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Synthesis, docking and *in vitro* anticancer evaluation of some new benzopyrone derivatives

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ABSTRACT

The synthesis of some new 3-alkyl-7-hydroxy-4-methyl-8-substituted-1*H*-benzopyran-2-ones, 6-alkyl-7-methyl-2-substituted amino-5*H*-pyrano[6,5-e] benzoxazol-5-ones, 7-alkyl-8-methyl-3-substituted-2,6-dihydropyrano[6,5-f]-1,4-benzoxazin-6-ones, 7,8-disubstituted-3-ethyl-4-methyl-1*H*-benzopyran-2-ones and 3-alkyl-4-methyl-7-substituted-1*H*-benzopyran-2-ones were described. Fourteen compounds were selected by National Cancer Institute (NCI), Bethesda, and evaluated for their *in vitro* anticancer activity in the full NCI 60 cell lines panel assay by a single dose test. Compounds **4a**, **18a**, **18b** and **23a** were found to be broad-spectrum antitumors showing effectiveness toward numerous cell lines that belong to different tumor subpanels. Furthermore, docking studies were undertaken to gain insight into the possible binding mode of these compounds with the binding site of the casein kinase II (CK2) enzyme which is involved in cell survival and proliferation through a number of downstream effectors.
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1. Introduction

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008 and deaths from cancer worldwide are projected to continue to rise to over 13.1 million in 2030 [1]. Cancer cells develop a degree of autonomy and grow uncontrollably disregarding the normal rules of cell division, resulting in uncontrolled growth and proliferation. In fact, almost 90% of cancer- related deaths are due to tumor spreading or dissemination [2]. Several techniques involving surgery, radiation, immunotherapy and chemotherapy were adopted for eradication of cancerous cells. Unfortunately, no currently available anticancer drugs would eradicate cancer cells without harming normal tissues [3]. Accordingly, continued research is needed to develop new and efficient antitumor agents.

Benzopyran-2-one comprises a group of natural compounds found in a variety of plant sources. Benzopyran-2-ones are recognized to possess a wide variety of biological activities against bacteria [4,5], fungi [6] and protozoa [7]. In addition, they are also reported to possess anti-inflammatory [8], antioxidant [6,9], antiallergic [10], antithrombotic [11], antiHIV [12], antidepressant [13–15], photosensitizing [16,17], estrogenic like [18] and anticancer activities [19–22]. Warfarin **A** (Fig. 1) reduced metastases from intestinal carcinomas to a great extent [23] and also used as an adjunct to the surgical treatment of malignant tumors [24].

The inhibition activity of benzopyran-2-one derivative **B** (Fig. 1) against different cancer cell lines showed a high selectivity for HUVEC that can be potentially utilized as lead compound to develop non toxic angiogenesis inhibitors and small molecular ligands to target HUVEC [25].

In addition, daphnetin **C** (Fig. 1) was proven to act as tyrosine kinase inhibitor. Daphnetin inhibited tyrosine kinase, epidermal growth factor receptor, serine/threonine- specific protein kinase, and protein kinase C *in vitro* [26]. Also, benzopyran-2-one derivative **D** (Fig. 1) was identified as a novel class of MEK 1 kinase inhibitors [27].

Furthermore, some heterocycles such as oxathiazolidine [28], triazole [29], oxazole [30] and thiadiazole [31] were found to possess potential antitumor activity.

These findings have encouraged us to prepare compounds containing the benzopyran-2-one nucleus substituted at 7-position with different bioisosteric moieties as triazole, thiadiazole, thiazolidinone, thiazole, hydrazone, oxathiazolidine, dihydropyrazole, dihydropyrrole and dioxopyrrolidine. Also, 8-substituted derivatives as chalcones, dihydropyridines, ureas and imidazolidinetriones in addition to oxazolo and oxazinobenzopyran-2-one derivatives were prepared. Fourteen compounds of the synthesized compounds were selected by National Cancer Institute (NCI),

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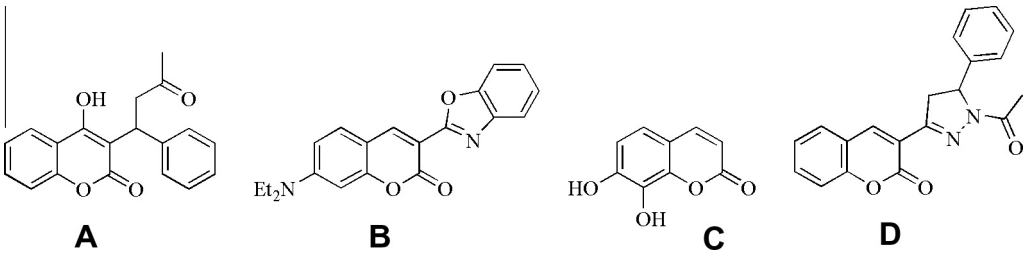

Fig. 1. Anticancer, anti-angiogenic and kinase inhibitors benzopyrone derivatives.

Bethesda, MD, U.S.A., for *in vitro* one dose testing in the full NCI 60 cell lines panel assay. In addition, attempt to elucidate a molecular target for activity was achieved via molecular docking of the prepared compounds in the active site of casein kinase II enzyme (CK2) using Molsoft ICM 3.4–8C program.

2. Experimental

2.1. Chemistry

Melting points were determined by open capillary tube method using Stuart SMP10 melting point apparatus and were uncorrected. Microanalysis was carried out at The Regional Center for Mycology and Biotechnology, Al-Azhar University. Infrared Spectra were recorded as potassium bromide discs on Schimadzu FT-IR 8400S spectrophotometer (Shimadzu, Kyoto, Japan) and Bruker FT-IR spectrophotometer and expressed in wave number υ_{max} (cm^{-1}). The ^1H NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer at 300 MHz and *JEOL-ECA500 NMR spectrometer at 500 MHz in chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6). Chemical Shifts are quoted in δ as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard and J values are reported in Hz. Mass spectra were performed as EI at 70 eV on Hewlett Packard Varian (Varian, Polo, USA) and Shimadzu Gas Chromatograph Mass spectrometer-QP 1000 EX and direct inlet unit of Shimadzu GC/MS-QP5050A. TLC were carried out using Macherey–Nagel Alugram Sil G/UV_{254} silica gel plates with fluorescent indicator UV_{254} and acetonitrile:methanol (9:1) as the eluting system and the spots were visualized at 366, 254 nm by UV Vilber Lourmat 77202 (Vilber, Marne La Vallee, France).

2.1.1. 3,4-Dimethyl-7-hydroxy-2H-1-benzopyran-2-one and 3-ethyl-7-hydroxy-4-methyl-2H-1-benzopyran-2-one ***1a,b***

were prepared as reported in literature [32].

2.1.2. General procedure for synthesis of 3-alkyl-7-hydroxy-4-methyl-8-phenylazo-2H-1-benzopyran-2-ones ***2a,b*** *(Scheme 1)*

Phenyl diazonium chloride {freshly prepared by addition of sodium nitrite solution (4 g, 0.06 mol) in water (20 ml) to a mixture of aniline (3.81 g, 0.041 mol) and hydrochloric acid (16 ml) dropwise while cooling in an ice bath 0–5 °C} was added slowly to a cooled solution of compound **1a,b** (0.041 mol) in 5% sodium hydroxide solution (45 ml). The reaction mixture was stirred for 1 h, filtered, washed and dried.

2.1.2.1. 3,4-Dimethyl-7-hydroxy-8-phenylazo-2H-1-benzopyran-2-one ***2a***. The crude product was crystallized from methanol. Yield 50%. mp 140–141 °C. IR υ_{max}/cm^{-1}: 3192 (OH), 2924, 2850 (CH aliphatic), 1670 (C=O), 1620, 1612, 1566, 1510 (N=N, C=C). ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 2.10 (s, 3H, CH_3 at C4), 2.38 (s, 3H, CH_3 at C3), 6.97 (d, 1H, J = 9.3 Hz, H-6 Ar), 7.60–7.67 (m, 3H, H-3′,4′,5′Ar), 7.82 (d, 1H, J = 9.3 Hz, H-5 Ar), 7.98 (d, 2H, J = 8.4 Hz, H-2′,6′ Ar), 13.37 (s, 1H, OH). MS m/z (%): 296, $M^+ + 2$ (16.49%). Anal. Calcd. for $C_{17}H_{14}N_2O_3$ (294.30): C, 69.38; H, 4.79; N 9.52. Found: C, 69.44; H, 4.82; N, 9.60.

2.1.2.2. 3-Ethyl-7-hydroxy-4-methyl-8-phenylazo-2H-1-benzopyran-2-one ***2b***. The crude product was crystallized from methanol. Yield 66%. mp 130–133 °C. IR υ_{max}/cm^{-1}: 3460 (OH), 3047 (CH Ar), 2968, 2910 (CH aliphatic), 1708 (C=O), 1629, 1593, 1550 (N=N, C=C). ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 1.07 (t, 3H, $CH_2C\underline{H_3}$), 2.42 (s, 3H, CH_3), 2.59 (q, 2H, $C\underline{H_2}CH_3$), 6.99 (d, 1H, J = 9.0 Hz, H-6 Ar), 7.57–7.67 (m, 3H, H-3′,4′,5′ Ar), 7.83 (d, 1H, J = 9.3 Hz, H-5 Ar), 7.98 (d, 2H, J = 7.8 Hz, H-2′,6′ Ar), 13.37 (s, 1H, OH). MS m/z (%): 308, M^+ (0.71%). Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.33): C, 70.12; H, 5.23; N, 9.09. Found: C, 70.14; H, 5.27; N, 9.14.

2.1.3. General procedure for synthesis of 3-alkyl-8-amino-7-hydroxy-4-methyl-2H-1-benzopyran-2-ones ***3a,b*** *(Scheme 1)*

A solution of sodium dithionite (7 g, 0.04 mol) in water (30 ml) was quickly added to a solution of the azo compound **2a,b** (0.01 mol) in 30% ammonium hydroxide solution (20 ml) and the reaction mixture was refluxed for 15 min. After cooling, the crude product was filtered off, washed and dried.

2.1.3.1. 8-Amino-3,4-dimethyl-7-hydroxy-2H-1-benzopyran-2-one ***3a***. The crude product was crystallized from isopropanol. Yield 69%. mp 228–230 °C. IR υ_{max}/cm^{-1}: 3444, 3365 (NH_2), 3199 (OH), 2927, 2856 (CH aliphatic), 1680 (C=O), 1616, 1568, 1510 (NH, C=C). ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 2.05 (s, 3H, CH_3 at C4), 2.30 (s, 3H, CH_3 at C3), 6.67 (s, 2H, NH_2), 6.89 (d, 1H, J = 8.7 Hz, H-6 Ar), 7.59 (d, 1H, J = 8.7 Hz, H-5 Ar), 10.31 (s, 1H, OH). MS m/z (%): 205, M^+ (0.54%). Anal. Calcd. for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.37; H, 5.39; N, 6.91.

2.1.3.2. 8-Amino-3-ethyl-7-hydroxy-4-methyl-2H-1-benzopyran-2-one ***3b***. The crude product was crystallized from isopropanol. Yield 58%. mp 176–178 °C. IR υ_{max}/cm^{-1}: 3325, 3296 (NH_2, OH), 3074 (CH Ar), 2970, 2872 (CH aliphatic), 1708 (C=O), 1620, 1610, 1602, 1566, 1510 (NH, C=C). ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 1.02 (t, 3H, $CH_2C\underline{H_3}$), 2.34 (s, 3H, CH_3), 2.55 (q, 2H, $C\underline{H_2}CH_3$), 3.80 (br s, 2H, NH_2), 6.78 (d, 1H, J = 8.7 Hz, H-6 Ar), 7.59 (d, 1H, J = 9.0 Hz, H-5 Ar), 9.98 (s, 1H, OH). MS m/z (%): 219, M^+ (0.06%). Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.78; H, 6.02; N, 6.46.

2.1.4. General procedure for synthesis of 1-(3-alkyl-4-methyl-7-hydroxy-2-oxo-2H-1-benzopyran-8-yl)-3-(4-(un)substituted phenyl) ureas ***4a–c*** *(Scheme 1)*

A mixture of the amino compound **3a,b** (0.01 mol), the appropriate isocyanate (0.01 mol) in dichloromethane (5 ml) was refluxed with stirring for 6 h. The obtained solid product was filtered off, washed with ether and dried.

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