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Research Article

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Synthesis, stereochemistry and antitumor evaluation of some novel chalcone derivatives

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ABSTRACT

*2-Chloroquinoline-3-carbaldehyde (**1**) was condensed with the acetyl reagents **2a−e** under the Claisen-Schmidt reaction conditions. In general, two products were formed, separated by column chromatography and proved by the spectroscopic data to be the two possible conformers E-s-cis-**3a-c** and E-s-trans-**3a-c** of the respective chalcones. However, reaction of **1** with **2d** gave only one product **3d** which has been attributed to the more stable E-s-cis conformer. Condensation of compound **1,** on the other hand, with **2e** gave the E-s-cis-**3e** conformer of the respective chalcone in addition to the cyclic flavanone **4**. Moreover, 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **(5)** condensed with the acetyl reagents **2a** and **6** to give the E-s-cis conformers **7a,b** of the respective chalcones. Similarly, ferrocenecarboxaldehyde **(8)** reacted with reagents **2c,d** yielding the respective E-s-cis chalcones **9a,b**. Structures and stereochemistry of the new products have been supported by the elemental microanalysis and the spectroscopic measurements including single crystal X−ray crystallography. The cytotoxicity and in vitro anticancer evaluation of the new compounds have been assessed, in detail, against four solid human cancer cell lines.*

Keywords: Anticancer activity, chalcones, conformational structures, flavanones, stereochemistry.

INTRODUCTION

Chalcones, open chain precursors of flavonoids and isoflavonoids, are present in edible plants. Their derivatives have attracted increasing attention due to their numerous potential pharmacological applications.[1−3] As chemoprotective and chemopreventive, chalcones were found to have antitubercular,[4] antimalarials,[5] anti-histaminic,[6] antioxidant,[7] antihyperglycemic,[8] antifilarial,[9] antimutagenic,[10] anti-invasive,[11] anti-angiogenic,[12] antiulcerative.[13] antifibrogenic,[14] antitrichomonal[15] and antitumor[16−18] activities. They also inhibit the activities of many enzymes, like the mammalian alpha-amylase,[19] cyclooxygenase,[20] monoamine oxidase, [21] malarial cysteine protaeases [22] and topoisomerase I.[23] Moreover, chalcones are regarded as promising anticancer agents against many human cancers.[24−26] Chalcones inhibit the ovarian cancer cell proliferation[27] and pulmonary carcinogenesis.[28] Since a number of anticancer drugs have genotoxic effects due to their interaction with nucleic acids, chalcones may be devoid of this side effects.[29] Therefore, some chalcones have been clinically marketed including metochalcone (choleretic and diuretic), sofalcone (an antiulcer and mucoprotective) and hesperidin methylchalcone (vascular protective) (Figure 1).[30] Apparently, existence of the reactive α,β−unsaturated carbonyl group in chalcones is responsible for their biological as well as chemical activities.[31] For many tumor types, the established treatments such as cytotoxic chemotherapy provides only transient therapeutic benefits despite severe side effects.[32] Thus, the need for better treatments has stimulated research to develop new efficient chemotherapeutic agents for management of cancer.[33−37]

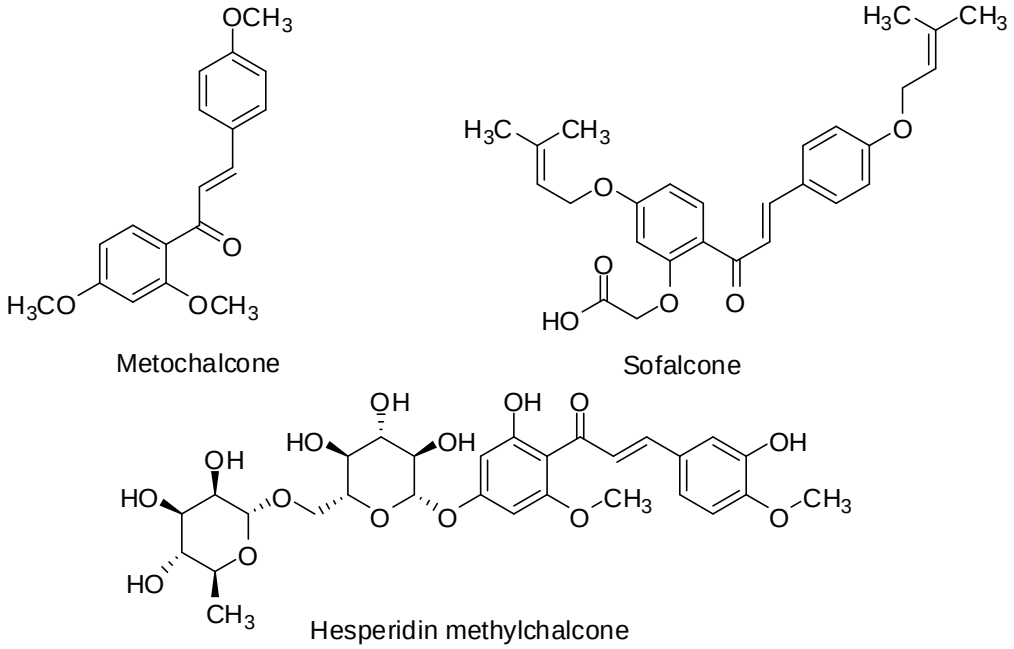


Figure 1. Examples of marketed or clinically tested chalcones

Therefore, in pursuing our efforts[38] to design and prepare new bioactive compounds, we have devoted the present study to prepare a series of novel chalcones accommodating more than one bioactive moiety like ferrocene,[39,40] quinoline,[41,42] furan,[43] benzofuran,[44,45] and/or coumarin[46,47] in the same molecule and evaluating their antitumor activities against liver (HepG2), breast (MCF-7), lung (A549) and colon (HCT116) human cancer cell lines.

EXPERIMENTAL SECTION

General. Solvents were purified and dried according to the usual procedures. The starting aldehydes were purified directly before use by distillation or recrystallization. The reactions were monitored (TLC) and the purity of the isolated products were controlled by using silica gel with fluorescent indicator F_{254} coated on aluminum sheets of layer thickness 0.2 mm [Fluka]. Column chromatography was performed on silica gel, grain size 0.063–0.2 mm (Merck). Melting points were recorded on Electrothermal melting point apparatus and were uncorrected. The IR spectra were measured in KBr pellets using a JASCO FT/IR-300E Fourier Transform Infrared Spectrophotometer and reported in cm^{-1}. NMR spectra were recorded on a Joel-500 MHz spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) and/or Mercury 300BB spectrophotometer (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz). The proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Finnigan SSQ 7000 Spectrometer at 70 eV (Electron Impact). Analytical data were obtained at the analytical laboratory of the National Research Centre (or in the Microanalytical unit, Cairo University, Giza, Egypt). Satisfactory elemental analyses were gained for the new products. The antitumor activity was carried out at Department of Biochemistry at the National Research Centre (NRC). X-ray diffraction analysis: The intensity data were performed with a κ-CCD Enraf Nonius FR 590 single crystal diffractometer, temperature 298 K, wavelength Mo *K*a (0.71073 Å). The structure was solved by direct methods using the *SIR*92 program[48] and refined using ma*X*us.[49] The molecular graphics were made with ORTEP.[50] Crystallographic data (CIF) for the structure reported in this article have been deposited in the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication No. CCDC 1489692. Copies of the data can be obtained, free of charge, upon application to the CCDC, 12 Union Road, Cambridge CB 12EZ, UK (FAX: + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk).

Condensation of 2-chloroquinoline-3-carbaldehyde 1 with the acetyl derivatives 2a−e

General procedure: To a mixture of 2-chloroquinoline-3-carbaldehyde (**1**) (0.01 mol, 1.92 g) and the appropriate acetyl derivative **2a−e** (0.01 mol) in ethanol (5 mL), an aqueous solution of KOH (30%, 4 mL) was added dropwise with stirring at room temperature. The red−coloured reaction mixture was stirred for further 12 hours then poured onto crushed ice and acidified with acetic acid. The separated solid products were filtered off, washed well with water, dried, recrystallized and/or chromatographed on silica gel and eluted with the appropriate solvent mixture to give compounds **3a−e** and **4.**

(*E*-*s*-*cis*)-3-(2-chloroquinolin-3-yl)-1-(ferrocenyl)prop-2-en-1-one (*E*-*s*-*cis*)-3a. Eluent: Petroleum ether (60 − 80 ºC)/acetone (93:7 v/v), brown crystals, yield: 58 % (2.3 g), mp 209 – 210 °C. IR (KBr, ν, cm^{-1}): 3084 (C—H, aromatic), 3032 (C—H, olefinic), 1646 (C=O, enone), 1585 (C=C, enone), 1480, 1446 (aromatic C=C, C=N), 749 (C—Cl, aromatic). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.26 (s, 5H, ferrocene), 4.65 (s, 2H, ferrocene), 4.95 (s, 2H, ferrocene), 7.21 (d, J_{HH} 16.1 Hz, CH=C***H***-C=O, 1H, α-ethylenic proton) , 7.62 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.78 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.91 (d, J_{HH} 7.6 Hz, 1H, aromatic), 8.04 (d, J_{HH} 7.6 Hz, 1H, aromatic), 8.19 (d, J_{HH} 16.1 Hz, 1H, C***H***=CH, β-ethylenic proton), 8.46 (s, 1H, aromatic). MS (EI, 70 eV): *m/z* (%) 402 (1) [M^+ + 1]. Anal. Calcd. for $C_{22}H_{16}ClFeNO$ (401.67): C, 65.78; H, 4.02; Cl, 8.83; Fe, 13.90; N, 3.49. Found: C, 65.89; H, 3.96; Cl, 8.77; N, 3.40%.

(*E*-*s*-*trans*)-3-(2-chloroquinolin-3-yl)-1-(ferrocenyl)prop-2-en-1-one (*E*-*s*-*trans*)-3a. Eluent: Petroleum ether (60 − 80 ºC)/acetone (95:5 v/v), red crystals, yield: 24 % (0.9 g), mp 159 − 161 °C. IR (KBr, ν, cm^{-1}): 3104 (C—H, aromatic), 3040 (C—H, olefinic), 1651 (C=O, enone), 1589 (C=C, enone), 1485, 1453 (aromatic C=C, C=N), 751 (C—Cl, aromatic). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.24 (s, 5H, ferrocene), 4.98 (s, 2H, ferrocene), 5.03 (s, 2H, ferrocene), 7.39 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.55 (d, J_{HH} 15.7 Hz, CH=C***H***-C=O, 1H, α-ethylenic proton) , 7.63 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.77 (d, J_{HH} 7.6 Hz, 1H, aromatic), 7.82 (d, J_{HH} 7.6 Hz, 1H, aromatic), 7.96 (d, J_{HH} 15.7 Hz, 1H, C***H***=CH-C=O, β-ethylenic proton), 8.24 (s, 1H, aromatic). MS (EI, 70 eV): *m/z* (%) 402 (2) [M^+ + 1]. Anal. Calcd. for $C_{22}H_{16}ClFeNO$ (401.67): C, 65.78; H, 4.02; Cl, 8.83; Fe, 13.90; N, 3.49. Found: C, 66.02; H, 3.95; Cl, 8.86; N, 3.41%.

(*E*-*s*-*cis*)-3-(2-chloroquinolin-3-yl)-1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)prop-2-en-1-one (*E*-*s*-*cis*)-3b. Eluent: Petroleum ether (60 − 80 ºC)/acetone (85:15 v/v), red crystals, yield: 53 % (2.2 g), mp 209 °C. IR (KBr, ν, cm^{-1}): 3430 (O—H), 3146, 3112 (C—H, aromatic), 3056 (C—H, olefinic), 3936 (C—H, aliphatic), 1619 (C=O, enone), 1559 (C=C, enone), 1505, 1467 (aromatic C=C, C=N), 750 (C—Cl, aromatic). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.08 (s, 3H, OC***H***$_3$), 4.11 (s, 3H, OC***H***$_3$), 6.90 (d, J_{HH} 2.4 Hz, 1H, C***H***=CH−O, furan), 7.55 (d, J_{HH} 2.4 Hz, 1H, CH=C***H***−O, furan), 7.60 (d, J_{HH} 15.9 Hz, CH=C***H***−C=O, 1H, α-ethylenic proton), 7.62 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.79 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.90 (d, J_{HH} 8.4 Hz, 1H, aromatic), 8.05 (d, J_{HH} 8.4 Hz, 1H, aromatic), 8.22 (d, J_{HH} 15.9 Hz, 1H, C***H***=CH−C=O, 1H, β-ethylenic proton), 8.47 (s, 1H, aromatic), 12.05 (s, 1H, OH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO, δ, ppm): 61.26 (***C***H_3O), 61.62 (***C***H_3O), 106.15, 106.40, 111.37, 115.79, 116.09, 127.32, 128.16, 128.32, 129.03, 138.04, 145.11, 146.32, 146.85, 149.80, 151.84 (aromatic, hetreoaromatic and/or olefinic carbons), 193.72 (***C***=O). MS (EI, 70 eV): *m/z* (%) 409 (16) based on ^{35}Cl and 411 (5) based on ^{37}Cl. Anal. Calcd. for $C_{22}H_{16}ClNO_5$ (409.82): C, 64.48; H, 3.94; Cl, 8.65; N, 3.42. Found: C, 64.58; H, 3.91; N, 3.46 %.

(*E*-*s*-*trans*)-3-(2-chloroquinolin-3-yl)-1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)prop-2-en-1-one (*E*-*s*-*trans*)-3b. Eluent: Petroleum ether (60 − 80 ºC)/acetone (93:7 v/v), yellow crystals, yield: 26 % (1.1 g), mp 114 °C. IR (KBr, ν, cm^{-1}): 3428 (O—H), 3151.11, 3116 (C—H, aromatic), 3064 (C—H, olefinic), 2947, 2847 (C—H, aliphatic), 1630 (C=O, enone), 1571 (C=C, enone), 1546, 1496 (aromatic C=C, C=N), 757.89 (C—Cl). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.04 (s, 3H, OC***H***$_3$), 4.09 (s, 3H, OC***H***$_3$), 6.91 (d, J_{HH} 2.4 Hz, 1H, C***H***=CH−O, furan), 7.41 (t, J_{HH} 7.6 Hz, 1H, aromatic), 7.54 (d, J_{HH} 2.4 Hz, 1H, CH=C***H***−O, furan), 7.66 (t, J_{HH} 7.6 Hz, 1H, aromatic), 7.77 (d, J_{HH} 8.4, 1H, aromatic), 7.79 (d, J_{HH} 17.7 Hz, 1H, CH=C***H***-C=O, α-ethylenic proton), 7.83 (d, J_{HH} 8.4 Hz, 1H, aromatic), 8.17 (d, J_{HH} 17.7 Hz, 1H, C***H***=CH-C=O, β-ethylenic proton), 8.28 (s, 1H, aromatic), 12.72 (s, 1H, O***H***, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 60.68 (O***C***H_3), 61.94 (O***C***H_3), 105.52, 111.62, 119.09, 124.62, 124.68, 126.42, 128.41, 130.98, 131.062, 137.79, 139.03, 144.50, 145.76, 146.17, 146.36, 149.15, 159.03 (aromatic, hetreoaromatic and/or olefinic carbons), 194.10 (C=O). MS (EI, 70 eV): *m/z* (%) 409 (32) based on ^{35}Cl and 411 (12) based on ^{37}Cl. Anal. Calcd. for $C_{22}H_{16}ClNO_5$ (409.82): C, 64.48; H, 3.94; Cl, 8.65; N, 3.42. Found: C, 64.52; H, 3.90; N, 3.42 %.

(*E*-*s*-*cis*)-3-(3-(2-chloroquinolin-3-yl)acryloyl)-2H-chromen-2-one (*E*-*s*-*cis*)-3c. Eluent: Petroleum ether (60 − 80 ºC)/acetone (65:35 v/v), pale brown crystals, yield: 56 % (2.0 g), mp 198−200 °C. IR (KBr, ν, cm^{-1}): 3061 (C—H, aromatic), 3005 (C—H, olefinic), 1704 (C=O, chromenone), 1647 (C=O, enone), 1607 (C=C, enone), 1487, 1452 (aromatic C=C, C=N), 754 (C—Cl, aromatic). ^{1}H NMR (300 MHz, DMSO−d_6, δ, ppm): 6.67 (d, J_{HH} 8.7 Hz, 1H, aromatic), 6.87 (d, J_{HH} 7.2 Hz, 1H, aromatic), 6.97 (d, J_{HH} 7.5 Hz, 1H, aromatic), 7.08 (t, J_{HH} 7.5 Hz, 1H, aromatic), 7.23−7.36 (m, 2H, aromatic), 7.49 (s, 1H, aromatic), 7.78 (d, J_{HH} 15.6 Hz, 1H, CH=C***H***−C=O, α−ethylenic proton), 7.90 − 8.08 (m, 2H, aromatic), 8.16 (s, 1H, aromatic), 9.03 (d, J_{HH} 15 Hz, 1H, C***H***=CH−C=O, β−ethylenic proton). MS (EI, 70 eV): *m/z* (%) 361 (<5) based on ^{35}Cl and 363 (<2) based on ^{37}Cl. Anal. Calcd. for $C_{21}H_{12}ClNO_3$ (361.78): C, 69.72; H, 3.34; Cl, 9.80; N, 3.87. Found: C, 69.80; H, 3.33; Cl, 9.74; N, 3.82 %.

(*E*-s-*trans*)-3-(3-(2-Chloroquinolin-3-yl)acryloyl)-2H-chromen-2-one (*E*-*s*-*trans*)-3c. Eluent: Petroleum ether (60 − 80 ºC)/acetone (95:5 v/v), golden yellow crystals, yield: 22 % (0.8 g), mp 182 − 184 °C. IR (KBr, ν, cm^{-1}):

3151 (C—H, aromatic), 3055 (C—H, olefinic), 1740 (C=O, chromenone), 1651 (C=O, enone), 1610 (C=C, enone), 1559 1485, 1450 (aromatic C=C, C=N), 749 (C—Cl, aromatic). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.87 (d, J_{HH} 7.8 Hz, 1H, aromatic), 7.01 (s, 1H, aromatic), 7.45 −7.62 (m, 5H, aromatic), 7.90 (t, J_{HH} 7.8 Hz, 1H, aromatic), 7.95 (d, J_{HH} 7.8 Hz, 1H, aromatic), 8.09 (d, J_{HH} 16.8 Hz, 1H, CH=C***H***−C=O, α−ethylenic proton), 8.17 (d, J_{HH} 16.8 Hz, 1H, C***H***=CH−C=O, β−ethylenic proton), 8.49 (s, 1H, aromatic). (EI, 70 eV): *m/z* (%) 361 (<5) based on ^{35}Cl and 363 (<2) based on ^{37}Cl. Anal. Calcd. for $C_{21}H_{12}ClNO_3$ (361.78): C, 69.72; H, 3.34; Cl, 9.80; N, 3.87. Found: C, 69.84; H, 3.29; Cl, 9.88; N, 3.83%.

(*E*-*s*-*cis*)-3-(3-(2-Chloroquinolin-3-yl)acryloyl)-4-hydroxy-2H-chromen-2-one (*E*-*s*-*cis*)-3d. Yellow crystals recrystallized from ethanol, yield: 82 % (3.1 g), mp 292 − 294 °C. IR (KBr, ν, cm^{-1}): 3412 (O—H), 3100 (C—H, aromatic), 3055 (C—H, olefinic), 1716 (C=O, chromenone), 1610 (C=O, enone), 1531 (C=C, enone), 1492, 1431 (aromatic C=C, C=N), 756 (C—Cl, aromatic). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.41 (m, 2H, aromatic), 7.72 (t, J_{HH} 7.6 Hz, 1H, aromatic), 7.78 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.88 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.96 (d, J_{HH} 7.6 Hz, 1H, aromatic), 8.03 (d, J_{HH} 7.6 Hz, 1H, aromatic), 8.16 (s, 1H, O***H***, D_2O exchangeable), 8.18 (d, J_{HH} 16.1 Hz, 1H, CH=C***H***−C=O, α−ethylenic proton), 8.21 (t, J_{HH} 7.6 Hz, 1H, aromatic), 8.36 (d, J_{HH} 16.1 Hz, 1H, C***H***=CH−C=O, β−ethylenic proton), 8.99 (s, 1H, aromatic). (EI, 70 eV): *m/z* (%) 377 (15) based on ^{35}Cl and 379 (6) based on ^{37}Cl. Anal. Calcd. for $C_{21}H_{12}ClNO_4$ (377.78): C, 66.77; H, 3.20; Cl, 9.38; N, 3.71. Found: C, 66.86; H, 3.17; Cl, 9.44; N, 3.73%.

(*E*-*s*-*cis*)-3-(2-Chloroquinolin-3-yl)-1-(6-hydroxy-4-methoxybenzofuran-5-yl)prop-2-en-1-one (*E*-*s*-*cis*)-3e. Eluent: petroleum ether (60 − 80 ºC)/acetone (95:5 v/v), orange crystals, yield: 58 % (2.2 g), mp 213 °C. IR (KBr, ν, cm^{-1}): 3425 (O—H), 3135 (C—H, aromatic), 3084 (C—H, olefinic), 2924 (C—H, aliphatic), 1628 (C=O, enone), 1558 (C=C, enone), 1481, 1442 (aromatic C=C, C=N), 753 (C—Cl, aromatic). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.18 (s, 3H, OC***H***$_3$), 6.85 (s, 1H, aromatic), 6.90 (d, J_{HH} 3.3 Hz, 1H, -C***H***=CH−O, furan), 7.50 (d, J_{HH} 3.3 Hz, 1H, -CH=C***H***−O, furan), 7.65 (t, J_{HH} 7.6 Hz, 1H, aromatic), 7.80 (t, J_{HH} 7.6, 1H, aromatic), 7.94 (d, J_{HH} 15.9 Hz, 1H, CH=C***H***-C=O, α−ethylenic proton), 7.98 (d, J_{HH} 8.1 Hz, 1H, aromatic), 8.06 (d, J_{HH} 8.1 Hz, 1H, aromatic), 8.21 (d, J_{HH} 15.9 Hz, 1H, C***H***=CH-C=O, β−ethylenic proton), 8.46 (s, 1H, aromatic), 12.63 (s, 1H, O***H***, D_2O exchangeable). MS (EI, 70 eV): *m/z* (%) 379 (30) [M$^+$] based on ^{35}Cl and 381 (10) [M$^+$] based on ^{37}Cl. Anal. Calcd. for $C_{21}H_{14}ClNO_4$ (379.79): C, 66.41; H, 3.72; Cl, 9.33; N, 3.69. Found C, 66.29; H, 3.77; Cl, 9.28; N, 3.62%.

7-(2-Chloroquinolin-3-yl)-4-methoxy-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (4). Eluent: petroleum ether (60 − 80 ºC)/acetone (88:12 v/v), pale yellow crystals, yield: 22 % (0.84 g), mp 177−179 °C. $[\alpha]_{D/25}$ +20. IR (KBr, ν, cm^{-1}): 3067 (C—H, aromatic), 2927 (C—H, aliphatic), 1625 (C=O, conjugated), 1591, 1483, 1433 (aromatic C=C, C=N), 748 (C—Cl, aromatic). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.26 (dd, J_{HHgem} 15.0 Hz, J_{HHvic} 6.8 Hz, 2H, cyclic methylene -C***H***$_2$-), 3.92 (t, J_{HH} 6.8 Hz, 1H, O−C***H***−CH$_2$), 4.13 (s, 3H, OC***H***$_3$), 6.76 (d, J_{HH} 2.4 Hz, 1H, C***H***=CH−O, furan), 6.87 (s, 1H, aromatic), 7.44 (d, J_{HH} 2.4 Hz, 1H, CH=C***H***−O, furan), 7.61 (t, J_{HH} 6.5 Hz, 1H, aromatic), 7.68 (t, J_{HH} 6.5 Hz, 1H, aromatic), 7.87 (d, J_{HH} 6.5 Hz, 1H, aromatic), 8.10 (d, J_{HH} 6.5 Hz, 1H, aromatic), 8.52 (s, 1H, aromatic). ^{13}C NMR (75 MHz, DMSO−d_6, δ, ppm): 52.37 (***C***H$_2$), 60.56 (***C***H$_3$O), 65.67 (***C***H−O), 93.17, 106.23, 109.73, 114.06, 127.65, 127.74, 127.91, 128.50, 130.91, 136.99, 137.30, 144.33, 146.61, 148.79, 153.18, 156.51, 158.56 (aromatic, hetreoaromatic and olefinic carbons), 202.63 (C=O). MS (EI, 70 eV): *m/z* (%) 379 (32) [M$^+$] based on ^{35}Cl and 381 (10) [M$^+$] based on ^{37}Cl. Anal. Calcd. for $C_{21}H_{14}ClNO_4$ (379.79): C, 66.41; H, 3.72; Cl, 9.33; N, 3.69. Found: C, 66.37; H, 3.77; Cl, 9.37; N, 3.64%.

Condensation of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (5) with acetyl ferrocene (2a) and acetyl furan (6), General procedure. To a mixture of aldehyde **5** (0.01 mol, 2.10 g) and the appropriate acetyl derivative **2a** or **6** (0.01 mol) in ethanol (5 mL), an aqueous solution of KOH (30%, 4 mL) was added dropwise with stirring at room temperature. The red−coloured reaction mixture was stirred for further 12 hours then poured onto crushed ice and acidified with acetic acid. The separated solid products were filtered off, washed well with water, dried and recrystallized from ethanol to give the corresponding chalcones **7a,b**.

(*E*-*s*-*cis*)-4-Chloro-3-(3-(ferrocenyl)−3-oxoprop-1-enyl)-2*H*-chromen-2-one *(E*-*s*-*cis*)-7a.
Brown crystals from ethanol, yield: 79 % (3.3 g), mp > 300 °C. IR (KBr, ν, cm^{-1}): 3060 (C—H, aromatic), 3025 (C—H, olefinic), 1698 (C=O, chromenone), 1660 (C=O, enone), 1610 (C=C, enone), 1540 (C=C, aromatic), 761 (C—Cl, aromatic). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 4.11 (s, 5H, ferrocene), 4.20 (s, 2H, ferrocene), 4.74 (s, 2H, ferrocene), 7.45 (d, J_{HH} 8.4 Hz, 1H, aromatic), 7.48 (d, J_{HH} 17.5 Hz, 1H, CH=C***H***−C=O, α−ethylenic proton), 7.50 (t, J_{HH} 7.6 Hz, 1H, aromatic), 7.71 (t, J_{HH} 8.4 Hz, 1H, aromatic), 7.91 (d, J_{HH} 17.5 Hz, 1H, C***H***=CH−C=O, β−ethylenic proton), 8.34 (d, J_{HH} 7.6 Hz, 1H, aromatic). MS (EI, 70 eV): *m/z* (%) 418 (23) based on ^{35}Cl and 420 (8) based on ^{37}Cl. Anal. Calcd. for $C_{22}H_{15}ClFeO_3$ (418.65): C, 63.12; H, 3.61; Cl, 8.47; Fe, 13.34. Found C, 63.03; H, 3.66; Cl, 8.39 %.

(*E*-*s*-*cis*)-4-Chloro-3-(3-(furan-2-yl)-3-oxoprop-1-enyl)-2*H*-chromen-2-one *(E-s-cis)*-7b.
Golden yellow crystals from ethanol, yield: 83 % (2.5 g), mp 284 − 286 °C. IR (KBr, ν, cm^{-1}): 3110 (C—H, aromatic), 3060 (C—H, olefinic), 1698 (C=O, chromenone), 1618 (C=O, enone), 1580 (C=C, enone), 1560 (C=C, aromatic), 755 (C—Cl, aromatic). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.10 (d, J_{HH} 5.0 Hz, 1H, C***H***=CH−O, furan), 7.15 (t, J_{HH} 7.5 Hz, 1H, aromatic), 7.42 (d, J_{HH} 15.0 Hz, 1H, CH=C***H***−C=O, α−ethylenic proton), 7.43 −7.49 (m, 4H, aromatic and furan), 7.84 (d, J_{HH} 5.0 Hz, 1H, CH=C***H***−O, furan), 8.23 (d, J_{HH} 15.0 Hz, 1H, C***H***=CH−C=O, β−ethylenic proton). MS (EI, 70 eV): *m/z* (%) 300 (40) based on ^{35}Cl and 302 (14) based on ^{37}Cl. Anal. Calcd. For $C_{16}H_9ClO_4$ (300.69): C, 63.91; H, 3.02; Cl, 11.79. Found: C, 64.08; H, 2.98; Cl, 11.66%.

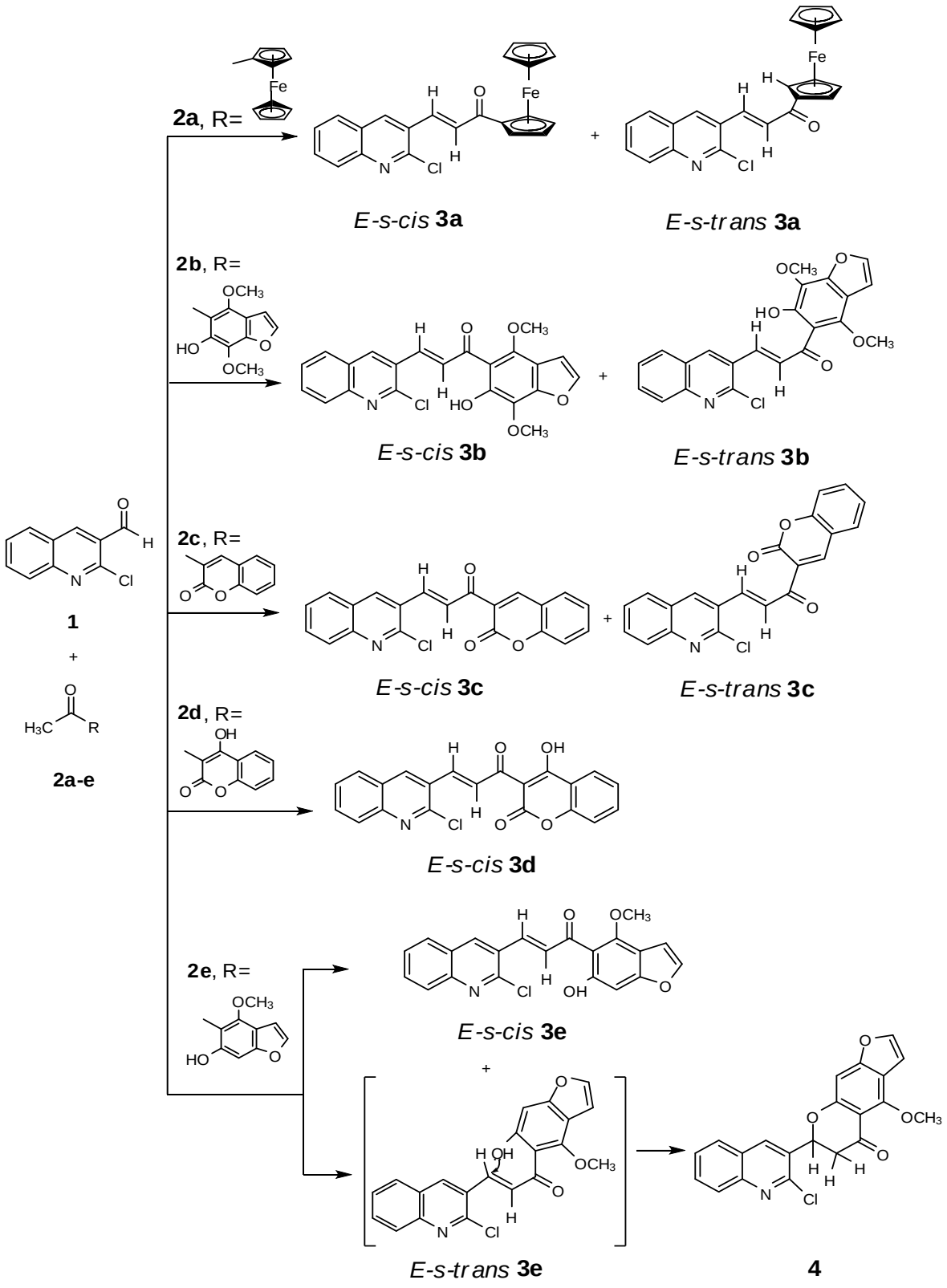
Condensation of ferrocenecarboxaldehyde (8) with the 3-acetyl-2*H*-chromen-2-one derivatives 2c,d. To a mixture of aldehyde **8** (0.01 mol, 2.14 g) and the appropriate 3-acetylchromen-2-one derivative **2c,d** in ethanol (5 mL), an aqueous solution of KOH (30%, 4 mL) was added dropwise with stirring at room temperature. The red−coloured reaction mixture was stirred for further 12 h then poured onto crushed ice and acidified with acetic acid. The separated solid products were filtered off, washed well with water, dried and recrystallized from ethanol to give the corresponding chalcones **9a,b**.

(*E*-*s*-*cis*)-3-(3-(Ferrocenyl)acryloyl)-2*H*-chromen-2-one *(E-s-cis)*-9a. Violet crystals from ethanol, yield: 83 % (3.2 g), mp 171 °C. IR (KBr, ν, cm^{-1}): 3091 (C**—**H, aromatic), 3057 (C**—**H, olefinic), 1725 (C=O, chromenone), 1658 (C=O, enone), 1612 (C=C, enone), 1582 (C=C, aromatic). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.22 (s, 5H, ferrocene), 4.52 (s, 2H, ferrocene), 4.65 (s, 2H, ferrocene), 7.35 − 7.42 (m, 3H, aromatic), 7.49 (d, J_{HH} 16.2 Hz, 1H, CH=C***H***−C=O, α−ethylenic proton), 7.66 (t, J_{HH} 7.8 Hz, 1H, aromatic), 7.83 (d, J_{HH} 16.2 Hz, 1H, C***H***=CH−C=O, β−ethylenic proton), 8.55 (s, 1H, aromatic). MS (EI, 70 eV): *m/z* (%) 384 (94). Anal. Calcd. for $C_{22}H_{16}FeO_3$ (384.21): C, 68.77; H, 4.20; Fe, 14.54. Found: C, 69.03; H, 4.14%.

(*E*-*s*-*cis*)-3-(3-(Ferrocenyl)acryloyl)-4-hydroxy-2*H*-chromen-2-one (*E*-*s*-*cis*)-9b. Dark violet crystals from ethanol, yield: 85 % (3.4 g), mp 134 − 136 °C. IR (KBr, ν, cm^{-1}): 3430 (O—H), 3062 (C—H, aromatic), 3030 (C—H, olefinic), 1730 (C=O, chromenone), 1611 (C=O, enone), 1547 (C=C, enone), 1495 (C=C, aromatic). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.23 (s, 5H, ferrocene), 4.50 (s, 2H, ferrocene), 4.61 (s, 2H, ferrocene), 7.37 − 7.39 (m, 3H), 7.78−7.85 (m, 2H), 7.99−8.02 (m, 2H). MS (EI, 70 eV): *m/z* (%) 400 (35). Anal. Calcd. for $C_{22}H_{16}FeO_4$ (400.21): C, 66.03; H, 4.03; Fe, 13.95. Found: C, 66.17; H, 3.98%.

RESULTS AND DISCUSSION

Novel chalcone derivatives **3a−e** (Scheme 1), **7a,b** (Scheme 2) and **9a,b** (Scheme 3) have been now obtained by using Claisen−Schimdt reaction[51] of 2-chloroquinoline-3-carbaldehyde **1**, 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **5** and/or ferrocenecarboxaldehyde **8** with the appropriate acetylated derivatives namely, acetyl ferrocene **(2a**), khellinone **(2b**), 3-acetyl-2H-chromen-2-one **(2c)**, 3-acetyl-4-hydroxy-2H-chromen-2-one **(2d)** visnaginone **(2e)**, and 2−acetylfuran **(6)** (Schemes 1−3). The reaction of compound **1** with compound **2a** (Scheme 1) in ethanol at r.t. in the presence of KOH gave a mixture of two products which were separated by column chromatography.



Scheme 1. The stereochemical behavior of 2-chloroquinoline-3-carbaldehyde 1 towards the acetyl derivatives 2a-e

The first red coloured compound (24%, 0.9 g) was eluted with petroleum ether (60−80 ºC)/acetone (95:5 v/v). The second product (58%, 2.3 g) was eluted with petroleum ether (60 − 80 ºC)/acetone (93:7 v/v) and obtained in the form of brown crystals, with identical mass spectra. Moreover, their microanalytical data were comparable (cf. Experimental). Therefore, the two products could be related to the same chalcone **3a** (Scheme 1). The ^{1}H NMR spectra (DMSO-d_6, δ ppm) of both products did not exhibit the signals due to protons of the aldehydic group and/or the acetyl group which usually appear around δ 9.00 and 2.50 ppm, respectively.[52] Moreover, the two doublets

due to the α- and β-ethylenic protons of the chalcone appeared at δ 7.55 and 7.96 ppm (each with J_{HH} 15.7 ppm) in the ^{1}H NMR spectrum of the first product and at δ 7.21 and 8.19 ppm (each with J_{HH} 16.1 Hz) in the spectrum of the second product. This is a characteristic feature indicating that both compounds exist in the more thermodynamically stable *E*−configuration[53] of the same chalcone (**3a**). No trace for the unfavorable ***Z***-isomer was detected in their ^{1}H NMR spectra. The instability of *Z*−configuration is due to the strong steric interaction between the carbonyl group of the enone system and the ring attached to the ethylenic β-carbon atom.[54] Therefore, the two products formed from the reaction of **1** with **2a** could be attributed to the two possible *E-s-cis* and and *E-s-trans* conformers. Such conformation with respect to the ethylenic bond is due to the free rotation along the single bond between the carbonyl-carbon and the ethylenic α-carbon.[54−58] Chalcones, which have an unsubstituted enone system, the *E-s-cis* conformer is more predominant. The *E-s-trans* conformer is thermodynamically unfavorable due to the steric interaction between the hydrogen atom on the ethylenic β-carbon and that on the *o*−position of the aromatic substituent linked to the carbonyl group. Such steric hindrance between the hydrogen atoms renders the *E-s-trans* conformer to be non-planar whereas the *E-s-cis* conformer seems to be planar. The equilibrium between the two conformers could be shifted by the substitution on the enone system, solvent and/or temperature.[53] In the ^{1}H NMR spectrum of both conformers, the chemical shift of the ethylenic β-proton is more downfield than that of the ethylenic α−proton. This is due to the existence of a positive formal charge on the ethylenic β-carbon due to the delocalization of the *π*-electron density of the enone system. Moreover, the β-proton in the *E-s-cis* conformer is *syn* with respect to the carbonyl group and lies near to its deshielding region. Such effect is absent in the *E-s-trans* conformer where the β-proton lies far from the carbonyl group. Therefore, the chemical shift of the β-ethylenic proton of the *E-s-cis* conformer is expected to be more downfield than that of the *E-s-trans* conformer. The opposite could be applied for the α-ethylenic proton where in the *E-s-cis* conformer it is *anti* with respect to the carbonyl group (lies away from the deshielding effect of the carbonyl group) while in the *E-s-trans* conformer, it lies in vicinity to the carbonyl group. Therefore, the α-ethylenic proton in the *E-s-cis* conformer is expected to be more upfield than that of the *E-s-trans* conformer. Based upon the aforementioned discussion, the second product that separated from the reaction of compound **1** with aldehyde **2a** is assigned as the *E-s-cis*-**3a** conformer while the first one is assigned as the *E-s-trans*-**3a** conformer due to the following reasons:

a) The second isolated product was obtained in a larger yield value (58 %) than the first one (24 %).This is consistent with the greater stability of the *E-s-cis* conformer compared with the *E-s-trans* conformer of the same chalcone.[54−58]

b) In the ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ ppm) of the *E-s-cis*-**3a** conformer, the β-ethylenic proton appeared as a doublet (J_{HH} 16.1 Hz) at δ 8.19 which is more downfield than that of the *E-s-trans*-**3a** conformer which appeared as a doublet (J_{HH} 15.7) at δ 7.96 ppm. The contrary is for the α-ethylenic proton of the *E-s-cis* conformer which appeared more upfield (δ 7.21 ppm, d, J_{HH} 16.1 Hz) than that of the *E-s-trans* conformer (δ 7.55 ppm, d, J_{HH} 15.7 Hz). The ^{1}H NMR spectrum of *E-s-cis*-**3a** conformer showed also signals at 4.26 (s, 5H, ferrocene), 4.65 (s, 2H, ferrocene), 4.95 (s, 2H, ferrocene), 7.62 (t, J_{HH} 6.9 Hz, 1H, aromatic) 7.78 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.91 (d, J_{HH} 7.6 Hz, 1H, aromatic), 8.04 (d, J_{HH} 7.6 Hz, 1H, aromatic) and 8.46 (s, 1H, aromatic). Similarly the ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) of the *E-s-trans*-**3a** conformer showed signals at: 4.24 (s, 5H, ferrocene), 4.98 (s, 2H, ferrocene), 5.03 (s, 2H, ferrocene), 7.39 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.63 (t, J_{HH} 6.9 Hz, 1H, aromatic), 7.77 (d, J_{HH} 7.6 Hz, 1H, aromatic), 7.82 (d, J_{HH} 7.6 Hz, 1H, aromatic) and 8.24 (s, 1H, aromatic).

c) Moreover, the non-planarity of the *E-s-trans* conformer weakens the delocalization of the π−electrons through the enone system in comparison with the *E-s-cis* conformer.[53,55,57,58] This increases the double bond characters of the C=O and C=C groups of the enone system of the *E-s-trans* conformer which results in an increase in their stretching frequencies (ν) in its IR spectrum in comparison with the more planar *E-s-cis* conformer.[59] Thus, the C=O and C=C bonds in the *E-s-trans*-**3a** conformer (the firstly separated product) have been recorded at ν 1651 and 1589 cm^{-1}, respectively, whereas they appeared at 1646 and 1585 cm^{-1}, respectively, in the spectrum of the more planar *E-s-cis*-**3a** conformer (the secondly separated product). Other characteristic bands in the IR spectrum (KBr, ν, cm^{-1}) of *E-s-trans*-**3a** are: 3104 (C—H, aromatic), 3040 (C—H, olefinic), 1485, 1453 (aromatic C=C, C=N), 751 (C—Cl, aromatic). The *E-s-cis*-**3a** conformer also recoded in its IR spectrum strong stretching absorption bands at 3084 (C—H, aromatic), 3032 (C—H, olefinic), 1480, 1446 (aromatic C=C, C=N) and 749 (C—Cl, aromatic). However, previous work has separated compound **3a** as only one conformer in a yield value of 96 % after the reaction of **1** with reagent **2a** under the conditions of ultrasound assisted method.[60]

Similarly, 2-chloroquinoline-3-carbaldehyde **1** reacted with khellinone **2b** (Schemes 1) in ethanol at r.t. in the presence of KOH to give a mixture of two different products which were separated by column chromatography. The first compound was eluted with petroleum ether (b. r. 60 − 80 ºC)/acetone (93:7 v/v) in a 26 % yield and was attributed to the *E-s-trans*-**3b** conformer while the second one was eluted with a relatively more polar solvent

mixture (petroleum ether (b. r. 60 − 80 ºC)/acetone; 85:15 v/v) in a 53 % yield and was attributed to the more stable *E-s-cis*-**3b** conformer.

Both products showed the molecular ion peak at 409 (based on ^{35}Cl) and 411 (based on ^{37}Cl) in their mass spectra which corresponded to a molecular formula of $C_{22}H_{16}ClNO_5$.

In their ^1H NMR spectra, the doublets due to the α- and β-ethylenic protons showed large coupling constants (15.9 Hz and 17.7 Hz for *E-s-cis* and *E-s-trans* conformers, respectively). However, the α- and β-ethylenic protons appeared at δ values of 7.60 and 8.22 ppm, respectively, for the *E-s-cis*-**3b** conformer while in the *E-s-trans*-**3b** analogue, the δ values were shifted downfield for the α−proton and upfield for the β−proton appearing thus at δ 7.79 and 8.17 ppm, respectively. In the IR spectra, the C=O and C=C bonds of the enone system appeared at ν 1619 and 1559 cm^{-1}, respectively, for the planar *E-s-cis*-**3b** conformer while their frequencies were shifted to higher values at 1630 and 1571 cm^{-1}, respectively, in the non-planar *E-s-trans*-**3b** conformer. For additional microanalytical and spectroscopic data that support the structures assigned for the two conformers of **3b**, *cf.* Experimental.

Compound **1** reacted also with the acetyl derivative **2c** to give the corresponding chalcone, namely, 3-(3-(2-chloroquinolin-3-yl)acryloyl)-2H-chromen-2-one **(3c)** in the form of its two possible *E-s-cis*-**3c** and *E-s-trans*-**3c** conformers (Scheme 1) which were separated by column chromatography. The MS spectra of both products recorded the molecular ion peak at m/z 361 (363) ($C_{21}H_{12}ClNO_3$) which is in accordance to the structure of the corresponding chalcone. The second isolated product was assigned to the *E-s-cis*-**3c** (56 %) while the first isolated product was attributed to the *E-s-trans*-**3c** (22 %). This is consistent with the relative more stability of the *E-s-cis* conformer in accordance with previously reported data.

In the IR spectra, the non−planar *E-s-trans*-**3c** conformer (the first isolated product) has recorded higher ν frequencies for the C=O and C=C bonds of the enone system (1651 and 1610 cm^{-1}, respectively) than those of the relatively planar *E-s-cis*-**3c** conformer (the second isolated product) for which the C=O and C=C groups have appeared at 1647 and 1607 cm^{-1}, respectively. Moreover, in the ^1H NMR spectra, the α- and β-ethylenic protons of both conformers appeared as two doublets with a large coupling constant around 16.0 Hz which is consistent with their *E*−configuration. However, the chemical shift of the α−ethylenic proton in the *E-s-trans*-**3c** (the first isolated product) has appeared more downfield (δ 8.09 ppm) than that of the *E-cis*-**3c** conformer (δ 7.78 ppm). This is expected due to presence of the α-ethylenic proton in the *E-s-trans*-**3c** conformer *syn* with respect to the C=O and could be affected by its anisotropy. On the other hand, the β−ethylenic proton in the *E-s-cis*-**3c** is now near to the deshielding region of the enone C=O bond. Therefore, it appeared more downfield (9.03 ppm) than that of the *E-s-trans*-**3c** conformer (8.17 ppm).

Next, the reaction of **1** with compound **2d** in ethanol at r. t. in presence of KOH gave only one product which was favorably assigned the more stable *E-s-cis* structure of the respective chalcone **3d** due to the following reasons:
a) Its microanalysis and molecular ion peak (*m/z* (%) 377 (15) based on ^{35}Cl and 379 (6) based on ^{37}Cl) corresponded to a molecular formula of $C_{21}H_{12}ClNO_4$ (377.78).
b) Its IR spectrum (KBr, cm^{-1}, ν_{max}) showed strong absorption bands at 3412 (O—H), 3100 (C—H, aromatic), 3055 (C—H, olefinic), 1716 (C=O, chromenone), 1610 (C=O, enone), 1531 (C=C, enone), 1492, 1431 (aromatic C=C, C=N) and 756 (C—Cl, aromatic).
c) The ^1H NMR spectrum (500 MHz, DMSO-d_6, δ ppm) lacks any signals due to protons of an aldehyde group and / or acetyl group which usually appear around δ 9.00 and 2.50,[52] respectively. However, it showed two doublets, each with a large coupling constant equals 16.1 Hz, at 8.18 and 8.36 ppm due to the α- and β-ethylenic protons, respectively, of the enone system. The spectrum showed also signals due to the D_2O exchangeable hydroxyl proton at δ 8.16 ppm. The aromatic protons appeared in the region 7.41-8.99 ppm (*cf.* Experimental).

On the other hand, the reaction of compound **1** with the acetyl derivative **2e** gave two products which were separated by column chromatography. The first product was eluted with a mixture of petroleum ether (b. r. 60 – 80 °C) / acetone (v/v 95:5) and was attributed to the *E-s-cis* conformer of the corresponding chalcone, 3-(2-chloroquinolin-3-yl)-1-(6-hydroxy-4-methoxybenzofuran-5-yl)prop-2-en-1-one (**3e**). The microanalytical results and molecular ion peak determination (MS: *m/z*, %): 379 (30) [M^+] based on ^{35}Cl and 381 (10) [M^+] based on ^{37}Cl of *E-s-cis*-**3e** corresponded to a molecular formula of $C_{21}H_{14}ClNO_4$ (379.79).

Its IR spectrum (KBr, ν, cm^{-1}) showed strong absorption bands at 1628 and 1558 due to the C=O and C=C bonds, respectively, of its enone system. The aromatic and olefinic C-H bonds absorbed at 3135 and 3084 cm^{-1}, respectively. The ^1H NMR spectrum (300 MHz, $CDCl_3$, δ ppm) showed two doublets each with a large coupling constant (J_{HH} 15.9 Hz) at 7.94 and 8.21 due to the α- and β-ethylenic protons, respectively. The aromatic and furyl

protons (8H) appeared in the 6.85 — 8.46 ppm region. The spectrum showed also signals at δ 4.18 ppm (OC***H***$_3$) and 12.63 ppm (O***H***) (*cf.* Experimental).

The structure and stereochemistry of **3e** were confirmed through its single crystal X-ray crystallographic analysis. The ORTEP overview (Figure 2) showed that compound **3e** exists in the expected *(E)*-configuration of the C=C bond and the *s−cis* conformation of the enone portion. The crystal structural data, selected bond lengths, bond angels and torsion angels of *E-s-cis*-**3e** are represented in tables 1, 2, 3 and 4, respectively. From tables 2 and 3, all the bond lengths and angels are within the normal ranges found for analogous molecules.[55] For example, the lengths of the C=O and C=C bonds of the enone system are 1.251 Å and 1.325 Å, respectively. The bond angle around the carbonyl carbon, that is, C18—C10—C7 is 123.4º which is very close to the ideal value of 120 º. An examination of the derived torsion angels (Table 4) C7−C10−C18−C19 (173.7º) and C10−C18−C19−C11 (178.8º) confirmed an almost overall planarity of the central enone system. The torsion angles C12−C7−C10−C18 (− 15.3º) and C15−C11−C19−C18 (26.1º) measured the orientation of the benzofuran and the chloroquinoline rings, respectively, with respect to the central enone system where the chloroquinoline ring is more deviated from the plane of the central enone system than the benzofuran ring.

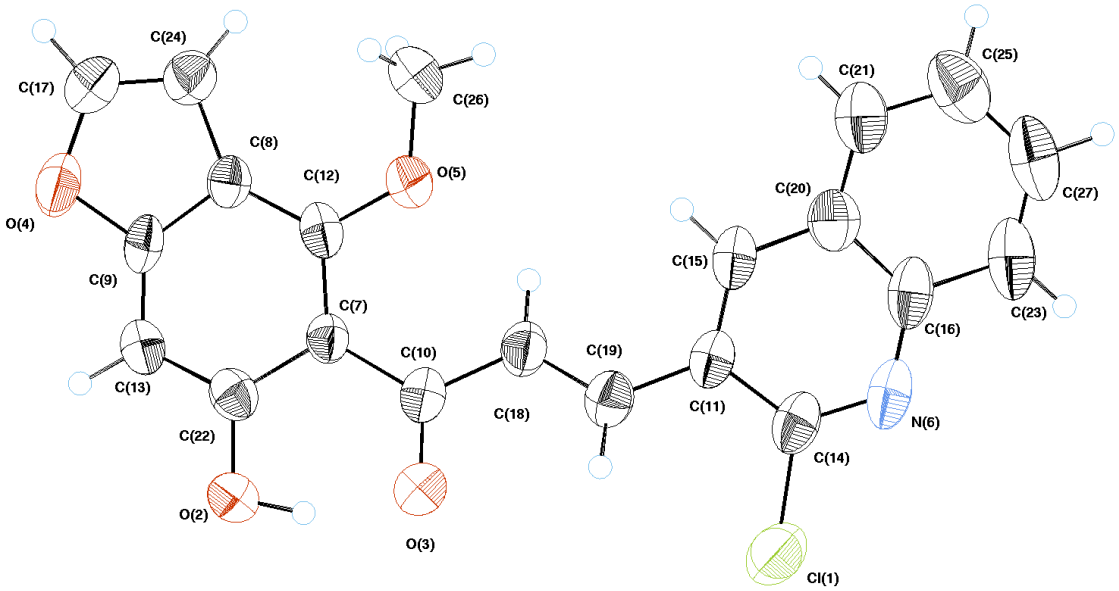


Figure 2. An ORTEP overview of Compound (*E−s-cis*)−3e

Table 1. Crystal Structure and data refinement parameters of compound (E−s-cis)−3e*

Empirical Formula	$C_{21}H_{14}ClNO_4$
Formula Weight	379.799
Crystal System / Space Group	Monoclinic / Cc
a / Å	31.399 (2)
b / Å	4.3317 (3)
c / Å	13.8684 (9)
α / º	90
β / º	114.651 (2)
γ / º	90.00°
V / Å^3	1714.3 (2)
Z	4
D_{calc} (g/cm^3)	1.471
μ (mm^{-1})	0.25
Colour / Shape	Brown / Needles
Theta range for collection / º	0.00 − 30.03
Reflections collected	4749
Independent reflections	4256
Data / restraints / parameters	4256 / 2 / 244
Goodness of fit on F2	0.709
Final R indices [I > 2σ (I)]	0.0499
R indices (all data)	0.1331
Largest difference peak / hole	0.184 / -0.185

** Temperature: 298 K, Wavelength: Mo Ka (0.71073 Å).*

Table 2. Selected bond lengths (Å) of compound (*E*−*s*-*cis*)−3e

Cl1— C14	1.747 (4)	C9—C13	1.360 (5)
O2—C22	1.358 (4)	C10—C18	1.466 (5)
O3—C10	1.251 (4)	C11—C15	1.366 (5)
O4—C9	1.376 (4)	C11—C14	1.417 (5)
O4—C17	1.390 (5)	C11—C19	1.459 (5)
O5—C12	1.349 (4)	C13—C22	1.365 (5)
O5—C26	1.407 (5)	C15—C20	1.407 (5)
N6—C14	1.297 (5)	C16—C23	1.419 (6)
N6—C16	1.360 (5)	C16—C20	1.424 (5)
C7—C12	1.424 (4)	C17—C24	1.310 (6)
C7—C22	1.449 (5)	C18—C19	1.325 (5)
C7—C10	1.466 (5)	C20—C21	1.403 (6)
C8—C12	1.386 (5)	C21—C25	1.360 (6)
C8—C9	1.404 (5)	C23—C27	1.365 (7)
C8—C24	1.465 (5)	C25—C27	1.402 (8)

Table 3. Selected bond angels (º) of compound (*E*−*s*-*cis*)−3e

C9—O4—C17	105.4 (3)	C11—C15—C20	122.4 (3)
C12—O5—C26	122.0 (3)	N6—C16—C23	119.3 (4)
C14—N6—C16	118.0 (3)	N6—C16—C20	121.7 (3)
C12—C7—C22	117.3 (3)	C23—C16—C20	119.0 (4)
C12—C7—C10	123.8 (3)	C24—C17—O4	113.1 (3)
C22—C7—C10	118.9 (3)	C19—C18—C10	122.5 (3)
C12—C8—C9	117.0 (3)	C18—C19—C11	125.8 (3)
C18—C10—C7	123.4 (3)	C15—C20—C21	124.8 (4)
C15—C11—C14	114.9 (3)	C15—C20—C16	116.5 (4)
C15—C11—C19	122.8 (3)	C21—C20—C16	118.7 (4)
C14—C11—C19	122.3 (3)	C25—C21—C20	121.3 (4)
O5—C12—C8	124.1 (3)	O2—C22—C13	117.2 (3)
O5—C12—C7	115.2 (3)	O2—C22—C7	120.4 (3)
C8—C12—C7	120.6 (3)	C13—C22—C7	122.4 (3)
C9—C13—C22	116.5 (3)	C27—C23—C16	119.8 (5)
N6—C14—C11	126.4 (4)	C17—C24—C8	106.6 (3)
N6—C14—Cl1	115.0 (3)	C21—C25—C27	119.9 (5)
C11—C14—Cl1	118.6 (3)	C23—C27—C25	121.2 (4)

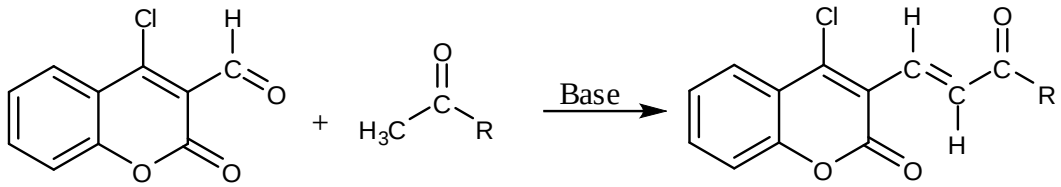
Table 4. Selected torsion angels (º) of compound (*E*−*s*-*cis*)−3e

C17−O4−C9−C8	1.4 (4)	C24−C8−C9−C13	− 177.9 (4)
C17−O4−C9−C13	178.6 (4)	C9−C8−C12−O5	− 177.4 (3)
C9−O4−C17−C24	− 1.5 (5)	C9−C8−C12−C7	− 0.1 (5)
C26−O5−C12−C7	179.7 (3)	C24−C8−C12−O5	2.6 (7)
C26−O5−C12−C8	− 2.9 (5)	C24−C8−C12−C7	179.8 (4)
C16−N6−C14−C11	1.2 (6)	C9−C8−C24−C17	− 0.2 (4)
C14−N6−C16−C20	1.1 (6)	C12−C8−C24−C17	179.9 (4)
C14−N6−C16−C23	− 179.5 (4)	O4−C9−C13−C22	− 177.5 (3)
C12−C7−C10−O3	169.2 (3)	C8−C9−C13−C22	− 0.8 (6)
C12−C7−C10−C18	− 15.3 (5)	O3−C10−C18−C19	− 10.7 (6)
C22−C7−C10−O3	− 11.7 (5)	C7−C10−C18−C19	173.7 (4)
C22−C7−C10−C18	163.9 (3)	C15−C11−C14−Cl1	179.8 (3)
C10−C7−C12−O5	− 6.0 (5)	C15−C11−C14−N6	− 1.2 (6)
C10−C7−C12−C8	176.5 (3)	C19−C11−C14−Cl1	− 1.4 (5)
C22−C7−C12−O5	174.8 (3)	C19−C11−C14−N6	177.6 (4)
C22−C7−C12−C8	−2.7 (5)	C19−C11−C15−C20	− 179.9 (4)
C10−C7−C22−O2	3.8 (5)	C14−C11−C19−C18	− 152.6 (4)
C10−C7−C22−C13	− 175.2 (3)	C15−C11−C19−C18	26.1 (6)
C12−C7−C22−O2	− 176.9 (3)	C9−C13−C22−O2	178.6 (3)
C12−C7−C22−C13	4.1 (5)	C9−C13−C22−C7	− 2.4 (5)
C12−C8−C9−O4	179.2 (3)	C11−C15−C20−C16	3.1 (6)
C12−C8−C9−C13	2.0 (6)	C11−C15−C20−C21	− 178.3 (4)
C24−C8−C9−O4	− 0.8 (4)	C10−C18−C19−C11	178.8 (4)

Moreover, the second product was eluted with petroleum ether (60 − 80 ºC)/acetone (88:12 v/v) and obtained in the form of pale yellow crystals. It is attributed to the cyclic flavanone structure, 7-(2-chloroquinolin-3-yl)-4-methoxy-6,7-dihydro-5H-furo[3,2-g]chromen-5-one **(4)**. The microanalytical results and molecular ion peak determination (MS: *m/z*, %): 379 (32) [M^+] (based on ^{35}Cl) and 381 (10) [M^+] (based on ^{37}Cl) of **4** corresponded to a molecular formula of $C_{21}H_{14}ClNO_4$ (379.79). The IR spectrum (KBr, ν, cm^{-1}) lacks any absorption bands due to (O—H)

group. However, it showed bands at 3067 (C—H, aromatic), 2927 (C—H, aliphatic), 1625 (C=O, conjugated), 1591, 1483, 1433 (aromatic C=C, C=N) and 748 (C—Cl, aromatic). The ^{1}H NMR spectrum of **4** is devoid of signals due to protons of the −CHO and the acetyl−CH_3 groups which usually appear around δ 9.00 and 2.50 ppm, respectively. The spectrum lacked also the presence of the two doublets which are characteristic for the *α*- and *β*-ethylenic protons of the corresponding chalcone. Instead, the spectrum showed a doublet of doublet (*J* 15.0, 6.8 Hz,) at 3.26 ppm due to the cyclic methylene protons (2H) and a triplet (*J* 6.8 Hz) at 3.92 ppm due to O−C***H***−CH_2 proton (1H). The ^{1}H NMR spectrum of **4** showed also signals at 4.13 (s, OC***H***$_3$), 6.76 (d, J_{HH} 2.4 Hz, 1H, furan), 6.87 (s, 1H, aromatic), 7.44 (d, J_{HH} 2.4 Hz, 1H, , furan), 7.61 (t, J_{HH} 6.5 Hz, 1H, aromatic), 7.68 (t, J_{HH} 6.5 Hz, 1H, aromatic), 7.87 (d, J_{HH} 6.5 Hz, 1H, aromatic), 8.10 (d, J_{HH} 6.5 Hz, 1H, aromatic), 8.52 (s, 1H, aromatic). The ^{13}C NMR spectrum of **4** exhibited 3 signals in the region of the saturated carbon atoms at 52.37, 60.56 and 65.67 and could be attributed to the carbon atoms of (***C***H_2), (***C***H_3O), (***C***H−O) groups, respectively. Moreover, the spectrum showed only eighteen signals due to unsaturated carbon atoms including the carbonyl group which appeared at 202.63 ppm. Apparently, compound **4** has been formed through the intramolecular heterocyclization of the *E-s-trans*- **3e** conformer. Such cyclization would create a ring with an asymmetric centre. Therefore, compound **4** was found to be optically active where it recorded an $[\alpha]_{D/25}$ value of + 20.

Condensation of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **(5)** with compound **2a** and acetyl furan **(6)** in ethanol in the presence of KOH gave the respective chalcones **7a,b** where only one product was isolated from each reaction (Scheme 2).



5 **2a,** R = 2-ferrocenyl **6,** R = 2-furyl ***E-s-cis*-7a,** R=2-ferrocenyl **b,** R=2-furyl

Scheme 2. Condensation of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde (5) with compounds 2c and 6

The α- and β-ethylenic protons were found to possess the *E* stereo−structure where they appeared in the ^{1}H NMR spectrum of compounds **7a** and **7b** as two doublets with large coupling constants which are 17.5 and 15.0 Hz, respectively. The more stable *s-cis* conformation [54,55,57,58] was assigned to the enone system of compounds **7a** and **7b**.

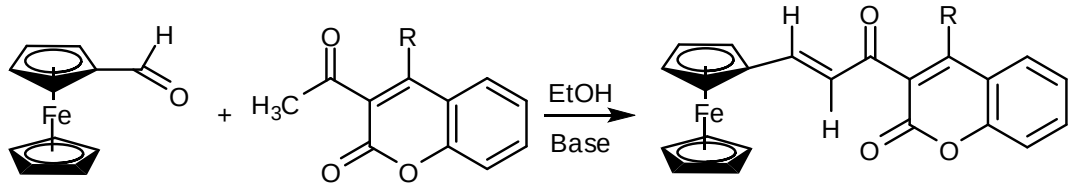
Additional spectral data which support the assigned structure of (*E-s-cis*)-4-chloro-3-(3-(ferrocenyl)−3-oxoprop-1-enyl)-2H-chromen-2-one (*E-s-cis*)-**7a**, as an example, are:

a) Its MS spectrum (m/z (%)) recorded the molecular ion peak at *m/z* 418 (23) (based on ^{35}Cl) and 420 (8) (based on ^{37}Cl) which corresponded to a molecular formula of $C_{22}H_{15}ClFeO_3$ (418.65).

b) The IR spectrum of **7a** showed strong bands at 3025 (C—H, olefinic), 1698 (C=O, chromenone), 1660 (C=O, enone), 1610 (C=C, enone)

c) The α- and β-ethylenic protons appeared as two doublets (each with *J* 17.5 Hz) at 7.48 and 7.91 ppm, respectively, in the ^{1}H NMR spectrum (500 MHz, DMSO-d_6 δ ppm) of compound **7a**. The spectrum showed also three singlets at 4.11 (5H), 4.20 (2H), 4.74 (2H) ppm due to the ferrocene ring protons. The four aromatic protons appeared at δ 7.45 (d, J_{HH} 8.4 Hz), 7.50 (t, *J* 7.6 Hz), 7.71 (t, *J* 8.4 Hz) and 8.34 (d, *J* 7.6 Hz). The spectrum revealed the absence of absorption due to an aldehydic proton and/or acetyl group protons.

The acetyl derivatives **2c,d** were also condensed with ferrocenecarboxaldehyde (**8**) in ethanol in presence of KOH to give the corresponding chalcones **9a,b,** based upon compatible elemental microanalyses and spectroscopic measurements. Only one product has been isolated from each reaction and it was favorably attributed to the more stable *E-s-cis* conformer (Scheme 3).



8 **2c**, R = H; **d**, R = OH **9a**, R = H; **b**, R = OH

Scheme 3. Condensation of ferrocenecarboxaldehyde (8) with compounds 2c,d

The molecular ion peak in the mass spectrum of **(***E-s-cis*)-3-(3-(ferrocenyl)acryloyl)-2H-chromen-2-one *(E-s-cis*)-**9a,** taken as a representative example, was recorded at m/z 384 (94) which corresponded to a molecular formula of $C_{22}H_{16}FeO_3$ (384.21). However, the ^{1}H NMR spectrum of **9a** exhibited two doublets (each with *J* 16.2 Hz) at 7.49 and 7.83 ppm and were attributed to the α− and β−ethylenic protons, respectively, of the central enone system. The characteristic signals of ferrocene protons appeared as three singlets at 4.22 (5H), 4.52 (2H) and 4.65 (2H). The aromatic protons appeared at δ 7.35− 7.42 (m, 3H), 7.66 (t, 1H) and 8.55 (s, 1H). In the IR spectrum (KBr, ν, cm^{-1}) of **9a**, the carbonyl groups due to the chromenone ring and enone system appeared at 1725 and 1658 cm^{-1}, respectively. The spectrum showed also bands at 3091 (C—H, aromatic), 3057 (C—H, olefinic) and 1612 (C=C, enone).

Biological Evaluation

Materials and methods. Fetal bovine serum (FBS) and L-glutamine, were obtained from Gibco Invitrogen Company (Scotland, UK). Dulbecco's modified Eagle's (DMEM) medium was provided from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and Sulfo-Rhodamine-B stain (SRB) (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) were obtained from Sigma Chemical Company (St. Louis, MO, USA). All other chemicals and reagents used in this study were of analytical grade and purchased from Sigma-Aldrich chemical Co. (St. Louis, MO, USA).

Selected new compounds were screened against four human tumor cell lines, namely, liver HepG2, breast MCF-7, lung A549 and colon HCT116 cell lines, obtained from the American Type Culture Collection (Rockville, MD, USA). The tumor cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat inactivated fetal calf serum (GIBCO), penicillin (100 U/ml) and streptomycin (100 µg/ml) at 37 ºC in humidified atmosphere containing 5% CO_2. Cells at a concentration of 0.50 x 10^6 were grown in a 25 cm^3 flask in 5 ml of complete culture medium.

***In Vitro* cytotoxicity assay**

The antiproliferative activity was measured *in vitro* using the Sulfo-Rhodamine-B stain (SRB) assay according to the reported standard procedure.[61] Cells were inoculated in 96-well microtiter plate (10^4 cells/ well) for 24 h before treatment with the tested compounds to allow attachment of cell to the wall of the plate. Test compounds were dissolved in DMSO at 1 mg/ml immediately before use and diluted to the appropriate volume just before addition to the cell culture. Different concentrations of tested compounds (0 - 100 µg/ml) and doxorubicin were added to the cells. Six wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h. at 37°C and in atmosphere of 5% CO_2. After 48 h cells were fixed, washed, and stained for 30 min. with 0.4% (w/v) SRB dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and attached stain was recovered with Tris-EDTA buffer. Colour intensity was measured in an ELISA reader at 540 nm wavelength. The relation between surviving fraction and drug concentration is plotted to get the survival curve for each cell line after the specified time. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and the results are represented in figure 3 compared with the antiproliferative effects of the reference control doxorubicin.[62] The antiproliferative activities were expressed by median growth inhibitory concentration (IC_{50}). The antiproliferative activity of the synthetic compounds was evaluated against human liver HepG2, breast MCF-7, lung A549 and colon HCT116 cancer cell lines using SRB assay, in comparison with doxorubicin (DOX) as a reference drug. The tumor cell lines showed normal growth in the culture system and DMSO did not seem to have any noticeable effect on cellular growth. A gradual decrease in viability of cancer cells was observed with increasing concentration of the tested compounds, in a dose-dependent inhibitory effect. The results are reported as Mean ± Standard Error (S.E.) for at least six times experiments.

Results of the antiproliferative activity of the examined compounds

For liver HepG2 cancer cells, *E-s-trans*-**3a** and **9b** were found to be the most potent of the examined compounds where they recorded IC_{50} values of 4.10±0.40 and 4.62±0.50 , respectively, which are very close to that of the

standard drug, doxorubicin (4.20±0.46). Compounds *E*-*s*-*cis*-**3a** and *E*-*s*-*cis*-**3d** showed also comparable marked activities where they recorded IC_{50} values of 6.86±0.78 and 7.50±0.80, respectively. Chalcone **7b** was found to be the least active among the examined compounds where it recorded an IC_{50} value of 38.20±4.60 (Figure **3**).

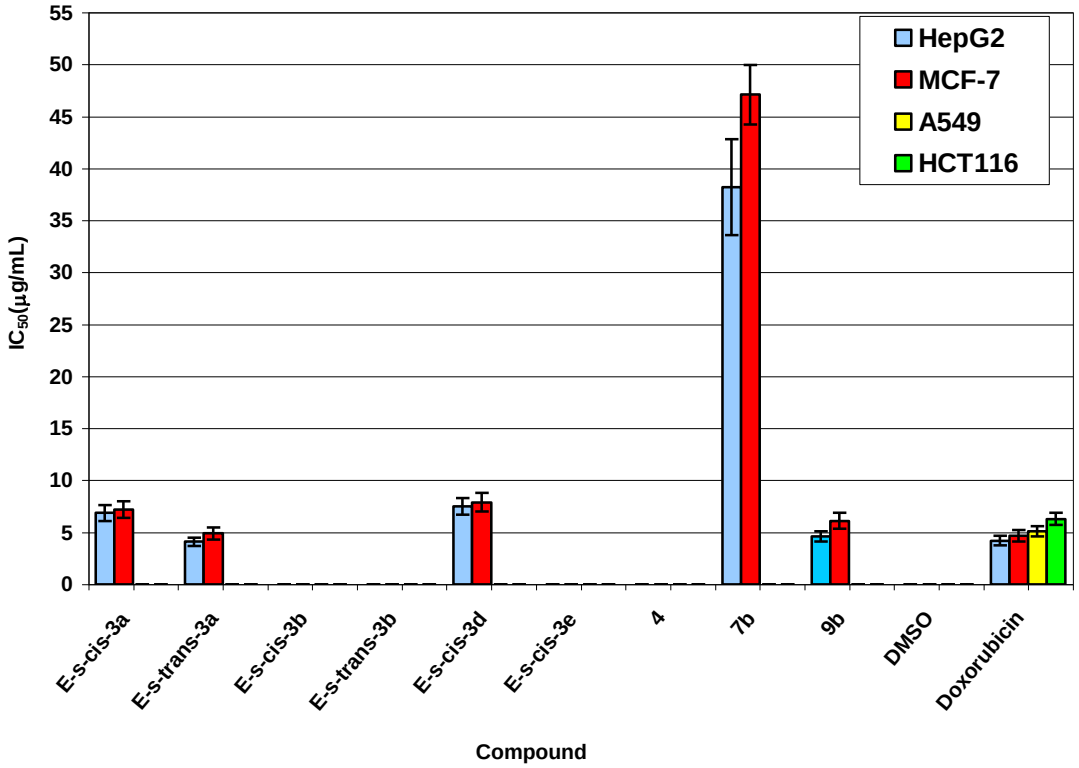


Figure 3. The *in vitro* cytotoxicity activity of the tested compounds expressed as IC_{50} values against HepG2, MCF-7, A549 and HCT−116 human cancer cell lines

Evaluation of the anticancer effect of the tested compounds against human breast MCF-7 cancer cells revealed that compound *E*-*s*-*trans*-**3a** showed an activity (IC_{50}: 4.90±0.60) that is very close to that of doxorubicin (IC_{50}: 4.7±0.55). Compounds *E*-*s*-*cis*-**3a,** *E*-*s*-*cis*-**3d** and **9b** showed also marked activities where they recorded IC_{50} values of 7.20±0.82, 7.90±0.90 and 6.10±0.75, respectively. From figure 3, the cytotoxic activities of the tested compounds against HepG2 cancer cells decreases in the order: *E*-*s*-*trans*-**3a** > DOX > **9b** > *E*-*s*-*cis*-**3a** > *E*-*s*-*cis*-**3d** > **7b** while they decrease in the order: DOX > *E*-*s*-*trans*-**3a** > **9b** > *E*-*s*-*cis*-**3a** > *E*-*s*-*cis*-**3d** > **7b** against the human breast MCF-7 cancer cells (Figure **3**) . The marked activity of compounds *E*-*s*-*cis*-**3a,** *E*-*s*-*trans*-**3a,** *E*-*s*-*cis*-**3d** and **9b** may be attributed to the presence of the ferrocene and/or 4-hydroxycoumarin groups which are well known for their biological activities.[39,40,47]

From the results (Figure **3**), it is also observed that, the *E*-*s*-*trans* conformer of chalcone **3a** is more active than that its *E*-*s*-*cis* analogue against the liver (HepG2) and human breast (MCF−7) cancer cell lines. Such disparity in activity between the two conformers is in the line with the relation between the stereochemistry of a given compound and its activity.[63-65] Recent studies have revealed the role such conformational changes can affect the biological activity of chalcones.[63,66] On the other hand, compounds *E*-*s*-*cis*-**3b**, *E*-*s*-*trans*-**3b,** *E*-*s*-*cis*-**3e** and **4** were found to be inactive against HepG2 and MCF-7 cells. Moreover, the results indicated that all the tested compounds did not exert any activity against human colon HCT116 and lung A549 cancer cells.

CONCLUSION

The present work fastens simple approaches for the synthesis of novel chalcones which contain bioactive nuclei like ferrocene, quinoline, furan or coumarin in their molecular structures. Conformers of the synthesized chalcones have been successfully separated by column chromatography and their stereochemical structures were fully characterized by making use of the spectral and X−ray crystallographic measurements. Some of the new products were found to exert antiproliferative effect against liver HepG2 and breast MCF-7 cancer cell lines . The biological screening also showed that the HepG2 cells were more sensitive to the tested compounds than the MCF-7 cells.

Structure−activity relationship (SAR) indicated the strong relevance of antitumor activity to the stereochemistry of conformers of the tested chalcone.

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