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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.

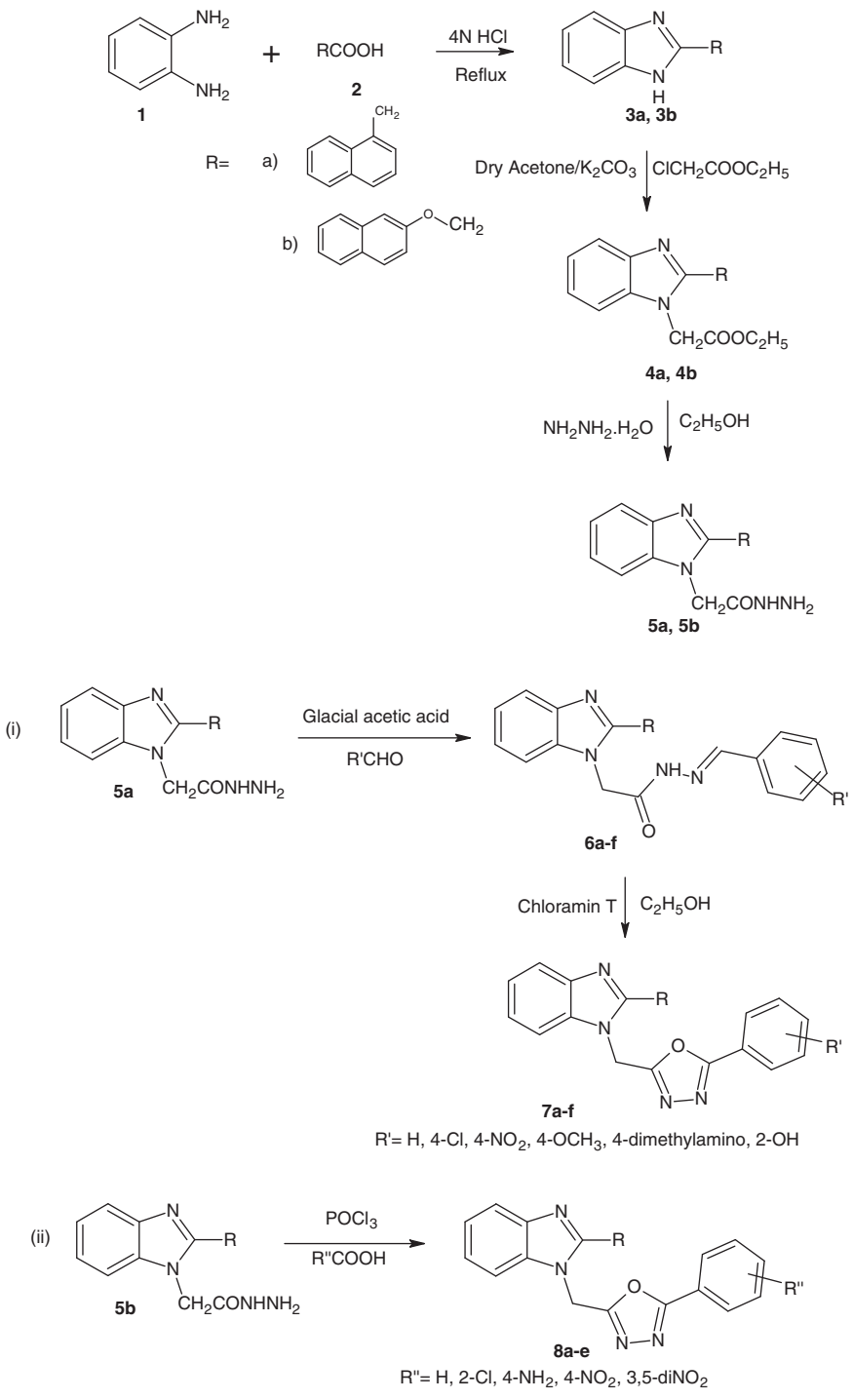
*2.1.2.2. Synthesis of ethyl {2-[(naphthalen-2-yloxy)methyl]-1H-benzimidazol-1-yl}acetate (**4b**).* Yield 69%, m.p. 105–109 °C, IR (KBr) cm^{-1}: 1226 (C–O), 1464 (C═N), 1736 (C═O), 2950 (CH, aromatic); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.72 (s, 2H, CH_2), 5.21 (s, 2H, CH_2O) 6.90–7.61 (m, 11H, aromatic); 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



Scheme 1

ppm: 2.53 (s, 1H, NH_2), 4.89 (s, 2H, CH_2), 5.35 (s, 1H, CH_2O), 6.92–7.70 (m, 11H, aroamtic), 9.05 (s, 1H, CONH); EI-MS 330 (M^+); Anal. Calcd. for: $C_{22}H_{18}N_4O_2C$, 69.35; H, 5.24; N, 16.17; O, 9.24 Found: C, 69.30; H, 5.21; N, 16.21; O, 9.27.

*2.1.4. Synthesis of 2-[2-(naphthylmethyl)-1H-benzimidazol-1-yl]-N'-[substituted phenylmethylidene] acetohydrazide (**6a–f**)*

A mixture of 2-[2-(naphthylmethyl)-1H-benzimidazol-1-yl]acetohydrazide 5 (0.0025 mol) and substituted benzaldehyde (0.0025 mol) in ethyl alcohol (10 ml) and few drops of glacial acetic acid were refluxed for 5 h. After completion of reaction, the reaction mixture was concentrated, cooled, poured in ice cold water, the precipitate so formed was filtered, dried and re-crystallized with ethanol to give desired compound.

*2.1.4.1. (2-Naphthalen-1-ylmethyl-benzimidazol-1-yl)-acetic acid benzylidene-hydrazide (**6a**).* Yield 76%; m.p. 208–209 °C, IR (KBr) cm^{-1}: 1134 (N–N), 1594 (C═N); 1669 (C═O), 3045 (CH–Ar), 3193 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.08 (s, 2H, CH_2 naphthyl), 4.46 (s, 2H, CH_2), 7.43–

8.66 (m, 16H, aroamtic), 11.81 (s, 1H, CONH); EI-MS 435 $(M + 1)^+$; Anal. Calcd. for $C_{27}H_{22}N_4O$: C, 77.49; H, 5.30; N, 13.39; O, 3.82 Found: C, 77.46; H, 5.33; N, 13.41; O, 3.80.

*2.1.4.2. (2-Naphthalen-1-ylmethyl-benzimidazol-1-yl)-acetic acid (4-chloro-benzylidene)-hydrazide (**6b**).* Yield 80%; m.p. 200–202 °C, IR (KBr) cm^{-1}: 1252 (N–N), 1489 (C═N); 1667 (C═O), 2962 (CH–Ar), 3181 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.05 (s, 2H, CH_2 naphthyl), 5.47 (s, 2H, CH_2), 7.42–8.26 (m, 15H, aroamtic), 11.51 (s, 1H, CONH); EI-MS 469 $(M + 1)^+$; Anal. Calcd. for $C_{27}H_{19}ClN_4O$: C, 71.60; H, 4.67; Cl, 7.83; N, 12.37; O, 3.53 Found: C, 71.60; H, 4.65; Cl, 7.82; N, 12.38; O, 3.52.

*2.1.4.3. (2-Naphthalen-1-ylmethyl-benzimidazol-1-yl)-acetic acid (4-nitro-benzylidene)-hydrazide (**6c**).* Yield 78%; m.p. 226–227 °C, IR (KBr) cm^{-1}: 1520 (N═C); 1662 (C═O); 3042 (CH–Ar); 3176 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.99 (s, 2H, CH_2 naphthyl), 4.41 (s, 2H, CH_2), 6.95–8.15 (m, 15H, aroamtic), 11.35 (s, 1H, CONH); EI-MS 478 (M^+); Anal. Calcd. for $C_{27}H_{21}N_5O_3$: C, 69.97; H, 4.57; N, 15.11; O, 10.36. Found: C, 69.95; H, 4.60; N, 15.10; O, 10.39.

*2.1.4.4. (2-Naphthalen-1-ylmethyl-benzimidazol-1-yl)-acetic acid (4-methoxy-benzylidene)-hydrazide (**6d**).* Yield 75%; m.p. 186–187 °C, IR (KBr) cm^{-1}: 1512 (N═C); 1661 (C═O); 3051 (CH–Ar); 3202 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.98 (s, 2H, CH_2 naphthyl), 4.40 (s, 2H, CH_2), 6.69–8.12 (m, 15H, aroamtic), 11.18 (s, 1H, CONH); EI-MS 465 $(M + 1)^+$; Anal. Calcd. for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39; N, 12.49; O, 7.13. Found: C, 74.98; H, 5.39; N, 12.49; O, 7.13.

*2.1.4.5. (2-Naphthalen-1-ylmethyl-benzimidazol-1-yl)-acetic acid (4-dimethylamino-benzylidene)-hydrazide (**6e**).* Yield 82%; m.p. 289–290 °C, IR (KBr) cm^{-1}: 1496 (N═C); 1654 (C═O); 3041 (CH–Ar); 3194 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.30 (s, 3H, CH_3), 4.05 (s, 2H, CH_2 naphthyl), 4.47 (s, 2H, CH_2), 7.43–8.25 (m, 15H, aroamtic), 11.58 (s, 1H, CONH); EI-MS 478 (M + 1); Anal. Calcd. for $C_{29}H_{27}N_5O$: C, 75.47; H, 5.91; N, 15.19; O, 3.50. Found: C, 75.43; H, 5.89; N, 15.14; O, 3.49.

*2.1.4.6. (2-Naphthalen-1-ylmethyl-benzimidazol-1-yl)-acetic acid (2-hydroxy-benzylidene)-hydrazide (**6f**).* Yield 82%; m.p. 289–290 °C, IR (KBr) cm^{-1}: 1466 (N═C); 1739 (C═O); 3048 (CH–Ar); 3294 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.04 (s, 2H, CH_2 naphthyl), 4.46 (s, 2H, CH_2), 6.98–8.21 (m, 15H, aroamtic), 10.18 (s, 1H, CONH), 11.39 (s, 1H, OH); EI-MS 451 $(M + 1)^+$; Anal. Calcd. for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89; O, 7.36. Found: C, 74.62; H, 5.13; N, 12.90; O, 7.39.

*2.1.5. General procedure for the synthesis of 2-Naphthalen-1-ylmethyl-1-(5-substituted phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole (**7a–f**)*

To an ethanolic solution of 2-[2-(Naphthylmethyl)-1H-benzimidazol-1-yl]-N'-[phenylmethylidene] acetohydrazide (0.0025 mol), chloramin T (0.0125 mol) was added. The solution was refluxed for 4 h, sodium chloride which separated out during the course of reaction was filtered off. Excess ethanol was completely removed from the filtrate by distillation under reduced pressure, leaving behind a solid mass which was crystallized from ethanol to give desired compound.

*2.1.5.1. 2-Naphthalen-1-ylmethyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole (**7a**).* Yield 65%; m.p. 172–174 °C, IR (KBr) cm^{-1}: 1034 (N–N); 1231 (C–O); 1598 (C═N); 2963 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.33 (s, 2H, CH_2 naphthyl), 5.55 (s, 2H, CH_2), 7.16–7.86 (m, 16H, aromatic); EI-MS 431 (M^+); Anal. Calcd. for $C_{27}H_{20}N_4O$: C, 77.87; H, 4.84; N, 13.45; O, 3.84. Found: C, 77.85; H, 4.85; N, 13.43; O, 3.80.

*2.1.5.2. 1-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-2-naphthalen-1-ylmethyl-1H-benzimidazole (**7b**).* Yield 71%; m.p. 221–223 °C, IR (KBr) cm^{-1}: 773 (C–Cl); 1085 (N–N); 1228 (C–O); 1489 (C═N); 2962 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.70 (s, 2H, CH_2 naphthyl), 5.24 (s, 2H, CH_2), 7.13–8.21 (m, 15H, aromatic); EI-MS 467 $(M + 1)^+$; Anal. Calcd. for $C_{27}H_{19}ClN_4O$: C, 71.92; H, 4.25; Cl, 7.86; N, 12.43; O, 3.55. Found: C, 71.92; H, 4.25; Cl, 7.83; N, 12.45; O, 3.51.

*2.1.5.3. 2-Naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole (**7c**).* Yield 71%; m.p. 245–246 °C, IR (KBr) cm^{-1}: 1070 (N–N); 1232 (C–O); 1519 (C═N); 3041 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.41 (s, 2H, CH_2 naphthyl), 5.65 (s, 2H, CH_2), 7.09–7.85 (m, 15H, aromatic); EI-MS 477 (M^+); Anal. Calcd. for $C_{27}H_{20}N_5O_3$: C, 70.27; H, 4.15; N, 15.18; O, 10.40. Found: C, 70.25; H, 4.17; N, 15.17; O, 10.40.

*2.1.5.4. 1-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-2-naphthalen-1-ylmethyl-1H-benzimidazole (**7d**).* Yield 82%; m.p. 170–172 °C, IR (KBr) cm^{-1}: 1168 (N–N); 1257 (C–O); 1508 (C═N); 3041 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.46 (s, 3H, CH_3), 4.05 (s, 2H, CH_2 naphthyl), 4.42 (s, 2H, CH_2), 7.35–8.93 (m, 15H, aromatic); EI-MS 463 $(M + 1)^+$; Anal. Calcd. for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55; O, 7.17. Found: C, 75.31; H, 4.97; N, 12.54; O, 7.18.

*2.1.5.5. Dimethyl-{4-[5-(2-naphthalen-1-ylmethyl-benzimidazol-1-ylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amine (**7e**).* Yield 71%; m.p. 187–190 °C, IR (KBr) cm^{-1}: 1139 (N–N); 1234 (C–O); 1531 (C═N); 2857 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.50 (s, 6H, CH_3), 3.97 (s, 2H, CH_2 naphthyl), 4.48 (s, 2H, CH_2), 7.16–8.27 (m, 15H, aromatic); EI-MS 344 $(M + 1)^+$; Anal. Calcd. for $C_{29}H_{25}N_5O$: C, 75.80; H, 5.48; N, 15.24, O, 3.48. Found: C, 75.82; H, 5.48; N, 15.21, O, 3.45.

*2.1.5.6. 2-[5-(2-Naphthalen-1-ylmethyl-benzimidazol-1-ylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (**7f**).* Yield 74%; m.p. 102–104 °C, IR (KBr) cm^{-1}: 1027 (N–N); 1216 (C–O); 1503 (C═N); 2979 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.01 (s, 2H, CH_2 naphthyl), 4.40 (s, 2H, CH_2), 7.30–8.11 (m, 15H, aromatic), 9.82 (s, 1H, OH); EI-MS 449 $(M + 1)^+$; Anal. Calcd. for $C_{27}H_{20}N_4O_2$: C, 74.98; H, 4.66; N, 12.95; O, 7.40. Found: C, 74.98; H, 4.66; N, 12.95; O, 7.40.

*2.1.6. Synthesis of 2-(Naphthalen-2-yloxymethyl)-1-(5-substituted phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole (**8a–e**)*

A mixture of 2-{2-[(naphthalen-2-yloxy)methyl]-1H-benzimidazol-1-yl}acetohydrazide **5b** (0.0025 mol) and suitable aromatic acid (0.0025 mol) was refluxed in the presence of

$POCl_3$ (5 ml) for 5 h at a temperature of 110–120 °C. After completion of reaction, the mixture was cooled at room temperature and poured onto crushed ice. On basification with sodium bicarbonate (5%), a solid mass separated out was filtered to get crude product. Finally the product was heated with charcoal in hydrated ethanol and then re-crystallized from ethanol to obtain **8a–e**.

*2.1.6.1. Synthesis of 2-(Naphthalen-2-yloxymethyl)-1-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole (**8a**).* Yield 67% m.p. 204–208 °C IR (KBr) cm^{-1}: 1031 (N–N), 1250 (C–O), 1605 (C═N); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.67 (s, 2H, CH_2), 5.64 (s, 2H, OCH_2), 7.09–7.76 (m, 16H, aromatic); EI-MS 416 (M^+); Anal. Calcd. for $C_{27}H_{20}N_4O_2$: C, 74.98; H, 4.66; N, 12.95; O, 7.40 Found: C, 74.95; H, 4.69; N, 12.93; O, 7.45.

*2.1.6.2. Synthesis of 1-[5-(2-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-2-(naphthalen-2-yloxymethyl)-1H-benzimidazole (**8b**).* Yield 63%; m.p. 108–110 °C, IR (KBr) cm^{-1}: 740 (C–Cl); 1028 (N–N), 1238 (C–O), 1583 (C═N), 3026 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.45 (s, 2H, CH_2), 5.03 (s, 2H, OCH_2), 6.73–7.79 (m, 15H, aroamtic), EI-MS 451 $(M + 1)^+$. Anal. Calcd. for $C_{27}H_{19}ClN_4O_2$: C, 69.45; H, 4.10;Cl, 7.59; N, 12.00; O, 6.85 Found: C, 69.41; H, 4.14; Cl, 7.61; N, 11.97; O, 6.83.

*2.1.6.3. Synthesis of 2-{5-[2-(Naphthalen-2-yloxymethyl)-benzoimidazol-1-ylmethyl]-[1,3,4]oxadiazol-2-yl}-phenylamine (**8c**).* Yield 66%; m.p. 220–222 °C, IR (KBr) cm^{-1}: 1037 (N–N), 1246 (C–O), 1598 (C═N), 3067 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.0 (s, 2H, NH_2), 4.91 (s, 2H, CH_2), 5.31 (s, 2H, OCH_2), 6.73–7.79 (m, 15H, aroamtic), EI-MS 432 $(M + 1)^+$. Anal. Calcd. for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.73; N, 15.65; O, 7.15 Found: C, 72.45; H, 4.77; N, 15.67; O, 7.13.

*2.1.6.4. Synthesis of 2-(Naphthalen-2-yloxymethyl)-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole (**8d**).* Yield 69%; m.p. 80-84 °C, IR (KBr) cm^{-1}: 1035 (N–N); 1239 (C–O); 1568 (NO_2); 1685 (C═N); 3032 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.50 (s, 2H, CH_2), 5.28 (s, 2H, OCH_2), 6.91–7.71 (m, 15H, aromatic); EI-MS 461 (M^+); Anal. Calcd. for $C_{27}H_{19}N_5O_4$: C, 67.92; H, 4.01; N, 14.67; O, 13.40 Found: 67.89; H, 4.05; N, 14.70; O, 13.37.

*2.1.6.5. Synthesis of 12-(Naphthalen-2-yloxymethyl)-1-[5-(3,5-dinitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole (**8e**).* Yield 74%; m.p. 155-157 °C, IR (KBr) cm^{-1}: 1035 (N–N); 1239 (C–O); 1566 and 1350 (NO_2); 1685 (C═N); 3063 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.12 (s, 2H, CH_2), 5.37 (s, 2H, OCH_2), 6.91–7.78 (m, 14H, aroamtic), EI-MS 507 $(M + 1)^+$; Anal. Calcd. for $C_{27}H_{18}N_6O_6$: C, 62.07; H, 3.47; N, 16.09; O, 18.37 Found: C, 62.12; H, 3.44; N, 16.11; O, 18.35.

Table 1 Anticancer screening data of title compounds.

Compound	60 cell lines assay in 1 dose 10–5 M conc.				
	NSC code	Mean growth %	Range of growth %	The most sensitive cell line	Growth % of the most sensitive cell line
3b	764,708	89.44	61.59–123.30	A-498 (renal cancer)	61.59
				HOP-92 (non-small cell lung cancer)	63.30
4b	764,709	79.28	47.08–97.79	NCI-H522 (Non-small Cell Lung Cancer)	47.08
				UO-31 (renal cancer)	57.33
6d	764,703	95.73	69.53–109.35	MOLT-4 (leukemia)	69.53
				UO-31 (renal cancer)	72.14
6f	764,706	94.99	63.19–108.33	UO-31 (renal cancer)	63.19
				UACC-62 (melanoma)	74.16
7a	764,700	84.91	25.17–110.90	HOP-92 (non-small cell lung cancer)	25.17
				UO-31 (renal cancer)	63.88
7b	764,701	91.53	51.36–107.82	SNB-75 (CNS cancer)	51.36
				NCI-H522 (non-small cell lung cancer)	72.21
7c	764,702	72.85	36.23–101.81	MDA-MB-468 (Breast Cancer)	36.23
				SK-MEL-28 (melanoma)	47.56
7d	764,704	74.09	32.73–100.64	NCI-H522 (non-small cell lung cancer)	32.73
				UO-31 (renal cancer)	40.53
7e	764,705	95.10	64.10–109.28	UO-31 (renal cancer)	64.10
				HOP-92 (non-small cell lung cancer)	70.12
7f	764,707	96.59	62.97–111.45	UO-31 (renal cancer)	62.97
				HOP-92 (non-small cell lung cancer)	78.32
8a	764,710	92.20	56.74–111.52	UO-31 (renal cancer)	56.74
				MOLT-4 (leukemia)	72.02
8b	764,711	80.54	40.96–111.19	UO-31 (renal cancer)	40.96
				MOLT-4 (leukemia)	41.37
8c	764,712	101.87	71.70–118.83	UO-31 (renal cancer)	71.70
				HOP-92 (non-small cell lung cancer)	74.53
8d	764,713	96.10	54.01–110.84	UO-31 (renal cancer)	54.01
				HOP-92 (non-small cell lung cancer)	76.98
8e	764,714	92.62	47.35–108.14	UO-31 (renal cancer)	47.35
				PC-3 (prostate cancer)	69.80

2.2. Anticancer activity

2.2.1. Treatment of tumor cell lines

All compounds submitted to the NCI 60 Cell screen were tested initially at a single high dose (10^{-5} M) on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancer cell lines, nearly 60 in number. The one-dose data were reported as a mean graph of the percent growth of treated cells. The number reported for the one-dose assay is growth relative to the no-drug control, and relative to the time zero number of cells. The anticancer screening was carried out as per the NCI US protocol reported elsewhere (http://dtp.nci.nih.gov; Turner, 1964; Monks et al., 1991; Boyd and Paull, 1995; Shoemaker, 2006). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentration levels.

Percentage growth inhibition is calculated as:

$$[(\mathrm{Ti}-\mathrm{Tz})/(\mathrm{C}-\mathrm{Tz})] \times 100 \text{ for concentrations for which } \mathrm{Ti} >/= \mathrm{Tz}$$

$$[(\mathrm{Ti}-\mathrm{Tz})/\mathrm{Tz}] \times 100 \text{ for concentrations for which } \mathrm{Ti} < \mathrm{Tz}.$$

3. Result and discussion

3.1. Chemistry

2-Naphthalen-1-yl/naphthoxy-methyl-1H-benzimidazole **3a**, **3b** were prepared by refluxing with o-phenylenediamine 1 and naphthalene-1-acetic acid/2-naphthoxyacetic acid 2 in the presence of 4NHCl. The compounds **3a**, **3b** on reacting with ethylchloroacetate in the presence of potassium carbonate in dry acetone gave ethyl [2-(naphthalen-1-yl/naphthalen-2-yl-oxymethyl)-1H-benzimidazol-1-yl]acetate **4a**, **4b** which on treatment with hydrazine hydrate result in the formation of 2-[2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1H-benzimidazol-1-yl]acetohydrazide **5a**, **5b**. The compound **5a** on treatment with aromatic aldehyde and alcohol gave Sciff base which is (2-Naphthalen-1-ylmethyl-benzoimidazol-1-yl)-acetic acid substituted benzylidene-hydrazide **6a–f**. Sciff base **6a–f** on reacting with ethyl alcohol and Chloramin-T gives 2-Naphthalen-1-ylmethyl-1-(5-substitutedphenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole **7a–f**. Finally the compound **5b** on treating with various aromatic acids and phosphorous oxychloride gave 2-(Naphthalen-2-yloxymethyl)-1-(5-substituted phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole **8a–d**.

3.2. Anticancer activity

The synthesized title compounds displayed moderate to low activity in the in vitro screen on all tested cancer cell lines and are given in Table 1. The compound **7c** was found to be the most active compound of the series that showed 72.85 growth percent (GP) and highly active on MDA-MB-468 (Breast cancer) and SK-MEL-28 (Melanoma) (GP = 36.23 and 47.56, respectively). The compounds **7d** and **4b** showing moderate activity were highly active on NCI-H522 (Non-small cell lung cancer) with GP of 32.73 and 47.08, respectively and on UO-31 (Renal cancer) with 40.53 and 57.33, respectively, while rest of the compounds showed less activity with an average growth percent of 84.91–96.59.

4. Conclusion

A novel 2-Naphthalen-1-ylmethyl-1-(5-substituted phenyl-[1,3,4] oxadiazol-2-ylmethyl)-1H-benzimidazole (**7a–f**) and 2-(Naphthalen-2-yloxymethyl)-1-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole (**8a–e**) have been synthesized by using chloramin-T from Schiff base and phosphrous oxychloride from hydrazides. The in vitro anticancer studies reveal that the compound with para substituent like p-NO_2 (**7c**) showed a prominent activity against MDA-MB-468 (Breast cancer) and SK-MEL-28 (Melanoma) (GP = 36.23 and 47.56, respectively) probably because of more electron withdrawing power of the other substituents. While the other compounds **7d** and **4b** showed moderate activity against selected cancer cell line. Thus the study revealed that these compounds have potential anticancer activity and structural modification may lead to the synthesis of more 1,3,4-oxadiazole derivatives and can be evaluated for their anticancer activities in vitro as well as in vivo.

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