues (**13**–**14**) from resorcinol and substituted aldehydes [36] (Fig. 7), followed by their cytotoxic evaluation against four human cancer lines consisting of lung cancer (A549), prostate cancer (DU-145), nasopharyngeal carcinoma (KB) and vincristine resistant KB subline (KB-VIN).

The substituted compounds were found to non-toxic against all cancer lines. Compound **13a** was found to be the most toxic against all cancer lines with EC_{50} value of 1.70 μM for DU-145, 1.62 μM for KB, 1.57 μM for KB-VIN and 4.08 μM for A549. Compound bearing pyridine rings (**14**) was less toxic than **13**, and showed anti-cancer activity against all target cell lines with EC_{50} ranging between 16.32 μM and 19.38 μM.

A series of α-branched α,β-unsaturated ketones and their chalcone analogues have been synthesized *via* acid catalysed reaction between carbaldehydes and arylalkynes [37], and evaluated for their anti-proliferative activity against five human solid tumour cell lines such as colon (WiDr), breast (T-47D), non-small cell lung (SW1573), cervix (HeLa) and breast (HBL-100) as shown in Fig. 8.

The calculated GI_{50} values range between 0.53 and >100 μM in case of HBL-100, 0.32–78 μM for HeLa, 0.45–>100 μM for SW1573, 0.37–52 for T-47D and 0.47–>100 μM for WiDr cancer cell lines. Compound **15** bearing $-OCH_3$ (electron releasing group) substituent at para position exhibited the highest anti-cancer activity with GI_{50} values of 0.53 μM (HBL-100), 0.32 μM (HeLa), 0.45 μM (SW1573), 0.37 μM (T-47D) and 0.47 μM (WiDr). The lowest activity was displayed by compound **16** with $-NO_2$ group (electron withdrawing), suggesting the dependence of electronic nature of substituents on the activity profiles of the tested compounds. Further, the *E*-isomers were generally found to be more active than the corresponding *Z*-isomers.

Using Claisen–Schmidt condensation method, a number of methoxychalcones were synthesized and investigated [38] for their cytotoxicity activity against five human cancer cell lines consisting of renal cell carcinoma (ACHN), pancreatic carcinoma (Pancc1), non-small cell lung carcinoma (Calu1), non-small cell lung carcinoma (H460) and colon carcinoma (HCT116) (Fig. 9).

Compound **17** bearing two methoxy substituents at *ortho* and *para* positions of B-ring showed more than 90% inhibition at 10 μM concentration. The SAR study suggested that the presence of