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Synthesis and Antiproliferative Activity of Chalcone-Imide Derivatives Based on 3,4-Dichloro-*1H*-Pyrrole-2,5-dione

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Abstract

A series of chalcone imide derivatives,4'-aminochalcones-based dichloromaleimides,was synthesized from the reaction of 1-(4-acetylphenyl)-3,4-dichloro-*1H*-pyrrole-2,5-dione with various substituted aldehydes, or by treating 4'-aminochalcone with 3,4-dichlorofuran-2,5-dione in an alternative path. The structures of chalcone imide derivatives were established using IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. Antiproliferative effects of the newly synthesized compounds have been screened on two human cancer types via the MTT assay. Compounds with *p*-tolyl-1*H*-pyrrole-2,5-dione, and 4-bromophenyl-1*H*-pyrrole-2,5-dione derivatives, are highly active on the human liver cancer (HepG-2).On the other hand, all compounds were found to be more effective against breast cancer cells (MCF-7)than the positive control doxorubicin. The results of this work provide a basis for further research of selected chalcone-imide moiety as antiproliferative agents.

Keywords: chalcones, maleimides, pyrrole-2,5-dione,antiproliferative, cytotoxicity.

1. Introduction

Cancer is one of the main health problems in the world, and chemotherapy is one of the familiar medicines for the treatments of cancer [1]. Chemotherapy drugs have a cytotoxic attack on normal cells and therefore cause many strong side effects [2]. Hence, it is important to find anticancer medicines that possess cytotoxic and antiproliferative action in tumor cells lacking ffect on normal cells. Despite the fact that several cytotoxic compounds have been established, a need to improve the use of other effective and safer chemotherapy drugs is still important [2]. Several compounds containing maleimide have been synthesized for this purpose, for example, chalcone-imide derivatives have been constructed and described for their cytotoxic activity on human CEM T lymphocytes, Molt 4/ C8, and murine L1210 cell lines [3]. As well, chalcones based on maleimide and dibromomaleimide have been synthesized and their antibacterial properties have been described [4-6]. Besides to the great antimicrobial properties, maleimides had also been extensively investigated in medicine as antianxiety [7], anti-inflammatory [8], anticancer [9-11], and neuroprotective agents. Similarly, natural products with important units of maleimide have excellent biological activities, including antibacterial [12-19] and enzyme inhibitory activities [20-22].In addition, the chalcone has shown a vital role in the biosynthesis of flavonoids and is ubiquitous in natural products.Moreover, chalcones have been investigated for their cytotoxic activity against several cancer types [23-28].Furthermore, pyrrole is a public unit in several natural products, and many widespread drugs have a pyrrole moiety in their building. Pyrrole derivatives appeared as substructure units for some bioactive applicants [29]. Also, pyrrole derivatives showed anti-microbial [30], anti-viral [31], antitumor [32], antitubulin [33], antimalarial [34] and anticancer activities [35-37], Fig. 1.

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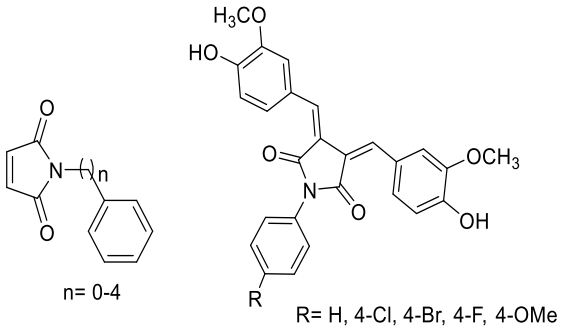

Figure 1. Bioactivemaleimide derivatives.

Extending our previous efforts that focused on the synthesis and development of biologically active compounds [38-50],in the current manuscript and in order to achieve constructive results, a combination between chalcones and maleimide wasaccomplished, sequentially a series of 4'-aminochalcone-based 3,4-dichloromaleimides was synthesized, and their cytotoxicity against breast cancer cells (MCF-7), and human hepatocellular carcinoma(HepG2) cells was investigated.

Experimental

Melting points were determined in open glass capillary tubes on an Electro Thermal Digital melting point apparatus (model: IA9100), and are uncorrected. Elemental analyses were carried out for elements C, H, N at Microanalytical Unit (at NRC). FT-IR spectral analyses (v, cm^{-1}) were recorded on a Nexus 670 FTIR Nicolet spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a Jeol 300 MHz in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard (chemical shifts are expressed in ppm). Mass spectra were measured on a MAT Finnigan SSQ 7000 spectrometer, using the electron impact technique (EI). TLC was performed on silica gel aluminum sheets, 60 F_{254} (E. Merck).Chalcones **4a-c** were synthesized according to reported procedure [51].

Synthesis of 1-(4-acetylphenyl)-3,4-dichloro-1H-pyrrole-2,5-dione(3).

To a solution of 3,4-dichlorofuran-2,5-dione (2mmol) **2** in acetic acid (10 ml), 4-acetyl aniline**1** (2mmol) was added. The reaction mixture was refluxed for 4h. After completion of the reaction, the produced mixture was cooled, poured into ice/water and left for 3h. The resulted solid was filtered and crystallized from ethanol.

Yellow solid, (78% yield); m.p. 293-295 ^oC. FT-IR:1740 (C=O), 1676 (2C=O). ^1H NMR (300 MHz,DMSO-d_6):2.60 (3H, s, CH_3), 7.56 (2H, d, *J* = 8.3 Hz, Ar-H), 8.01 (2H, d, *J* = 8.3 Hz, Ar-H),; ^{13}C NMR (125 MHz, DMSO-d_6):26.83, 126.51, 129.03, 132.89, 134.96, 136.15, 161.87, 197.21.EI-MS (m/z):283 $[M]^+$.Anal. calcd. for$C_{12}H_7Cl_2NO_3$: C, 50.73; H, 2.48; N, 4.93%. Found: C, 50.78; H, 2.45; N, 4.97%.

General procedure for the synthesis of 3,4-dichloro-1-(4-(3-(4-aryl)acryloyl)phenyl)-1H-pyrrole-2,5-dione derivatives (5a–g).

Method A: A solution of 1-(4-acetylphenyl)-3,4-dichloro-*1H*-pyrrole-2,5-dione **3** (10 mmol), and appropriate aldehydes (10 mmol) in ethanol, was stirred under an ice bath for 5 min. The reaction was initiated by dropwise addition of 10 ml of 60 % sodium hydroxide solution in 30 min interval. To ensure the end of the reaction, the mixture was allowed for continuous stirring for another 2-3 h at room temperature. The reaction mixture was kept in a refrigerator for overnight and diluted with ice-cold distilled water (40 mL). The precipitated chalcone was filtered, washed well with cold water and air dried. Then, the chalcone was recrystallized from ethanol.

Method B. To a solution of 3,4-dichlorofuran-2,5-dione**2** (2 mmol) inacetic acid (10 ml), chalcones **4a-c** (2 mmol) was added. The reaction mixture was refluxed for 4h. The reaction left to cool, and poured into ice/water and stand up for 3h. The solid was filtered and crystallized from ethanol.

*(E)-3,4-Dichloro-1-(4-(3-(4-nitrophenyl)acryloyl)phenyl)-1H-pyrrole-2,5-dione (5a).*Yellow solid, Yield 89 %; m.p. 212-214^{o}C.FT-IR: 1730 (C=O), 1670 (2C=O).^1H NMR (300 MHz,DMSO-d_6):7.58 (1H, d, *J* = 15.6 Hz,*E*-olefinic-H), 7.82 (1H, d, *J* = 15.6 Hz, *E*- olefinic-H), 8.05 (2H, d, *J* = 8.3 Hz, Ar-H), 8.10 (2H, d, *J* = 8.6 Hz, Ar-H), 8.13 (2H, d, *J* = 8.3 Hz, Ar-H), 8.29 (2H, d, *J* = 8.6 Hz, Ar-H); ^{13}C NMR (DMSO-d_6):123.95, 125.94, 126.60, 129.58, 129.94, 132.94,135.26, 136.51, 141.08, 141.47, 148.16, 161.87, 188.29.MS: m/z: 416 $[M]^+$. Anal. calcd. for$C_{19}H_{10}Cl_2N_2O_5$: C, 54.70; H, 2.42; N, 6.71%. Found: C, 54.77; H, 2.35; N, 6.76%.

*(E)-1-(4-(3-(4-Bromophenyl)acryloyl)phenyl)-3,4-dichloro-1H-pyrrole-2,5-dione (5b).*Yellow solid, Yield 83 %; m.p. 206-208^{o}C.FT-IR: 1720 (C=O), 1665 (2C=O). ^1H NMR (300 MHz,DMSO-d_6):7.56 (2H, d, *J* = 8.1 Hz, Ar-H), 7.68 (2H, d, *J* = 8.3 Hz, Ar-H), 7.72 (1H, d, *J* = 15.4 Hz, *E*-olefinic-H), 7.84 (2H, d, *J* = 8.3 Hz, Ar-H),7.97 (1H, d, *J* = 15.4 Hz, *E*-olefinic-H), 8.27 (2H, d, *J* = 8.1Hz, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6):122.71, 126.59, 129.43, 130.87, 131.92, 132.92, 135.05, 136.58, 138.10,

138.43, 143.02, 161.88, 188.24. EI-MS (m/z): 449[M]$^+$. Anal. calcd. for$C_{19}H_{10}BrCl_2NO_3$: C, 50.59; H, 2.23; N, 3.11%. Found: C, 50.64; H, 2.20; N, 3.14%.

*(E)-3,4-Dichloro-1-(4-(3-(4-chlorophenyl)acryloyl)phenyl)-1H-pyrrole-2,5-dione(5c).*Yellow solid, Yield 83 %; m.p. 195-197ºC.FT-IR: 1725 (C=O), 1668 (2C=O). ^{1}H NMR (300 MHz,DMSO-d_6):7.50 (2H, d, *J* = 8.2 Hz, Ar-H), 7.56 (2H, d, *J* = 8.4 Hz, Ar-H), 7.73 (1H, d, *J* = 15.8 Hz, *E*-olefinic-H), 7.91 (2H, d, *J* = 8.4 Hz, Ar-H), 7.95 (1H, d, *J* = 15.8 Hz, *E*-olefinic-H, 8.26 (2H, d, *J* = 8.2 Hz, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6):122.67, 126.59, 128.99, 129.44, 130.68, 132.91, 133.60, 135.04, 135.25, 136.83, 142.92, 161.89, 188.32. EI-MS (m/z): 405 [M$^+$]. Anal. calcd. for$C_{19}H_{10}Cl_3NO_3$: C, 56.12; H, 2.48; N, 3.44%. Found: C, 56.17; H, 2.42; N, 3.39%.

*(E)-3,4-Dichloro-1-(4-(3-(2-hydroxyphenyl)acryloyl)phenyl)-1H-pyrrole-2,5-dione(5d).*Yellow solid, Yield 83 %; m.p. 221-223ºC.FT-IR: 1345 (OH), 1725 (C=O), 1668 (2C=O). ^{1}H NMR (300 MHz,DMSO-d_6):6.9-7.15 (3H, m, Ar-H), 7.51 (1H, d, *J* = 8.1 Hz, Ar-H), 7.56 (2H, d, *J* = 8.4 Hz, Ar-H), 7.74 (1H, d, *J* = 15.6 Hz, *E*-olefinic-H), 7.98 (2H, d, *J* = 8.4 Hz, Ar-H), 8.10 (1H, d, *J* = 15.8 Hz, *E*-olefinic-H), 10.67 (1H, OH, D_2O exchange); ^{13}C NMR (125 MHz, DMSO-d_6):123.14, 126.48, 127.87, 129.49, 132.39, 133.21, 135.13, 135.27, 136.44, 141.13, 154.46, 161.78, 188.61.EI-MS (m/z): 387 [M$^+$]. Anal. calcd. for$C_{19}H_{11}Cl_2NO_4$: C, 58.79; H, 2.86; N, 3.61%.Found: C,58.85; H, 2.82; N, 3.60%.

*(E)-3,4-Dichloro-1-(4-(3-(4-hydroxyphenyl)acryloyl)phenyl)-1H-pyrrole-2,5-dione (5e).*Yellow solid, Yield 83 %; m.p. 199-201ºC.FT-IR: 1335 (OH), 1720 (C=O), 1660 (2C=O). ^{1}H NMR (300 MHz,DMSO-d_6):7.38 (2H, d, *J* = 8.2 Hz, Ar-H), 7.51 (2H, d, *J*= 8.4 Hz, Ar-H), 7.71 (1H, d, *J* = 15.8 Hz, *E*-olefinic-H), 7.93 (2H, d, *J* = 8.4 Hz, Ar-H), 8.03 (1H, d, *J* = 15.8 Hz, *E*-olefinic-H), 8.23 (2H, d, *J* = 8.2 Hz, Ar-H) 10.34 (1H, OH, D_2O exchange); ^{13}C NMR (125 MHz, DMSO-d_6):123.32, 127.11, 127.95, 129.66, 131.32, 134.40, 135.31, 135.58, 136.40, 142.08, 155.12, 161.46, 188.22.EI-MS (m/z): 387 [M$^+$].Anal. calcd. for$C_{19}H_{11}Cl_2NO_4$: C, 58.79; H, 2.86; N, 3.61%.Found: C, 58.83; H, 2.80; N, 3.63%.

*(E)-3,4-Dichloro-1-(4-(3-(p-tolyl)acryloyl)phenyl)-1H-pyrrole-2,5-dione (5f).*Yellow solid, Yield 83 %; m.p. 185-187ºC.FT-IR: 1715 (C=O), 1658 (2C=O). ^{1}H NMR (300 MHz,DMSO-d_6):2.43 (3H, s, CH_3), 7.33 (2H, d, *J* = 8.2 Hz, Ar-H), 7.46 (2H, d, *J* = 8.4 Hz, Ar-H), 7.74 (1H, d, *J* = 15.2 Hz, *E*-olefinic-H), 7.92 (2H, d, *J* = 8.4 Hz, Ar-H), 7.98 (2H, d, *J* = 8.2 Hz, Ar-H),8.01 (1H, d, *J* = 15.2 Hz, *E*-olefinic-H); ^{13}C NMR (125 MHz, DMSO-d_6): 22.44, 123.16, 126.18, 128.35, 129.11, 131.81, 132.69, 133.78, 135.52, 136.12, 137.38, 141.93, 161.76, 188.41.EI-MS (m/z): 385 [M$^+$]. Anal. calcd. for$C_{20}H_{13}Cl_2NO_3$: C, 62.20; H, 3.39; N, 3.63%. Found: C, 62.25; H, 3.32; N, 3.66%.

(E)-3,4-Dichloro-1-(4-(3-(thiophen-2-yl)acryloyl)phenyl)-1H-pyrrole-2,5-dione (5g).

Yellow solid, Yield 83 %; m.p. 167-1697ºC.FT-IR: 1712 (C=O), 1655 (2C=O). ^{1}H NMR (300 MHz,DMSO-d_6): 7.27 (1H, m, thiophene H-4), 7.54 (2H, d, *J* = 8.1 Hz, Ar-H), 7.57 (1H, d, thiophene H-3), 7.71 (1H, d, *J* = 15.2 Hz, *E*-olefinic-H), 7.79 (1H, d, thiophene H-4), 7.98 (2H, d, *J* = 8.1 Hz, Ar-H), 8.06 (1H, d, *J* = 15.2 Hz, *E*-olefinic-H); ^{13}C NMR (125 MHz, DMSO-d_6):120.19, 126.50, 128.77,129.22, 130.78, 132.90, 133.20,134.87, 136.89, 137.18, 139.64, 161.88, 187.91 EI-MS (m/z): 377 [M$^+$]. Anal. calcd. for$C_{17}H_9Cl_2NO_3S$: C, 53.99; H, 2.40; N, 3.70; S, 8.48%. Found C, 54.07; H, 2.37; N, 3.72; S, 8.42%.

Cell culture conditions

The cells of human liver carcinoma (HepG-2), and human breast adenocarcinoma (MCF-7) were purchased from the American Type Culture Collection (Rockville, MD). All cells were maintained in a DMEM medium, which was supplemented with 10% of heat-inactivated fetal bovine serum (FBS), 100U/ml of each of penicillin and streptomycin. The cells were grown at 37°C in a humidified atmosphere of 5% CO_2.

MTT antiproliferative assay

The antiproliferative activities on the HepG-2, and MCF-7 human cancer cell lines were estimated, using the 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, which was grounded on the reduction of the tetrazolium salt by the mitochondrial dehydrogenases in viable cells [52, 53]. The cells were dispensed in a 96 well sterile microplate (3 x 10^4 cells/well), followed by their incubation at 37ºC with a series of different concentrations of 10 µl of each compound or Doxorubicin® (positive control, in DMSO) for 48 h in a serum free medium prior to the MTT assay. Subsequently, the media were carefully removed, 40 µL of MTT (2.5 mg/mL) were added to each well, and then incubated for an additional 4 h. The purple formazan dye crystals were solubilized by the addition of 200 µL of DMSO. The absorbance was measured at 570 nm applying a SpectraMax® Paradigm® Multi-Mode microplate reader. The relative cell viability was

expressed as the mean percentage of viable cells relative to the untreated control cells. All experiments were conducted in triplicate and were repeated on three different days. All the values were represented as mean ± SD. The IC_{50}s were determined by the SPSS probit analysis software program (SPSS Inc., Chicago, IL).

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Results and Discussion

Chemistry

Continuing our previous efforts to develop successful anticancer agents, a series of 4'-aminochalcones-based on dichloro-*1H*-pyrrole-2,5-dione**5a-g**has been designed and synthesized. Consequently, 4-acetyl aniline **1** reacted with 3,4-dichlorofuran-2,5-dione **2** in acetic acid at refluxed temperature for 4h to give 1-(4-acetylphenyl)-3,4-dichloro-*1H*-pyrrole-2,5-dione **3** in a good yield. The structure of **3** was elucidated according to spectral data IR, NMR, and mass analysis. Spectral data are in a good agreement with the proposed structure (Scheme 1). The IR (KBr, cm^{-1}) spectra of this compound released absorption bands at 1676-1740 cm^{-1} for three carbonyl groups. Similarly, ^{1}H-NMR data of compound **3** shows the CH_3 protons signal at 2.60 ppm and the aromatic signal at 7.56–8.01 ppm and the ^{13}C-NMR indicated that there were three carbonyl carbons at 161 and 197 ppm.

Subsequently, chalcone-imides **5a-g** were synthesized by Claisen–Schmidt condensation of compound **3** with appropriate aldehydes. The structures of chalcone derivatives **5a-g** were elucidated according to spectral data IR, NMR, and mass analysis. Spectral data are in a good agreement with the suggested structure. For example, the IR spectra of compound **5a** released absorption bands at 1670-1730 cm^{-1} for three carbonyl groups. Also, ^{1}H-NMR data of compound **5a**exhibited two doublet signals at 7.58-7.82 ppm of α,β-unsaturated protons in addition to aromatic signals at 8.05-8.29 ppm. The ^{13}C-NMR revealed three carbonyl carbons at 161.86 and 188.29 ppm. In addition, the DEPT experiment (Fig. 2) revealed six odd protons, (CH), (two α,β-unsaturated protons plus eight aromatic protons with two para-substituted benzene rings). The *J*-coupling (*J* = 15.6 Hz) of compound 5a-g was established their *E*-isomers. Furthermore, an alternative high coast route for the synthesis of compound **5a-g** was carried out, but with low yield, (Scheme 2).

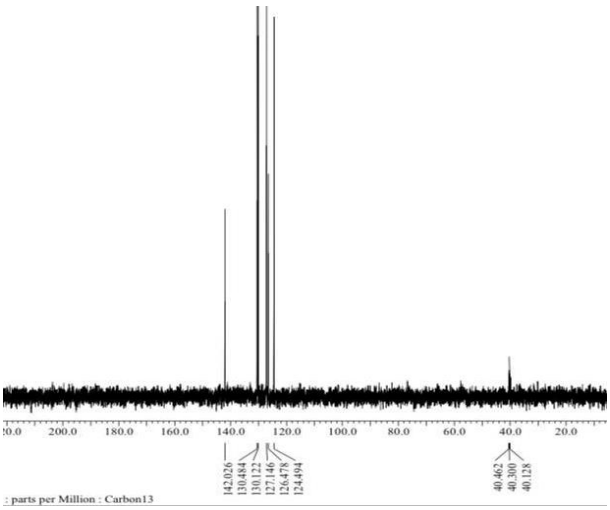
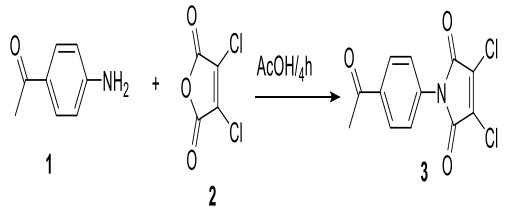
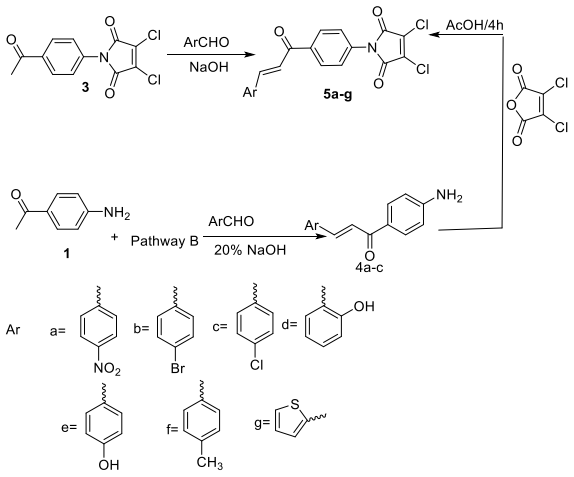


Fig 2. DEPT-NMR of compound **5a**



Scheme 1. Synthetic routes to maleimide **3**



Scheme 2. Synthetic routes to chalcone-imide derivatives **5a-g.**

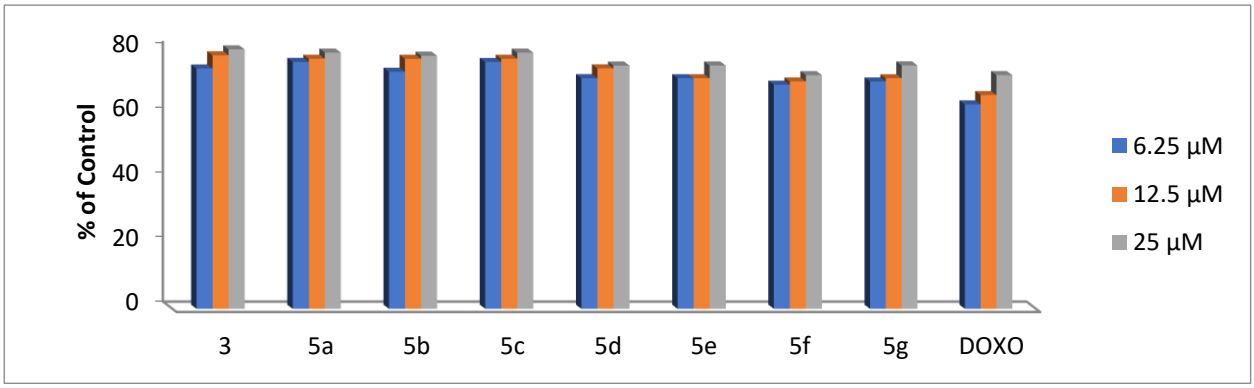


Fig. 3: Dose-dependent antiproliferative data of the compounds on the HepG-2 human cancer type, according to the MTT assay after 48 h of exposure.

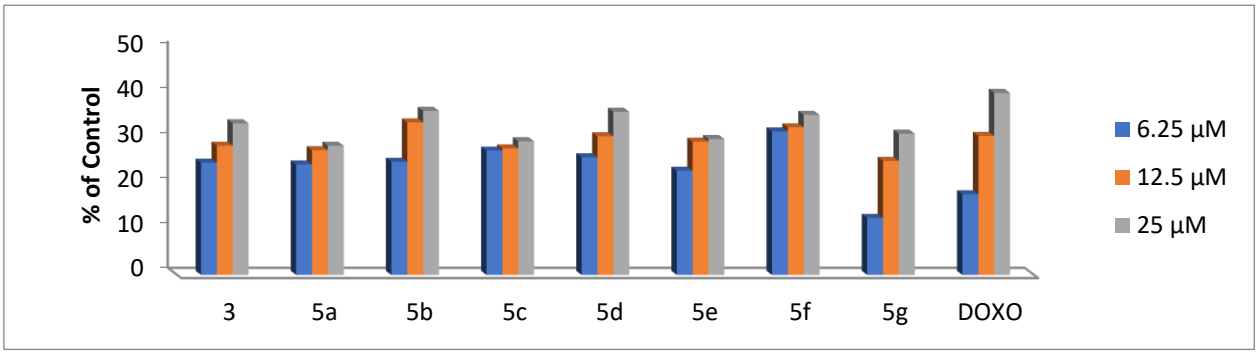


Fig. 4: Dose dependent antiproliferative data of the compounds on the MCF-7 human cancer type according to the MTT assay after 48 h of exposure

Antiproliferative activity

Selected compounds were tested *in vitro* for their antiproliferative activities on the HepG-2 and MCF-7 human cancer cell lines through the employment of the MTT assay. The percentages of the viable cells and their IC_{50} values were measured and were, subsequently, assessed with those of the control, Doxorubicin (table, Figs. 3, and 4). The results obtained revealed that all compounds showed dose-dependent antiproliferative activity against both cells (Figs. 3, and 4). Constructed deduction from these outcomes is that, in assessment with the positive control Doxorubicin, for human liver cancer (HepG-2), compounds 5f, 5b, and 5d, respectively, have comparable activities; the rest of the compounds had slightly less activities than the positive control (table, Fig. 3). In breast cancer cells (MCF-7); all compoundsare more potent relative to the positive control (table 1, Fig.4).

Table 1: The antiproliferative IC_{50} values of the compounds according to the MTT assay on the two human cell types.

Compounds	**IC_{50} (µM) ± SD**	
	HepG-2	MCF-7
3	30.8 ± 3.1	7.5 ± 0.5
5a	32.1 ± 3.1	7.7 ± 0.9
5b	29.1 ± 2.9	7.9 ± 0.6
5c	31.1 ± 2.6	7.6 ± 0.5
5d	29.6 ± 2.8	9.0 ± 1.1
5e	31.7 ± 3.1	9.2 ± 0.9
5f	28.1 ± 2.5	10.0 ± 1.1
5g	35.1 ± 3.3	9.4 ± 0.9
Doxorubicin	28.5 ± 1.9	10.3 ± 0.8

Conclusion

In the current manuscript, a series of promising chalcone-imides, **5a–g** was synthesized, characterized and their anticancer activity against HepG-2, and MCF-7 human cancer cell lines was investigated.

Compounds **5f**, **5b,** and **5d,** were highly active on the human liver cancer (HepG-2).On the other hand, all compounds are more effective against breast cancer cells (MCF-7)than the positive control doxorubicin. The results of this manuscript offer a basis for further research on selected chalcone-imide derivatives as antiproliferative agents (especially for breast cancer cells (MCF-7)).

In the view of **SAR** correlations compounds**5f**, **5b,** and **5d**, with 4-methyl, 4-bromo, and 2- hydroxyphenyl linked to chalcone-imides were more active on the human liver cancer (HepG-2). While all compounds are more effective against breast cancer cells (MCF-7) than the positive control doxorubicin specially compound **5a** with 4-nitophenyl substituted.

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Consent for Publication

Not applicable.

Conflict of Interests

The authors declare no conflict of interests, financial or otherwise.

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