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ORIGINAL ARTICLE

2nd Cancer Update

Synthesis, characterization and anticancer evaluation of 2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1-[5-(substituted phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole

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Abstract In the present study o-phenylenediamine and naphtene-1-acetic acid/2-naphthoxyacetic acid were used as a starting material through a series of steps and 2-(naphthalen-1-ylmethyl/Naphthalen-2-yloxymethyl)-1H-benzimidazol-1-yl]acetohydrazide **5a**, **5b** were obtained. In the first series 1,3,4-oxadiazole derivatives have been synthesized from Schiff base of the corresponding hydrazide i.e. 2-[2-(naphthalen-1-ylmethyl)-1H-benzimidazol-1-yl]acetohydrazide **5a** by using Chloramin-T. In the second series 1,3,4-oxadiazole has been synthesized from 2-{2-[(naphthalen-2-yloxy)-methyl]-1Hbenzimidazol-1-yl}acetohydrazide **5b** by using phosphorous oxychloride and aromatic acid. These compounds were evaluated by IR, NMR, Mass spectrometry, elemental analysis and finally in vitro anticancer evaluation was carried out by NCI 60 Cell screen at a single high dose (10–5 M) on various panel/cell lines. One compound **7c** was found to be the most active on breast cancer cell line and compounds **4b** and **7d** were moderately active.

1. Introduction

Cancer is a group of various diseases and medically known as malignant neoplasm, involving unregulated cell growth. It is a major health problem in developing as well as undeveloped countries (Abdel-Aziz, 2007; Choo et al., 2002; Al-Rasood

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et al., 2006). The incidence of cancer worldwide increases the search for new, safer and efficient anticancer agents, aiming the prevention or the cure of this illness. Research laboratories are still involved deeply for the research of a new anticancer drug. Product development involves application of existing products to meet the therapeutic need in addition to the discovery of new drugs. Literature review revealed that many compounds bearing a five membered heterocyclic ring containing nitrogen and oxygen like oxadiazole have been synthesized and showed a variety of biological activities like anticancer (Sengupta et al., 2008; Jin et al., 2006; Holla et al., 2005), anticonvulsant (Almasirad et al., 2004; Aziz et al., 2009), antimicrobial (Shetgiri and Nayak, 2005; Manjunatha et al., 2010; Shailaja et al., 2010; Mulwad and Chaskar, 2006; Ansari and Lal, 2009), anti-inflammatory analgesic (Bhandari et al., 2008; Dewangan et al., 2010; Amir et al., 2007; Kumar et al., 2008; Jayashankar et al., 2009), dyes and pigments (ShuiLv et al., 2010), ulcerogenic (Gilani et al., 2010), antitubercular (Ali and Shaharyar, 2007) etc.

2. Experimental

2.1. Instrumentation

The chemicals used for experimental work were commercially procured from various chemical units viz E. Merck India Ltd., CDH and S.D. Fine chem. and Qualigens. These solvents and reagents were of LR grade and purified before use. The silica gel G (160–120 mesh) used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. Two solvent systems were used Benzene:Acetone (9:1) and (8:2), Toluene:Ethyl Acetate:Formic acid (5:4:1). Ashless Whattman No. 1 filter paper was used for vacuum filtration. Melting points were determined in an open glass capillary using melting point apparatus and are uncorrected. The Proton Magnetic Resonance spectra (^{1}HNMR) were recorded on a Bruker 300 MHz instrument in DMSO-d_6/$CDCl_3$ using tetramethylsilane [$(CH_3)_4Si$] as internal standard. The Infrared spectra of compound were recorded in KBr on Perkin-Elmer FTIR Spectrometer and iodine Chamber and UV-lamp were used for visualization of TLC spots. The commercially available grades of solvents and reagents were found to be of adequate purity. However, the presence of undesirable impurities and others were likely to be used for experimental work was purified/dried.

2.1.1. Procedure for the synthesis of 2-naphthalen-1-yl/naphthoxy-methyl-1H-benzimidazole (**3a**, **3b**)

A mixture of o-phenylenediamine 1 (0.05 mol; 5.40 g) and naphthylacetic acid/naphthoxyacetic acid 2 (0.05 mol) was refluxed in 4N HCl for 4 h on a heating mantle. After completion of reaction, the solution was poured onto crushed ice, ammonia solution was added drop wise to neutralize and the resulting solid was filtered, washed with cold water, dried and recrystallized with ethanol (see Scheme 1).

*2.1.1.1. Synthesis of 2-(naphthalen-1-ylmethyl)-1H-benzimidazole (**3a**).* Yield 85%, m.p. 125–126 °C, IR (KBr) cm^{-1}: 1528 (C═N), 3302 (N-H): ^{1}H-NMR (DMSO-d_6) δ ppm: 4.62 (s, 2H, CH_2), 7.06–8.19 (m, 11H, aromatic), 12.37 (s, 1H, NH). EI-MS 274 (M^+); Anal. Calcd. for $C_{18}H_{14}N_2C$, 83.69; H, 5.46; N, 10.84. Found: C, 83.67; H, 5.49; N, 10.82.

*2.1.1.2. Synthesis of 2-[(naphthalen-2-yloxy)methyl]-1H-benzimidazole (**3b**).* Yield 84%, m.p. 205–207 °C, IR (KBr) cm^{-1}: 1226 (C–O), 1464 (C═N), 3297 (N–H), 3010 (CH, aromatic): ^{1}H-NMR (DMSO-d_6) δ ppm: 5.34 (s, 2H, CH_2O), 7.26–7.70 (m, 11H, aromatic); EI-MS 258 (M^+); Anal. Calcd. for $C_{18}H_{14}N_2O$ C, 78.81; H, 5.14; N, 10.21; O, 5.83 Found: C, 78.84; H, 5.15; N, 10.25; O, 5.80.

2.1.2. Synthesis of ethyl [2-(naphthalen-1-yl/naphthalen-2-yloxymethyl)-1H-benzimidazol-1-yl]acetate (**4a**, **4b**)

To a suspension of 2-(naphthylmethyl)-1H-benzimidazole 3 (0.01 mol), anhydrous potassium carbonate (2 g) in dry acetone, ethyl chloroacetate (0.01 mol; 1.2 ml) was added drop wise at room temperature for a period of 20–30 min. The reaction mixture was stirred at room temperature for 10–12 h. The inorganic solid was filtered off and the filtrate was concentrated under reduced pressure.

*2.1.2.1. Synthesis of ethyl [2-(naphthalen-1-ylmethyl)-1H-benzimidazol-1-yl]acetate (**4a**).* Yield 72%, m.p. 108–112 °C, IR (KBr) cm^{-1}: 1229 (C–O), 1436 (C═N), 3206 (N–H), 3010 (CH, aromatic); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.14 (s, 2H, CH_2 naphthyl), 5.06 (s, 2H, CH_2) 7.46–7.79 (m, 11H, aromatic); EI-MS 360 (M^+); Anal. Calcd. for $C_{22}H_{20}N_2O_2$, C, 76.72; H, 5.85; N, 8.13; O, 9.29. Found: C, 76.70; H, 5.88; N, 8.12; O, 9.29.

*2.1.2.2. Synthesis of ethyl {2-[(naphthalen-2-yloxy)methyl]-1H-benzimidazol-1-yl}acetate (**4b**).* Yield 69%, m.p. 105–109 °C, IR (KBr) cm^{-1}: 1226 (C–O), 1464 (C═N), 1736 (C═O), 2950 (CH, aromatic); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.72 (s, 2H, CH_2), 5.21 (s, 2H, CH_2O) 6.90–7.61 (m, 11H, aromatic); EI-MS 344 (M^+); Anal. Calcd. for $C_{22}H_{20}N_2O_3C$, 73.32; H, 5.59; N, 7.77; O, 13.32. Found: C, 73.29; H, 5.60; N, 7.80; O, 13.35.

2.1.3. Synthesis of 2-[2-(naphthalen-1-yl/naphthalen-2-yloxy methyl)-1H-benzimidazol-1-yl]acetohydrazide (**5a**, **5b**)

To an ethanolic solution of ethyl [2-(naphthalen-1-ylmethyl)/(naphthalen-2-yloxy)methyl]-1H-benzimidazol-1-yl]acetate **4a**, **4b** (0.01 mol), hydrazine hydrate (98%) (0.01 mol; 0.49 ml) was added and the mixture was refluxed for 3 h. After completion of the reaction, the mixture was cooled and the solid so obtained was filtered, washed with cold water and recrystallized from methanol.

*2.1.3.1. Synthesis of 2-[2-(naphthalen-1-ylmethyl)-1H-benzimidazol-1-yl]acetohydrazide (**5a**).* Yield 82% mp. 147–150 °C, IR (KBr) cm^{-1}: 1233 (N–N), 1528 (C═N); 1643 (C═O), 3043 (CH–Ar), 3302 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.50 (s, 1H, NH_2), 4.90 (s, 2H, CH_2), 7.13–8.15 (m, 11H, aromatic), 9.25 (s, 1H, CONH); EI-MS 346 (M^+); Anal. Calcd. for: $C_{22}H_{18}N_4OC$, 72.71; H, 5.49, N, 16.96; O, 4.84 Found: C, 72.71; H, 5.50, N, 16.94; O, 4.82.

*2.1.3.2. Synthesis of 2-{2-[(naphthalen-2-yloxy)methyl]-1H-benzimidazol-1-yl}acetohydrazide (**5b**).* Yield 82% mp. 208–210 °C, IR (KBr) cm^{-1}: 1254 (N–O), 1466 (C═N); 1668 (C═O), 3056 (CH–Ar), 3292 (N–H); ^{1}H-NMR (DMSO-d_6) δ