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ORIGINAL ARTICLE

Synthesis and *in vitro* biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents

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Abstract Synthesis and characterization of new heterocyclic pyrazole chalcones (**4a–e**) and diamide (**6a–e**) derivatives are described. Pyrazole chalcones were synthesized by the reaction of pyrazole aldehydes and suitable aromatic ketones. Diamides were synthesized by the reaction of phthalic acid and amines. Newly synthesized compounds were characterized by spectral studies and their biological activity was assessed *in vitro* using MCF-7 (human breast adenocarcinoma) and HeLa (human cervical tumor cells) cell lines. Few of the synthesized molecules inhibited the growth of the human breast cancer cell lines and human cervical tumor cell lines at low micromolar to nanomolar concentrations.

1. Introduction

Cancer, a diverse group of diseases characterized by uncontrolled growth of abnormal cells, is a major worldwide health problem. It is a fatal disease standing next to the cardiovascular diseases in terms of morbidity and mortality. Although the cancer research has led to a number of new and effective solutions, the medicines used as treatments have clear limitations and unfortunately cancer is projected as the primary cause of death in the future (Gibbs, 2000; Varmus, 2006). Currently there is a huge scientific and commercial interest in the discovery of potent, safe and selective anticancer drugs. Among the currently identified antitumor agents, chalcones represent an important class of molecules that are abundant in edible plants (Modzelewska et al., 2006). Chalcones comprise a class of compounds with important therapeutic potential. The ease of preparation, the potential of oral administration, (Wattenberg

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et al., 1994; Wattenberg, 1995; Baba et al., 2002) and safety (Phillpotts et al., 1984) also support the feasibility of chalcone-based compounds as therapeutic agents. Chalcone and its functionalized derivatives display diverse medicinal properties including anti-inflammatory (Hsie et al., 1998), immunomodulatory (Barfod et al., 2002), anticancer (Kumar et al., 2003), anti-HIV (Artico et al., 1998), antiproliferative (Liu and Go, 2007), and a-glucosidase inhibitory activities (Seo et al., 2005).

A new class of anthranilic diamides has been found to exhibit their action by binding to ryanodine receptors and activating the uncontrolled release of calcium stores (Lahm et al., 2004; Caspar et al., 2004)). Also many of the heterocyclic diamides act as CFTR (Cystic fibrosis transmembrane conductance regulator) modulators (Hirth et al., 2005). Several research groups have been interested in designing various groups of dimeric agents of diverse chemical structure and biological properties, such as echinomycin antibiotics (Tseng et al., 2005; Wakelin and Waring, 1976; Low et al., 1984), 7-H pyridocarbazole derivatives (Pelaprat et al.,1980; Peek et al., 1995), bisanthracyclines (Wakelin, 1986; Chaires et al., 1997), bisnaphthalimides (Bousquet et al., 1995), bisacridines (Kirshenbaum et al., 1994; Moloney et al., 2001), and bisimidazoacridones (Gamage et al., 1999; Kosakowska-Cholody et al., 2005). Many of these turned out to be potent anticancer drugs such as Elinafide (LU79553), bisnaphthalimide that progressed to clinical trials against solid tumors (Hariprakasha et al., 2007).

These findings have motivated us to synthesize biologically active heterocycles, particularly for anticancer class. In our search for new therapeutic agents (Vijesh et al., 2010, 2011; Sunil et al., 2010; Isloor et al., 2012), we have synthesized chalcones, dimeric phthalimide derivatives and performed a first evaluation of their anticancer property. Few molecules have shown significant activity as compared to standard.

2. Experimental

2.1. Materials and methods

Melting points were recorded (uncorrected) on a Buchi Melting Point B-545 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400-MHz and Bruker spectrometers, respectively. IR spectra (in KBr pellets) were recorded on a Thermo Nicolet avatar 330-FT-IR spectrophotometer. Elemental analyses were performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. The reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel. 60 F254, 0.25 mm) and was visualized by fluorescence quenching under UV light (254 nm). All the compounds (**4a**–**e**) and (**6a**–**e**) were synthesized in-house from the corresponding commercially available acetophenones, amines and acids.

2.2. General procedure for synthesis of chalcone derivatives *4(a–e)*

3-Substituted-1H-pyrazole-4-carbaldehydes (**3**) were synthesized by the Vilsmayer Haack reaction of semicarbazones as described in the procedure (Vijesh et al, 2011). To a well stirred solution of aldehydes (1 mol), acetophenones (1 mol) in 50% ethanol-water (10 Vol) was added sodium hydroxide (2 mol) at 10 °C and the reaction mixture was stirred at room temperature for 15 hs. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to 0 °C, diluted with water and the solid separated was filtered, dried to get pure chalcone derivatives **4**(**a**–**n**). Synthesized compounds were recrystallized using ethanol as a solvent.

2.2.1. *(E)-3-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(pyridin-2-yl) prop-2-en-1-one (**4a**)*

(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.1), Yield: 62%; Yellow solid; m.p. 157–159 °C. IR (KBr) cm^{-1}: 3320 (NH), 3041 (CH), 1662 (C═N and C═O). ^{1}H NMR (400 MHz, δH, $CDCl_3$): 8.68 (d, 1H, Pyridine-H), 8.2 (s, 1H, Pyrazole-H), 7.72–7.93 (m, 2H, Ar-H), 7.6 (m, 1H, Ar-H), 7.33–7.45 (m, 2H, Ar-H), 7.21 (m, 2H Ar-H), 6.57 (d, 1H, –CO–CH═CH), 5.8 (d, 1H, CH═CH) ppm. MS: *m*/*z* = 294.1 (M + 1). Anal. Calcd for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.65; H, 4.22; N, 14.29.

2.2.2. *(E)-3-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(quinolin-2-yl)prop-2-en-1-one (**4b**)*

(TLC, Pet-ether/EtOAc, 8:2, R_f = 0.1), Yield: 74%; Yellow solid; m.p. 168-170 °C. IR (KBr) cm^{-1}: 3318 (NH), 3045 (CH), 1661 (C═N and C═O). ^{1}H NMR (400 MHz, δ H, $CDCl_3$): 8.56 (d, 1H, quinoline-H), 8.2 (m, 4H, Pyrazole-H, Ar-H), 7.70–7.74 (dd, 2H, Ar-H), 7.4 (d, 2H, Ar-H), 7.20–7.33 (m, 2H Ar-H), 6.59 (d, 1H, CH═CH), 5.9 (d, 1H, CH═CH) ppm. MS: *m*/*z* = 344.3 (M + 1). Anal. Calcd for $C_{21}H_{14}FN_3O$: C, 73.46; H, 4.11; N, 12.24. Found: C, 73.40; H, 4.15; N, 12.18.

2.2.3. *(E)-3-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(5-fluoropyridin-2-yl)prop-2-en-1-one (**4c**)*

(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.2), Yield: 69%; Brown solid; m.p. 150–152 °C. IR (KBr) cm^{-1}: 3324 (NH), 3089 (CH), 1661 (C═N and C═O). ^{1}H NMR (400 MHz, δH, $CDCl_3$): 8.78 (d, 1H, Pyridine-H), 8.09 (s, 1H, Pyrazole-H), 7.82–7.93 (m, 2H, Pyridine-H), 7.44 (m, 2H, Ar-H), 7.23–7.28 (m, 2H, Ar-H), 7.21 (d, 1H, Ar-H) 6.50 (d, 1H, CH═CH), 5.8 (d, 1H, CH═CH) ppm. MS: *m*/*z* = 312.2 (M + 1). Anal. Calcd for $C_{17}H_{11}F_2N_3O$: C, 65.59; H, 3.56; N, 13.50. Found: C, 65.57; H, 3.51; N, 13.45.

2.2.4. *(E)-1-(pyridin-2-yl)-3-(3-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)prop-2-en-1-one (**4d**)*

(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.2), Yield: 70%; Yellow solid; m.p. 149–151 °C. IR (KBr) cm^{-1}: 3330 (NH), 3040 (CH), 1660 (C═N and C═O). ^{1}H NMR (400 MHz, δH, $CDCl_3$): 8.68 (d, 1H, Pyridine-H), 8.2 (s, 1H, Pyrazole-H), 7.70–7.83 (m, 2H, Pyridine-H), 7.6 (m, 3H, Ar-H), 7.33 (m, 2H, Ar-H), 6.50 (d, 1H, CH═CH), 5.7 (d, 1H, CH═CH) ppm. MS: *m*/*z* = 344.3 (M + 1). Anal. Calcd for $C_{18}H_{12}F_3N_3O$: C, 62.97; H, 3.52; N, 12.24. Found: C, 62.90; H, 3.48; N, 12.04.

2.2.5. *(E)-1-(thiophen-2-yl)-3-(3-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)prop-2-en-1-one (**4e**)*

TLC, Pet-ether/EtOAc, 1:1, R_f = 0.3), Yield: 76%; Yellow solid; m.p. 135–138 °C. IR (KBr) cm^{-1}: 3328 (NH), 3040 (CH), 1661 (C═N and C═O). ^{1}H NMR (400 MHz, δH,