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Original article

Chalcones with electron-withdrawing and electron-donating substituents: Anticancer activity against TRAIL resistant cancer cells, structure–activity relationship analysis and regulation of apoptotic proteins

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ABSTRACT

In the present study, a series of 46 chalcones were synthesised and evaluated for antiproliferative activities against the human TRAIL-resistant breast (MCF-7, MDA-MB-231), cervical (HeLa), ovarian (Caov-3), lung (A549), liver (HepG2), colorectal (HT-29), nasopharyngeal (CNE-1), erythromyeloblastoid (K-562) and T-lymphoblastoid (CEM-SS) cancer cells. The chalcone **38** containing an amino (-NH_2) group on ring A was the most potent and selective against cancer cells. The effects of the chalcone **38** on regulation of 43 apoptosis-related markers in HT-29 cells were determined. The results showed that 20 apoptotic markers (Bad, Bax, Bcl-2, Bcl-w, Bid, Bim, CD40, Fas, HSP27, IGF-1, IGFBP-4, IGFBP-5, Livin, p21, Survivin, sTNF-R2, TRAIL-R2, XIAP, caspase-3 and caspase-8) were either up regulated or down regulated.

1. Introduction

Worldwide, cancer is one of the leading causes of death. Patients diagnosed with cancer often experience a poor quality of life due to the adverse events associated with cancer. Chemotherapy is one of the effective approaches in suppressing tumour growth and eradication of tumours. However, many patients undergoing chemotherapy suffer from associated side effects such as nausea, vomiting, cachexia, lethargy and poor oral intake. Although, many research studies have reported potential chemotherapeutic effects of novel compounds, the search for new anti-cancer agents with improved efficacy and reduced side effects continues. [1]

Chalcones have attracted much attention due to their diverse biological activities, such as anti-cancer, anti-oxidant, anti-inflammatory, and/or anti-infective activities. Chalcones consist of two aromatic rings connected by an α,β-unsaturated carbonyl group. It has been shown that the removal of α,β-unsaturated carbonyl system could hinder their biological activities [2]. A number of synthetic modifications, viz., such as oxathiolone fused [3], boron substituted [4], heterocyclic infused [5], biphenyl based [6], imidazolones linked [7], coumarin based chalcones [8] or other substitutions [9–13]; have also been reported to affect the biological activities including anticancer activities of chalcones.

Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is an attractive target in cancer research because it is capable of selectively inducing apoptosis in cancer cells without affecting normal cells [14]. Five receptors, such as TRAIL-R1 (DR4, death receptor 4), TRAIL-R2 (DR5), DR6, TRAILR-3 (decoy receptor (DcR)1) and TRAIL-R4 (DcR2); have been identified for TRIAL. Two of these receptors DR4 and DR5 have cytoplasmic death domains and trigger TRAIL induced apoptosis [15]. Other receptors, DcR1 and DcR2, are expressed on the cell surface and protect the cancer cells from TRAIL induced apoptosis [16]. The last TRAIL receptor, osteoprotegerin, is a less studied receptor and is known to inhibit the tumouricidal activity of TRAIL [17]. Interaction of TRAIL with DR4 and DR5 results in caspase-8 activation, which induces apoptosis by activating either caspase-3 or the intrinsic mitochondria-mediated apoptotic pathway [18]. However, TRAIL

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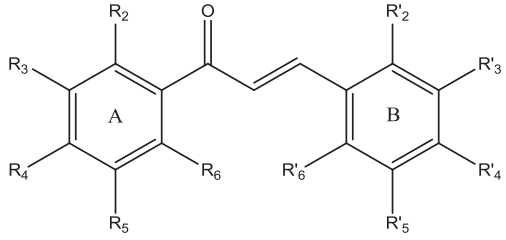
Table 1
Chalcone derivatives and their Lipinski's rule of five parameters.



Chalcone	Ring A					Ring B					Lipinski rule of 5 parameters			
No.	R_2	R_3	R_4	R_5	R_6	R'_2	R'_3	R'_4	R'_5	R'_6	MW	*A* log *P*	HBA	HBD
1	H	H	H	H	H	H	H	H	H	H	208.26	3.70	1	0
2	H	H	H	H	H	OH	H	H	H	H	224.26	3.46	2	1
3	H	H	H	H	H	H	OH	H	H	H	224.26	3.46	2	1
4	H	H	H	H	H	H	H	OH	H	H	224.26	3.46	2	1
5	OH	H	H	H	H	H	H	H	H	H	224.26	3.46	2	1
6	OH	H	H	H	H	OH	H	H	H	H	240.25	3.22	3	2
7	OH	H	H	H	H	H	OH	H	H	H	240.25	3.22	3	2
8	OH	H	H	H	H	H	H	OH	H	H	240.25	3.22	3	2
9	OH	H	H	H	H	H	H	OCH_3	H	H	254.28	3.44	3	1
10	OH	H	H	H	H	H	OCH_3	OCH_3	H	H	284.31	3.43	4	1
11	OH	H	H	H	H	H	OCH_3	OCH_3	OCH_3	H	314.33	3.41	5	1
12	OH	H	H	H	H	H	1,3-dioxolane		H	H	268.26	3.23	4	1
13	OH	H	H	H	H	H	H	CH_3	H	H	238.28	3.95	2	1
14	OH	H	H	H	H	H	H	Cl	H	H	258.70	4.12	2	1
15	OH	H	H	H	H	H	Phenyl		H	H	274.31	4.37	2	1
16	OH	H	OCH_3	H	OCH_3	H	H	$N(CH_3)_2$	H	H	327.37	3.59	5	1
17	OH	H	OCH_3	H	OCH_3	H	H	OCH_3	H	H	314.33	3.41	5	1
18	OH	OCH_3	OCH_3	H	H	H	H	Br	H	H	363.20	4.18	4	1
19	OH	H	OCH_3	H	OCH_3	H	H	H	H	H	284.31	3.43	4	1
20	OH	H	OCH_3	H	OCH_3	NO_2	H	H	H	H	329.30	3.32	6	1
21	OH	H	OCH_3	H	OCH_3	H	H	NO_2	H	H	329.30	3.32	6	1
22	OCH_3	H	OCH_3	H	H	H	H	NO_2	H	H	313.31	3.56	5	0
23	OCH_3	H	OCH_3	H	H	H	H	Cl	H	H	302.75	4.33	3	0
24	OCH_3	H	OCH_3	H	H	H	H	Br	H	H	347.20	4.42	3	0
25	OCH_3	H	OCH_3	H	H	H	1,3-dioxolane		H	H	312.32	3.44	5	0
26	OCH_3	H	H	OCH_3	H	H	1,3-dioxolane		H	H	312.32	3.44	5	0
27	OCH_3	H	H	OCH_3	H	H	OCH_3	OCH_3	OCH_3	H	358.39	3.62	6	0
28	H	OCH_3	OCH_3	H	H	H	H	Cl	H	H	302.75	4.33	3	0
29	H	OCH_3	OCH_3	H	H	H	H	SCH_3	H	H	314.40	4.21	4	0
30	OCH_3	H	H	H	H	H	H	F	H	H	256.27	3.89	2	0
31	H	H	OCH_3	H	H	OCH_3	H	H	H	H	268.31	3.67	3	0
32	H	H	OCH_3	H	H	H	H	Cl	H	H	272.73	4.35	2	0
33	H	H	OCH_3	H	H	H	Phenyl		H	H	288.34	4.59	2	0
34	H	H	CH_3	H	H	H	H	$N(CH_3)_2$	H	H	265.35	4.35	2	0
35	H	H	CH_3	H	H	H	H	F	H	H	240.27	4.39	1	0
36	H	H	CH_3	H	H	H	H	Cl	H	H	256.73	4.85	1	0
37	H	H	CH_3	H	H	H	H	SMe	H	H	268.37	4.73	2	0
38	NH_2	H	H	H	H	H	H	H	H	H	223.27	2.96	2	1
39	NH_2	H	H	H	H	H	H	NO_2	H	H	268.27	2.85	4	1
40	NH_2	H	H	H	H	H	H	Cl	H	H	257.72	3.62	2	1
41	NH_2	H	H	H	H	H	H	OCH_3	H	H	253.30	2.94	3	1
42	NH_2	H	H	H	H	H	Phenyl		H	H	273.33	3.86	2	1
43	H	H	NH_2	H	H	H	H	H	H	H	223.27	2.96	2	1
44	H	H	NH_2	H	H	Cl	H	H	H	H	257.72	3.62	2	1
45	H	H	NH_2	H	H	H	H	Cl	H	H	257.72	3.62	2	1
46	H	H	NH_2	H	H	Cl	H	Cl	H	H	292.16	4.28	2	1

MW: Molecular Weight; *A* log *P*: logarithm of octanol–water partition coefficient; HBA: number of hydrogen bond acceptor; HBD: number of hydrogen bond donor.

resistance in cancer cells have been reported elsewhere in the literature [19–21]. Few recent studies have reported the potential of chalcones in inducing apoptosis in TRAIL-resistant cancer cells [22,23].

In the current study, we have synthesised 46 chalcones consisting wide range of electron-withdrawing and electron-donating substituents that obey Lipinski's rule of five. The apoptosis inducing capability of these chalcones in 10 TRAIL-resistant cancer cells and selective toxicity towards cancer cells compared to normal cells was determined with an aim to derive the important structure activity relationships. Regulation of the various apoptotic proteins in the most sensitive cancer cell, HT-29, by the most potent chalcone **38**, was also determined.

2. Results and discussion

2.1. Chemistry

The chalcones were classified into 12 groups according to their substitution patterns on ring A. Group 1 chalcones (**1**–**4**) have no