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Antiobesity, antioxidant and cytotoxicity activities of newly synthesized chalcone derivatives and their metal complexes

Mohamed Ramadan El Sayed Aly [a,b,*], Hamadah Hamadah Abd El Razek Fodah [c,d], Sherif Yousef Saleh [e]

[a] Chemistry Department, Faculty of Science, Taif University, Hawyah-Taif, Kingdom of Saudi Arabia, Saudi Arabia
[b] Chemistry Department, Faculty of Applied Science, Port Said University, 42522 Port Said, Egypt
[c] Chemistry Department, Faculty of Science, Taif University, Kingdom of Saudi Arabia, Saudi Arabia
[d] Chemistry Department, Faculty of Science, Damietta University, New Damietta 34517, Egypt
[e] Biochemistry Department, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt

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Dedicated to Professor R. R. Schmidt on the occasion of his 79th birthday.

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ABSTRACT

Four sets of rationally designed chalcones were prepared for evaluation of their antiobesity, antioxidant and cytotoxicity activities. These sets include nine oleoyl chalcones as mimics of oleoyl estrone, three monohydroxy chalcones (chalcone ligands), Schiff base-derived chalcones and four copper as well as zinc complexes. Oleoyl chalcones **4d**, **4e** and particularly **6a** as an isosteric isomer of oleoyl estrone, were as active as Orlistat on weight loss and related metabolic parameters using male SD rats *in vivo*. Chalcone ligands **10a**–**c** and Schiff base-derived chalcones **11** and **14a**,**b** were weakly antioxidants, while, the copper and zinc complexes **15a**–**d** were good antioxidants with zinc chelates **15b**,**d** being more active than their copper analogues **15a**,**c** *in vitro*. Compounds **10c** and **14a** showed good cytotoxicity activities as Doxorubicin against PC3 cancer cell line *in vitro*, while, the copper complex **15c** showed promising activity with IC_{50} value of 5.95 μM. The estimated IC_{50} value for Doxorubicin was 8.7 μM. Chalcones **14a,b** are bifunctional probes for potential investigations in cancer diagnosis and radiotherapy by complexation with Gd^{3+} or metal radioisotopes followed by posttranslation of Shiga toxin B-subunits that target globotriosyl ceramide expressing cancer cells.

1. Introduction

Chalcones **I** (1,3-diaryl-2-peopen-1-ones) (Scheme 1) are structurally divergent natural products in edible and medicinal plants having benefits for human health from life style to protection from life threatening diseases [1,2]. Besides being natural products, they are precursors for flavones, isoflavones, aurones and anthocyanins which are regarded as cyclic chalcones and have closely related physiological and medical relevancies. Of the biological significant aspects of natural as well as synthetic chalcones are their antiobesity [3,4], antioxidant [5,6] and anticancer activities [7,8].

Oleoyl estrone (OE) **II**, is an estrone hormone synthesized in the white adipose tissue then released into the blood stream in animal and human as well [9–11]. It is able to produce rapid and sustained weight loss through induction of body fat loss while preserving protein stores, a common side effect of antiobesity formulations. Besides being able to reduce circulating plasma lipids, OE is able to reduce plasma insulin and improve insulin resistance [12,13]. It functions through hampering the uptake of substrates essential for lipogenesis and thus favoring lipolysis indirectly, *i.e.* imbalance the lipogenesis–lipolysis equilibrium. Its sustained action arises from its tendency to decrease expression of lipogenic enzyme genes without affecting expression of lipolytic enzyme genes [14]. Obesity accounts for approximately 20% of all cancer cases; weight loss was reported to reduce risk for, at least, breast cancer [15]. The

Abbreviations: OE, oleoyl estrone; ROS, reactive oxygen species; SD, sprague–dawley; Pgp, P-glycoprotein; BCRP, breast cancer resistant protein; MRP1, multi-drug resistance-associated protein 1; TGA, thermal gravimetric analysis; DTG, differential thermogravimetry; TNF-α, tumor necrosis factor-α; FFAs, free fatty acids; PTPs, protein tyrosine phosphatase; IRS-1, insulin receptor substrate-1; LDL, low density lipoprotein; HDL, high density lipoprotein; LFD, low fat diet; HFD, high fat diet; FI, free insulin; ISI, insulin sensitivity index; TG, triglycerides; FBs, fasting blood sugar; DPPH, 1,1-diphenyl-2-picryl-hydrazyl; Trolox, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; AsAc, ascorbic acid; ELISA, enzyme-linked immunosorbent assay; ANOVA, analysis of variance.

* Corresponding author. Chemistry Department, Faculty of Applied Science, Port Said University, 42522 Port Said, Egypt; and Chem. Dep., Faculty of Science, Taif Uni., Taif, KSA.
E-mail address: mrea34@hotmail.com (M.R. El Sayed Aly).

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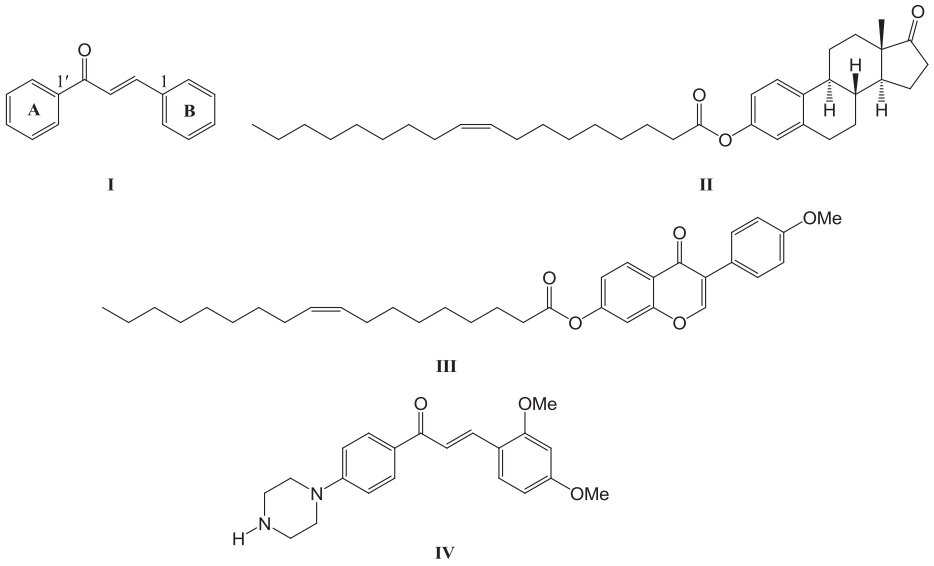

Scheme 1. Structure of model compounds.

physiologic disorders accompanying obesity include hyperglycaemia, insulin resistance and growth factors excretion. All these factors are involved in a complex physiologic pathways lead to hormone receptor-positive tumors or the so-called obesity-related cancer [16].

Based on the known benefits of natural isofavones on human obesity and plasma cholesterol levels, besides, their close similarity to estrogen ring structure, Xiang et al. [17], reported the synthesis of fatty acid substituted isoflavone derivatives, *e.g.* **III**, as potential antiobesity candidates that might retain the antiobesity effect of OE and bypass the estrogenic effect of OE if applied as antiobesity agent. **III** was able to lower the body weight gain, adiposity, improved plasma lipid profile and reduced plasma insulin with low toxicity LD_{50} 2.1638 g/kg. Isoflavone derivatives with other lipid chains were not as active as **III**, thus, reflecting the known importance of the oleoyl moiety for the antiobesity effect [18].

As antioxidants, hydroxylated, methoxylated and prenylated chalcones are known for their powerful antioxidant activities. They are able to scavenge reactive oxygen species (ROS), free radicals and inhibit their implication in damage of cell membranes, DNA, proteins and consequent potential prognosis of ageing, cancer and atherosclerosis [5].

Chalcone derivatives of diverse chemical architectures are quite significant in anticancer drug discovery. They are known to induce apoptosis [19], DNA [20] and mitochondrial damage [21], inhibit angiogenesis [22], tubulin [23], Kinases [24] and drug efflux protein activities [25–27]. They are implemented in cancer diagnosis too [28].

In this paper, a series of oleoylamidochalcones were prepared as easily accessible isosteric isomers of OE and oleoylisoflavones and screened as antiobesity agents on SD rat model. Another set of monohydroxy chalcones (chalcone ligands), Schiff base-derived chalcones and their copper and zinc complexes were also prepared and investigated as antioxidants and anticancer agents. While zinc and chalcones are individually antioxidants we welled that merging should enhance the overall antioxidant power. On the other hand, cancer cells are known for their high affinity to copper ions [29], thus, upon chelation of chalcones with copper they will be more liable to target cancer cells in micro Dendron architecture. Copper (II) complexes of Schiff base-derived curcumin ligands are highly cytotoxic [30].

Putting in mind the affinity of the oleoyl chain to cross cellular membranes [31], it might be concluded that the oleoyl moiety as well as the copper ions might act as penetration enhancers of chalcones into cancer cells. Even if they are non cytotoxic to cancer cells, they might act as inhibitors of drug efflux proteins characteristic to cancer cells and responsible for drug resistance of cancer cells, for instance, P-glycoproteins (Pgp), breast cancer resistance protein (BCRP) [25,26] and multidrug resistance-associated protein 1 (MRP1) [26]. Chalcones with basic functionalities on Ring A, for instance **IV** [25], were proven to act as Pgp-inhibitors, thus, exerted synergistic effect with doxorubicin [25,27].

2. Results and discussion

2.1. Chemistry

To obtain 4′-(*N*-oleoylamido)chalcones **4**–**6** as oleoyl estrone analogues for screening mainly as potential antiobesity agents, *p*-aminoacetophenone **1** was treated with oleoyl chloride **2** in Et_3N to afford substrate **3** in nearly quantitative yield (Scheme 2). Claisen–Schmidt condensation of **3** with a set of aromatic aldehydes, including basically 2-furancarboxaldehyde and 2-thiophenecarboxaldehyde, afforded the desired chalcones in very good yields (63%–qu) except in the case of aldehydes having *p*-electron withdrawing groups, chalcones **4e**,**f**. Molecular ion peaks were recognizable with good intensities and were in accordance with the calculated empirical formulas and the same was for elemental analyses except for **5** where it was not possible to obtain complete right analysis for it. In the IR spectra, diagnostic bands for NH stretching, enone C=O stretching overlapped with *Amide I* and finally *Amide II* bands were all clearly visual near to 3275, 1655 and 1610 cm^{-1}, respectively. In some cases, for instance **4f**, the enone C=O stretching band was shifted a little to a higher frequency 1675 cm^{-1} while the NO_2 symmetric and asymmetric stretching vibrations were strongly visible at 1515 and 1340 cm^{-1}, respectively. ^1H NMR spectra of compounds **4**–**6** showed the oleoyl olefinic protons as multiplet at δ 5.43 ppm and well separated from the aromatic protons. The H_β of the enone system was more deshielded than the H_α due to π-bond delocalization and both appeared in the aromatic region with large coupling constant *J* 15.6 Hz characteristic for *S-trans* configuration of the enone system [32].