Research Article

Synthesis, characterisation and evaluation of oxadiazole as promising anticancer agent

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Abstract
A unique series oxadiazoles were synthesized by cyclization of benzophenone hydrazide, followed by the nucleophillic alkylation of heterocyclic scaffold. Synthesized title compounds were characterized by the FT-IR, LCMS and NMR spectral techniques. The newly synthesized compounds were screened for the anticancer activity. IC_{50} values of the 7h observed for in-vitro anti-cancer activities were 112.6 µg/ml and 126.7 µg/ml, against the MCF-7 and KB cell lines respectively. Most active compounds were found to be less toxic, which were determined by MTT assay method with normal cell line (L292). Biological screening of the synthesized series of compounds reveals that, Compound **7h** was the potent molecule.

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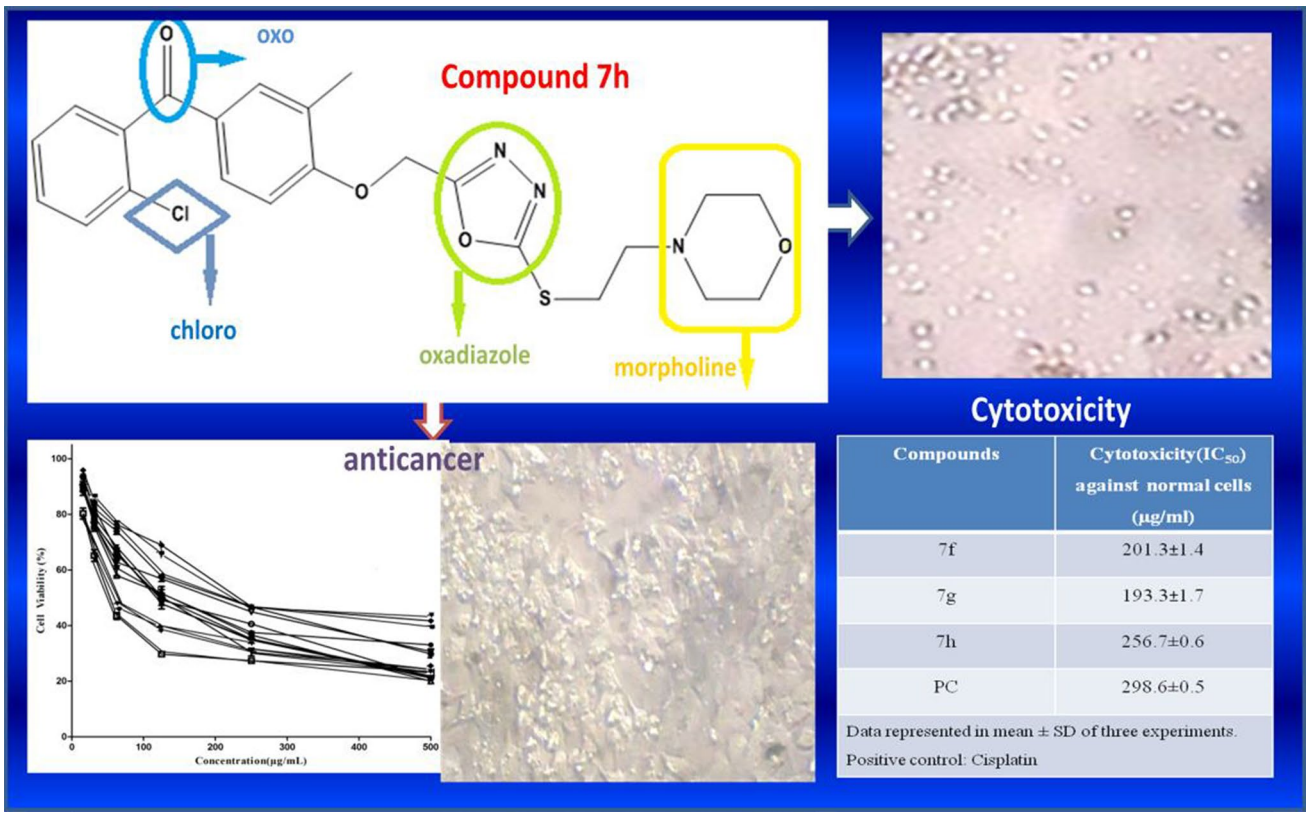
Graphic abstract



Keywords Benzophenone · Oxadiazole · Anti-cancer · Morpholine · Piperidine

1 Introduction and experimental

The recognition of prime molecular targets for cancer therapy has paved the way to a paradigm shuffle in drug discovery and thus more up thrust is now placed on molecules for drug designing. A plethora of heterocycles containing nitrogen have been the center of attention for their high therapeutic values in the past few decades. Cancer is one of the most life threatening diseases for mankind. Approximately 38.4% of men and women will be diagnosed with cancer at some point during their lifetimes and according to the World Health Organization (WHO), in 2018 globally 9.6 million deaths was due to the cancer and one in six deaths is from the cancer. When diseases become tolerant to pharmaceutical treatments this phenomenon is known as Drug resistance [1]. Multidrug resistance continues to be the principal limiting factor to achieving cures in patients with cancer. To overcome the MDR limitations many research has taken place and in that oxadiazole is one of the promising scaffold in the medicinal chemistry [2]. Oxadiazoles are physiologically active heterocyclic compounds owing to a vast sphere of biological activities, including anticancer [3–11], antidiabetic [12], antiviral [13, 14], anti-inflammatory [15, 16], antibacterial [17, 18], antifungal [19], antimycobacterial [20], analgesic [21], anticonvulsant [22], tyrokinase inhibitor [23] and cathepsin K inhibitor [24] antioxidant [25] properties.

The presence of morpholine and piperidine kernels in several categories of pharmaceutical agents has made these irreplaceable anchors for the development of new therapeutic agent. Piperidine and morpholine are heterocyclic organic compounds which are major class of elementary units in organic synthesis. Morpholine and piperidine derivatives are known to display various pharmacological properties such as antimicrobial, antitubercular, anticonvulsant, anti-inflammatory, analgesic [26], tachykinin receptor binding [27] and antiviral [28, 29]. An awareness of morpholine for their several factors, firstly, the participation of oxygen atom in donor–acceptor type

interactions and secondly, electronegative effects of the oxygen atom is on a high fame.

As the synthesis of heterocyclic compounds comprising of multi-structured framework is gaining an incredible progress in recent years. Conjugation of the different types of the functional unit makes the hybrid molecular structure, which exhibit the different phase of the activities. Benzophenone based compounds is known to exhibit a broad range of biological activity. Primarily, it acts as target specific anti-angiogeneic pharmacophores which is in the processes of drug development progression, it encouraged us to envisage the combination of oxadiazole, benzophenone, morpholine and piperidine. In the current context and continuation of our drug discovery research [30, 31], a new series of morpholine and piperidine tagged oxadiazole compounds have been synthesized and evaluated for anticancer activity.

2 Materials and methods: chemistry

The chemicals were procured from Sigma Aldrich Chemical Co. Ltd, Mumbai. TLC was performed on aluminium-backed silica plates and visualized by UV-light. Melting points were measured by the open capillary method and were uncorrected. FT-IR spectra were determined on Perkin Elmer spectrophotometer version 10.03.09 instrument over the range of 600–4000 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz in deuterated chloroform and the chemical shifts were recorded in ppm downfield using TMS as the internal standard. Mass spectra were obtained with a VG70-70H spectrophotometer and the elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. The results of elemental analyses were within ± 0.4% of the theoretical values.

2.1 Synthesis of benzophenone-mercapto oxadiazole derivatives

The protocol for the synthesis of hydroxy benzophenone analogues and benzophenone-mercapto oxadiazole derivatives are shown in Schemes 1 and 2, respectively.

2.1.1 General procedure for the synthesis of substituted hydroxy benzophenone analogues (3a–g)

The starting benzoates were synthesized by the reaction of substituted phenols with substituted benzoyl chlorides in 10% sodium hydroxide solution. The reaction mixture was stirred for 3–4 h at 0–5 °C and was monitored by thin layer chromatography (TLC) using 8:2 (*n*-hexane: ethyl acetate) solvent mixture. Further, hydroxy benzophenones **3a–g** was synthesized by Fries rearrangement. Substituted benzoates and anhydrous aluminium chloride (0.002 mol) were homogenized and the mixture was heated upto 150–170 °C without solvent for 2–3 h. Then the reaction mixture was cooled to 0 °C and quenched with 6 N hydrochloric acid in ice cold water. The reaction mixture was stirred for about 2–3 h. The solid was filtered and recrystallized with ethanol. Compound 3a is taken as a representative example to explain characterization data.

2.1.2 Synthesis of hydroxy benzophenone (3a)

Yield 85%; M.P: 133–135 °C FT-IR (KBr, cm^{-1}): 1640 (C=O), 3518 (OH); ^{1}H NMR ($CDCl_3$): 6.76–7.86 (m, 9H, Ar–H), 12.2 (bs, 1H, OH); ^{13}C-NMR ($CDCl_3$): δ 116.1, 129.08, 131.1, 132.6,132.9, 133.5, 139.1, 163.13, 195.1; LC–MS *m/z* 199 (M + 1). Elemental Analysis: Calcd. for $C_{13}H_{10}O_2$: C, 79.22; H, 5.70%. Found: C, 78.88; H, 5.69%.

2.1.3 General protocol for the synthesis of (4-benzoyl phenoxy)-acetic acid ester analogues (4a–g)

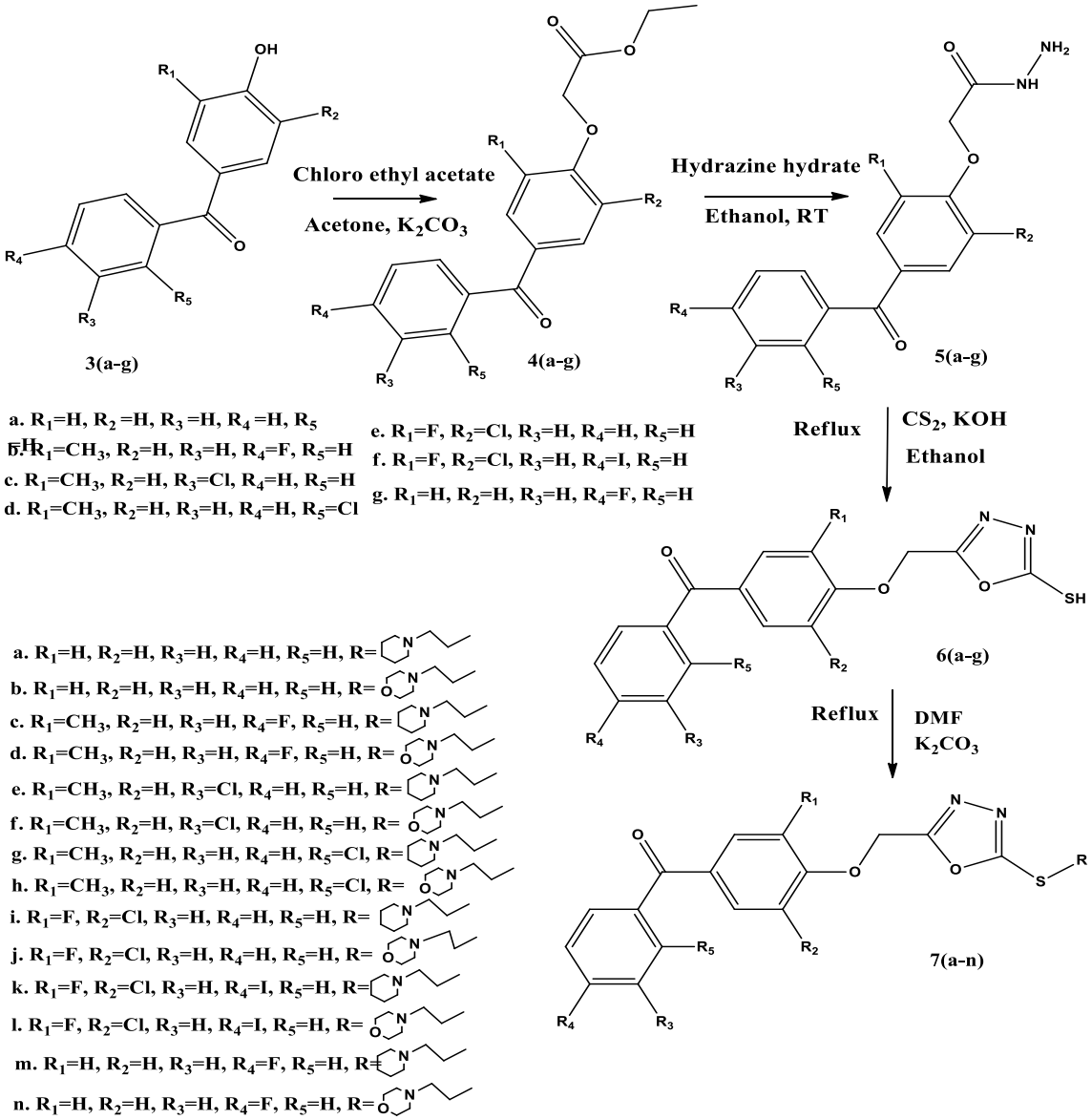
To a mixture of substituted hydroxy benzophenones 3a–g (0.05 mol) and chloro ethyl acetate (0.075 mol) in dry acetone (40 ml), anhydrous potassium carbonate (0.075 mol) was added and were refluxed for 8–10 h. The reaction mixture was cooled and solvent removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate, and extracted with ether (3 × 30 ml). The ether layer was washed with 10% sodium hydroxide solution (3 × 30 ml) followed by water (3 × 30 ml) and then dried over anhydrous sodium sulphate and evaporated to afford compounds 4a–g. Compound 4a is taken as a representative example to explain characterization data.

2.1.4 Synthesis of (4-benzoyl phenoxy)-acetic acid ester (4a)

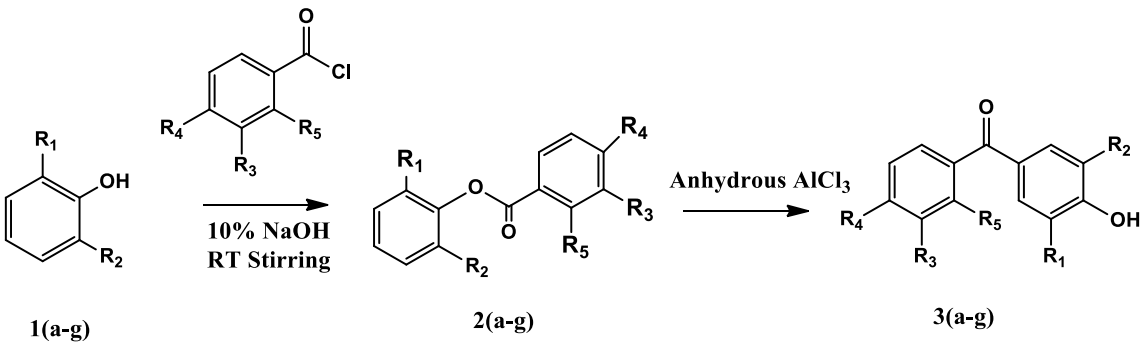
Yield: 93%. M.P: 52–54 °C. IR (KBr) vmax (cm^{-1}): 1672 (C=O), 1719 (ester, C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, 3H, CH_3 of ester), 4.21 (q, 2H, CH_2 of ester), 5.01 (s, 2H, OCH_2), 6.81–7.85 (m, 9H, Ar–H). ^{13}C-NMR ($CDCl_3$): δ 14.5, 61.15, 65.8, 115.3, 129.08, 131.8, 132.1,133.3, 133.9, 139.4, 161.7, 169.8, 194.6; LC–MS *m/z* 285 (M + 1). Elemental Analysis: Cal. for $C_{17}H_{16}O_4$ (212): C, 72.22; H, 5.70. Found: C, 72.20; H, 6.16%.

2.1.5 General protocol for the synthesis of (4-benzoyl phenoxy)-acetic acid hydrazide derivatives (5a–g)

To the solution of ester analogs 4a–g (0.05 mol) in ethanol (20 ml), hydrazine hydrate (0.06 mol) was added and the reaction mixture was stirred at room temperature for 5–6 h.



Scheme 1 Synthesis of oxadiazole conjugated benzophenone derivatives



Scheme 2 Synthesis of benzophenone derivatives

Reaction completion was monitored by thin layer chromatography using hexane:ethylacetate (3:1) solvent mixture and the reaction mixture was allowed to stand overnight. The white crystals 5a–g formed were filtered, washed and after drying recrystallized from ethanol. Compound 5a is taken as a representative example to explain characterization data [32].

2.1.6 Synthesis of (4-benzoyl phenoxy)-acetic acid hydrazide (5a)

Yield 92%; M.P: 115–117 °C; FT-IR (KBr, cm^{-1}): 3318 (NH_2), 3230 (NH), 1675 (amide, C=O), 3240–3350 (NH-NH); 1642 (C=O); ^{1}H NMR ($CDCl_3$): δ 3.86 (d, 2H, NH_2), 5.09 (s, 2H, OCH_2), 8.46 (t, 1H, NH), 6.81–7.85 (m, 9H, Ar–H). ^{13}C-NMR ($CDCl_3$): δ 65.9, 116.3, 129.78, 131.6, 132.3, 133.6, 133.9, 132.4, 161.7, 169.8, 194.9; LC–MS *m/z* 271 (M + 1). Elemental Analysis: Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.89; H, 5.52; N, 10.96. Found: C, 66.78; H, 5.56; N, 10.08%.

2.1.7 General procedure for the synthesis of (4-benzoyl phenoxy)-[1,3,4]oxadiazole-2-thiol derivatives (6a–g)

A mixture of hydrazide analogs 5a–g (3 mmol), carbon disulfide (3 ml) and potassium hydroxide (6 mmol) in ethanol (60 ml) was refluxed till evolution of hydrogen sulfide was ceased. Afterwards the reaction mixture was cooled to room temperature. The solvent was removed at reduced pressure, poured to cold water and acidified with dil HCl solution to precipitate [1,3,4]oxadiazole-2-thiol derivatives by bringing the pH between 3 and 4. The precipitate thus separated out was allowed to stand overnight, filtered, washed, dried and recrystallized from acetone. Compound 6a is taken as a representative example to explain characterization data [33].

2.1.8 Synthesis of (4-benzoyl phenoxy)-[1,3,4] oxadiazole-2-thiol (6a)

Yield 84%; M.P: 140–142 °C; FT-IR (KBr, cm^{-1}): 1612 (C = N), 2557 (SH), 1164 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 5.05 (s, 2H, OCH_2), 6.95 (d, *J* = 8.80 Hz, 2H, Ar–H), 7.32 (d, *J* = 8.85 Hz, 2H, Ar–H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), 10.72 (s, 1H, SH); LC–MS m/z 243 (M + 1). Elemental Analysis: Calcd. for $C_9H_7N_2O_2S$: C, 44.54; H, 2.91; N, 11.54. Found: C, 44.70; H, 2.82; N, 11.65.

2.1.9 General synthetic procedure for [(4-benzoyl phenoxy)-[1,3,4] oxadiazol-2-ylsulfanyl)-ethyl]-morpholine/piperidine derivatives (7a–n)

A mixture of 1,3,4 oxadiazole-2-thiol derivatives 6a–g (1 mmol), 4-(2-chloroethyl) morpholine/piperidine hydrochloride (3 mmol) and anhydrous potassium carbonate (3 mmol) in DMF (30 ml) was refluxed for 10–15 h. After completion of the reaction, the reaction mixture was cooled down, excess of solvent was evaporated under reduced pressure. The residual crude was poured into crushed ice to precipitate the desired target compound as potassium carbonate is highly soluble in water.

2.1.10 Synthesis of Phenyl(4-((5-((2-(piperidin-1-yl) ethyl)thio)-1,3,4-oxadiazol-2-yl)methoxy) phenyl) methanone (7a)

Yield 88%; M.P: 58–60 °C; FT-IR (KBr, cm^{-1}): 1654 (C=O), 1333 (C = N), 1272 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.52 (t, 4H, CH_2NCH_2 of piperidine ring), 2.74 (t, 2H, N CH_2), 3.44 (t, 2H, CH_2S), 1.54 (m, 4H, CH_2CH_2 of piperidine ring), 1.44 (t, 2H, CH_2 of piperidine ring), 5.12 (s, 2H, OCH_2), 6.81–7.85 (m, 9H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 24.66, 26.2, 30.7, 56.8, 57.80, 71.99, 114.2, 128.8, 130.6, 130.8, 131.6, 132.6, 138.9, 160.1, 162.9, 163.5, 194.7; LC–MS m/z 424 $(M + 1)^+$. Elemental Analysis: Calcd. for $C_{23}H_{25}N_3O_3S$: C, 65.23; H, 5.95; N, 9.92; S, 7.57%. Found: C, 65.29; H, 5.90; N, 9.98; S, 7.67%.

2.1.11 Synthesis of (4-((5-((2-morpholinoethyl) thio)-1,3,4-oxadiazol-2-yl)methoxy) phenyl) methanone (7b)

Yield 85%; M.P: 63–66 °C; FT-IR (KBr, cm^{-1}): 1650 (C=O), 1338 (C = N), 1278 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.46 (t, 4H, CH_2NCH_2 of morpholine ring), 2.65 (t, 2H, NCH_2), 3.41 (t, 2H, CH_2S), 3.59 (t, 4H, CH_2OCH_2 of morpholine ring), 5.22 (s, 2H, OCH_2), 6.71–7.95 (m, 9H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 30.9, 55.9, 57.9, 56.8, 57.80, 71.99, 114.2, 128.8, 130.6, 130.8, 131.6, 132.6, 138.9, 160.1, 162.9, 163.5, 194.7; LC–MS m/z 426 $(M + 1)^+$. Anal. Calcd. for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.45; N, 9.88; S, 7.54%. Found: C, 62.29; H, 5.50; N, 9.99; S, 7.65%.

2.1.12 Synthesis of (4-fluorophenyl){3-methyl-4-[(5-((2-(piperidin-1-yl)ethyl)thio)-1,3,4-oxadiazole-2-yl) methoxy] phenyl}methanone (7c)

Yield 84%; M.P: 54–58 °C; FT-IR (KBr, cm^{-1}): 1652 (C=O), 1330 (C=N), 1270 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.59 (t, 4H, CH_2NCH_2 of piperidine ring), 2.79 (t, 2H, N CH_2), 3.47 (t, 2H, CH_2S), 1.59 (m, 4H, CH_2CH_2 of piperidine ring), 1.48 (t, 2H, CH_2 of piperidine ring), 5.18 (s, 2H, OCH_2), 6.90–7.95 (m, 7H,

Ar–H); ^{13}C-NMR ($CDCl_3$): δ 15.6, 24.66, 25.9, 30.4, 56.9, 57.6, 71.9, 113.6, 115.6, 124.5, 128.28, 131.7, 131.9, 133.8, 134.4, 160.2, 162.9, 163.5, 166.54, 194.3; LC–MS m/z 456 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{24}H_{26}FN_3O_3S$: C, 63.28; H, 5.75; F, 4.17; N, 9.22; S, 7.04% Found: C, 64.29; H, 5.80; F, 4.19 N, 9.28; S, 7.07%.

2.1.13 Synthesis of 4-(fluorophenyl) {3-methyl-4-[(5-((2-morpholinoethyl) thio)-1,3,4oxadiazol-2-yl) methoxy] phenyl} methanone (7d)

Yield 83%; M.P: 49–52 °C; FT-IR (KBr, cm^{-1}): 1651 (C=O), 1340 (C=N), 1280 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.48 (t, 4H, CH_2NCH_2 of morpholine ring), 2.69 (t, 2H, NCH_2), 3.48 (t, 2H, CH_2S), 3.64 (t, 4H, CH_2OCH_2 of morpholine ring), 5.36 (s, 2H, OCH_2), 6.88–7.97 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 15.7, 30.9, 55.9, 57.9, 66.9, 72.4, 113.9, 115.8, 124.9, 128.3, 132.4, 132.9, 134.4, 135.1, 160.2, 163.2, 164.5, 166.64, 195.3; LC–MS m/z 458 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{23}H_{24}FN_3O_4S$: C, 60.38; H, 5.29; F, 4.15; N, 9.18; S, 7.01%. Found: C, 60.29; H, 5.40; F, 4.45; N, 9.19; S, 7.05%.

2.1.14 Synthesis of (2-chlorophenyl)(3-methyl-4-((5-((2 -(piperidin-1-yl)ethyl)thio)-1,3,4 oxadiazol-2-yl) methoxy) phenyl) methanone (7e)

Yield 81%; M.P: 58–60 °C; FT-IR (KBr, cm^{-1}): 1658 (C=O), 1337 (C=N), 1275 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.53 (t, 4H, CH_2NCH_2 of piperidine ring), 2.74 (t, 2H, N CH_2), 3.43 (t, 2H, CH_2S), 1.75 (m, 4H, CH_2CH_2 of piperidine ring), 1.52 (t, 2H, CH_2 of piperidine ring), 5.3 (s, 2H, OCH_2), 7.29–8.69 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 15.8, 24.7, 25.7, 30.7, 56.8, 57.5, 71.7, 113.8, 115.7, 124.8, 128.4, 131.9, 132.3, 134.8, 139.4, 160.2, 162.9, 163.5, 166.54, 198.3; LC–MS m/z 472 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{24}H_{26}ClN_3O_3S$: C, 61.28; H, 5.55; Cl, 7.57; N, 8.92; S, 7.04% Found: C, 62.29; H, 5.70; Cl, 7.67; N, 8.28; S, 7.07%.

2.1.15 Synthesis of (2-chlorophenyl) {3-methyl-4-[(5-((2-morpholinoethyl) thio)-1,3,4-oxadiazol-2-yl) methoxy]phenyl} methanone (7f)

Yield 89%; M.P: 51–55 °C; FT-IR (KBr, cm^{-1}): 1656 (C=O), 1346 (C=N), 1286 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.49 (t, 4H, CH_2NCH_2 of morpholine ring), 2.66 (t, 2H, NCH_2), 3.44 (t, 2H, CH_2S), 3.66 (t, 4H, CH_2OCH_2 of morpholine ring), 5.34 (s, 2H, OCH_2), 6.99–7.97 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 15.7, 30.9, 55.9, 57.9, 66.9, 72.4, 113.9, 115.8, 124.9, 128.3, 132.4, 132.9, 134.8, 139.1, 160.2, 163.2, 164.5, 166.64, 195.3; LC–MS m/z 474 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{23}H_{24}ClN_3O_4S$: C, 58.38; H, 5.29; Cl, 7.45; N, 9.18; S, 6.71%. Found: C, 58.29; H, 5.40; Cl, 7.49; N, 9.19; S, 6.85%

2.1.16 Synthesis of (2-chlorophenyl){3-methyl-4-[(5-((2 -(piperidin-1-yl)ethyl)thio)-1,3,4-oxadiazol-2-yl) methoxy] phenyl} methanone (7g)

Yield 80%; M.P: 54–56 °C; FT-IR (KBr, cm^{-1}): 1654 (C=O), 1334 (C=N), 1279 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.53 (t, 4H, CH_2NCH_2 of piperidine ring), 2.77 (t, 2H, N CH_2), 3.48 (t, 2H, CH_2S), 1.76 (m, 4H, CH_2CH_2 of piperidine ring), 1.54 (t, 2H, CH_2 of piperidine ring), 5.33 (s, 2H, OCH_2), 7.55–8.65 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 15.7, 24.9, 25.8, 30.9, 56.4, 57.9, 71.6, 113.8, 124.8,126.8, 128.4, 128.7, 129.9, 131.9, 131.3, 133.8, 136.5, 139.4, 160.2, 162.9, 163.5, 198.3; LC–MS m/z 472 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{24}H_{26}ClN_3O_3S$: C, 61.28; H, 5.55; N, 8.92; S, 7.04% Found: C, 62.29; H, 5.70; N, 8.28; S, 7.07%.

2.1.17 Synthesis of (2-chlorophenyl) {3-methyl-4-[(5-((2-morpholinoethyl) thio)-1,3,4-oxadiazol-2-yl) methoxy]phenyl} methanone (7h)

Yield 89%; M.P: 49–52 °C; FT-IR (KBr, cm^{-1}): 1656 (C=O), 1346 (C=N), 1286 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.42 (t, 4H, CH_2NCH_2 of morpholine ring), 2.63 (t, 2H, NCH_2), 3.44 (t, 2H, CH_2S), 3.66 (t, 4H, CH_2OCH_2 of morpholine ring), 5.34 (s, 2H, OCH_2), 6.99–7.97 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 15.5, 30.6, 55.5, 57.6, 66.7, 72.1, 113.4, 124.95, 126.7, 128.7, 128.5,129.9, 131.4, 131.9, 133.8, 136.4, 139.1, 160.2, 162.2, 163.5, 195.5; LC–MS m/z 474 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{23}H_{24}ClN_3O_4S$: C, 58.38; H, 5.29; N, 9.18; S, 6.71%. Found: C, 58.29; H, 5.40; N, 9.19; S, 6.85%.

2.1.18 Synthesis of phenyl{3-chloro-5-fluoro-4-[- (5-((2-(piperidin-1-yl)ethyl) thio)-1,3,4-oxadiazol-2-yl) methoxy]phenyl} methanone (7i)

Yield 80%; M.P: 52–56 °C; FT-IR (KBr, cm^{-1}): 1654 (C=O), 1334 (C=N), 1279 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.53 (t, 4H, CH_2NCH_2 of piperidine ring), 2.79 (t, 2H, N CH_2), 3.52 (t, 2H, CH_2S), 1.98 (m, 4H, CH_2CH_2 of piperidine ring), 1.65 (t, 2H, CH_2 of piperidine ring), 5.67 (s, 2H, OCH_2), 7.67–8.75 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 24.8, 25.4, 30.6, 56.4, 57.9, 71.2, 114.4, 123.8,126.4, 128.9, 130.4, 132.9, 135.5, 138.4, 153.4, 153.6, 160.2, 163.5, 195.3; LC–MS m/z 476 $(M+1)^+$. Anal. Calcd. for $C_{23}H_{23}ClFN_3O_3S$: C, 58.28; H, 4.85; N, 8.82; S, 6.74% Found: C, 58.29; H, 4.70; N, 8.88; S, 6.77%.

2.1.19 Synthesis of phenyl {3-chloro-5-fluoro-4-[(5-((2-morpholinoethyl) thio)-1,3,4-oxadiazol-2-yl) methoxy]phenyl} methanone (7j)

Yield 84%; M.P: 59–62 °C; FT-IR (KBr, cm^{-1}): 1660 (C=O), 1344 (C=N), 1283 (C–O–C); ^{1}H NMR ($CDCl_3$):δ 2.47 (t, 4H, CH_2NCH_2 of morpholine ring), 2.73 (t, 2H, NCH_2), 3.54 (t, 2H, CH_2S), 3.76 (t, 4H, CH_2OCH_2 of morpholine ring), 5.69 (s, 2H, OCH_2), 7.97–8.95 (m, 7H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 30.6, 55.5, 57.6, 66.7, 71.5, 114.6, 123.6,126.8, 128.4, 130.9, 132.7, 135.6, 138.8, 153.1, 153.3, 160.2, 163.6, 195.6; LC–MS m/z 478 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{22}H_{21}ClFN_3O_4S$: C, 55.38; H, 4.66; N, 8.72; S, 6.74% Found: C, 55.29; H, 4.70; N, 8.88; S, 6.77%.

2.1.20 Synthesis of (4-iodophenyl){3-chloro-5-fluoro-4-[(5-((2-(piperidin-1-yl)ethyl)thio)-1,3,4-oxadia-zol-2-yl) methoxy]phenyl}methanone (7k)

Yield 79%; M.P: 54–57 °C; FT-IR (KBr, cm^{-1}): 1654 (C=O), 1334 (C=N), 1279 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.63 (t, 4H, CH_2NCH_2 of piperidine ring), 2.70 (t, 2H, N CH_2), 3.55 (t, 2H, CH_2S), 1.99 (m, 4H, CH_2CH_2 of piperidine ring), 1.75 (t, 2H, CH_2 of piperidine ring), 5.77 (s, 2H, OCH_2), 7.69–8.89 (m, 6H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 24.8, 25.4, 30.6, 56.6, 57.6, 71.2,98.3, 114.8, 123.9,126.8, 131.9, 135.9, 137.5, 137.9, 153.4, 153.6, 160.2, 163.6, 194.3; LC–MS m/z 602 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{23}H_{22}ClFIN_3O_3S$: C, 45.98; H, 3.68; N, 6.98; S, 5.33% Found: C, 45.99; H, 3.70; N, 6.95; S, 5.44%.

2.1.21 Synthesis of (4-iodophenyl) {3-chloro-5-fluoro-4-[(5-((2-morpholinoethyl) thio)-1,3,4-oxadiazol-2-yl)meth-oxy] phenyl} methanone (7l)

Yield 84%; M.P: 56–59 °C; FT-IR (KBr, cm^{-1}): 1659 (C=O), 1344 (C=N), 1289 (C–O–C); ^{1}H NMR ($CDCl_3$):δ 2.47 (t, 4H, CH_2NCH_2 of morpholine ring), 2.73 (t, 2H, NCH_2), 3.54 (t, 2H, CH_2S), 3.76 (t, 4H, CH_2OCH_2 of morpholine ring), 5.69 (s, 2H, OCH_2), 7.97–8.95 (m, 6H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 30.6, 55.6, 57.7, 66.9, 71.2,98.7, 114.3, 123.3,126.3, 131.6, 135.3, 137.6, 137.8, 153.3, 153.8, 160.2, 163.8, 194.7; LC–MS *m/z* 604 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{22}H_{20}ClFIN_3O_4S$: C, 55.38; H, 4.66; N, 8.72; S, 6.74% Found: C, 55.29; H, 4.70; N, 8.88; S, 6.77%.

2.1.22 Synthesis of (4-fluorophenyl) {4-[(5-((2-(piperidin-1-yl)ethyl) thio)-1,3,4-oxadiazole-2-yl) methoxy] phenyl} methanone (7m)

Yield 83%; M.P: 54–58 °C; FT-IR (KBr, cm^{-1}): 1652 (C=O), 1330 (C=N), 1270 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.59 (t, 4H, CH_2NCH_2 of piperidine ring), 2.79 (t, 2H, N CH_2), 3.47 (t, 2H, CH_2S), 1.59 (m, 4H, CH_2CH_2 of piperidine ring), 1.48 (t, 2H, CH_2 of piperidine ring), 5.18 (s, 2H, OCH_2), 6.90–7.95 (m, 8H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 24.66, 25.9, 30.4, 56.9, 57.6, 71.9, 113.6, 114.6, 115.6, 130.4, 131.4, 133.7, 134.4, 160.2, 162.4, 163.5, 166.54, 194.3; LC–MS m/z 442 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{23}H_{24}FN_3O_3S$: C, 62.28; H, 5.85; N, 9.82; S, 7.24%. Found: C, 62.29; H, 5.88; N, 9.98; S, 7.37%.

2.1.23 Synthesis of 4-(fluorophenyl) {4-[(5-((2-morpholinoethyl) thio)-1,3,4-oxadiazol-2-yl) methoxy] phen yl} methanone (7n)

Yield 82%; M.P: 55–59 °C; FT-IR (KBr, cm^{-1}): 1677 (C=O), 1334 (C=N), 1267 (C–O–C); ^{1}H NMR ($CDCl_3$): δ 2.48 (t, 4H, CH_2NCH_2 of morpholine ring), 2.69 (t, 2H, NCH_2), 3.48 (t, 2H, CH_2S), 3.64 (t, 4H, CH_2OCH_2 of morpholine ring), 5.36 (s, 2H, OCH_2), 6.88–7.97 (m, 8H, Ar–H); ^{13}C-NMR ($CDCl_3$): δ 30.9, 55.9, 57.9, 66.9, 72.4,113.7, 114.8, 115.7, 130.5, 131.3, 133.8, 134.4, 160.2, 162.4, 163.3, 166.5, 194.5;LC–MS m/z 444 $(M+1)^+$. Elemental Analysis: Calcd. for $C_{22}H_{22}FN_3O_4S$: C, 59.68; H, 5.09; N, 9.28; S, 7.21%. Found: C, 59.79; H, 5.10; N, 9.29; S, 7.25%.

3 Biology

3.1 Anticancer activity studies using MTT Assay

The cell lines used for the study were MCF-7 (Breast cancer), KB (Oral cancer), L929 (normal cell line for cytotoxicity) procured from NCCS, Pune. The cell lines were maintained in 96 wells micro titer plate containing DMEM media with low glucose supplemented with 10% heat inactivated fetal bovine serum (FBS), and 1% antibiotic–antimycotic 100X solution and incubated in CO_2 incubator at 37°C in 5% CO_2 and 95% humidity until the completion of reaction.

The cells were seeded at a density of approximately 5×10^3 cells/well in a 96-well flat-bottom micro plate and maintained at 37 °C in 95% humidity and 5% CO_2 for overnight. Different concentrations (500, 250, 125, 62.5, 31.25, 15.625 µg/mL) of samples were treated. The cells were incubated for another 48 h. The cells in well were washed twice with phosphate buffer solution, and 20 µL of the MTT staining solution (5 mg/ml in phosphate buffer solution) was added to each well and plate was incubated at 37 °C. After 4 h, 100 µL of di-methyl sulfoxide (DMSO) was added to each well to dissolve the formazan crystals, and absorbance was recorded with a 570 nm using micro plate reader [34]. Statistical analysis of the data was performed on *GraphPad Prism*. All the experiments were conducted in triplicate. Surviving cells (%) = mean OD of test compound/

mean OD of Negative control × 100. Using graph Pad Prism Version 5.1, the IC_{50} of compounds were calculated.

3.1.1 In-vitro cytotoxicity assay

Toxicity of the most active compounds (7f, 7g and 7h) was determined on the basis of measurement of in-vitro growth of the normal cell line (L292) using MTT assay [35]. The IC_{50} values (50% inhibitory concentration) were calculated. In vitro growth inhibition effect of test compounds was assessed by MTT assay by the normal cell line L929 (procured from NCCS, Pune).

4 Results and discussion

4.1 Chemistry

The synthetic protocol of the title compounds **7a–n** is outlined in the Scheme 1. Initially, the benzoylated products **2a–g** were prepared by the benzoylation of substituted phenols **1a–g** with substituted benzoyl chlorides. In the presence of anhydrous aluminium chloride, the compounds **2a–g** have undergone Fries rearrangement, to afford hydroxy benzophenones **3a–g**, which were established by the disappearance of the carbonyl stretching band of the ester group and appearance of the –OH stretching band in IR spectra and also, the appearance of broad singlet for –OH proton and decrease in one aromatic proton in ^{1}H NMR spectra. The compounds, benzoyl phenoxy acetic acid ethyl esters, **4a–g** were obtained by refluxing substituted 3**a–g** with ethyl chloro acetate and were evidenced by the loss of –OH stretching and emergence of carbonyl stretching band for the ester group in the IR absorption spectra. The ^{1}H NMR confirmed the disappearance of broad singlet for –OH group and an appearance of triplet and quartet for $–CH_3$ and $–CH_2$ protons respectively. Upon treating the compounds **4a–g** with hydrazine hydrate, phenoxy-acetic acid hydrazide analogues **5a–g** were obtained, which were confirmed by the appearance of $–NH_2$ stretching band of amide in the IR spectrum. The appearance of the peaks for $–NH_2$ and –NH protons and concealing of triplet and quartet peaks for $–CH_3$ and $–CH_2$ protons respectively in ^{1}H NMR, confirmed the formation of the product. Upon cyclization of acid hydrazide analogues **5a–g** with carbon disulfide in the presence of KOH, claimed the corresponding 1,3,4-oxadiazol-2-thiol **6a–g**, which clearly evident with the absence of carbonyl and $–NH_2$ stretching bands in the IR spectra. The presence of –SH proton and the absence of $–NH_2$ and –NH protons of amide in the NMR spectrum also confirmed the product. Finally, the title compounds **7a–n** were obtained by alkylation of benzophenone tagged 1,3,4-oxadiazol-2-thiol derivatives **6a–g** with 4-(2-chloroethyl) morpholine/piperidine hydrochloride in boiling DMF with fused potassium carbonate. This was validated by the disappearance of SH stretching in the IR spectrum and also the disappearance of –SH proton and appearance of methylene protons of morpholine/piperidine in the ^{1}H NMR spectra. Further, the mass spectral data of these compounds displayed molecular ion peaks which confirmed their molecular weights.

4.1.1 Biological activity

The synthesized unique molecules play a prime role in the development of multi target drugs with target precise action. Novel heterocyclic compounds were synthesized with benzophenone and oxadiazole cores as backbones with nucleophillic alkylation of heterocyclic analogs.

4.1.2 Structure activity relationship (SAR)

4.1.2.1 Anti-cancer study Anti-cancer activity was studied by MTT assay. The cytotoxicity of the synthesized title compounds in two different cancer cell lines MCF-7 (Breast cancer) and KB (Oral cancer) had been executed in comparison with standard paclitaxel by MTT assay and images of MCF-7 cell line and KB cell line photographed by Phase Contrast Microscope are shown in Fig. 1. The title compounds induced a cytotoxic effect in a concentration-dependent manner. The IC_{50} values of each compound were calculated and are summarized in Table 1.

In the series, compound **7h**, with one methyl group on the phenoxy ring and one chlorine group on the ortho position of the benzoyl ring, conjugated to morpholine, executed potent activity by inducing minimum viability at inhibitory concentrations of 112.6 µg/ml and 126.7 µg/ml, against the MCF-7 cell line and KB cell line respectively under identical experimental conditions. Followed by Compound **7f** with one methyl group on the phenoxy ring and one 3-position chlorine group on the benzoyl ring, conjugated to morpholine, exhibited IC_{50} values 113.8 µg/ml and 127.0 µg/ml against the MCF-7 cell line and KB cell line respectively by inducing approximately minimum viability, which was nearly potent to compound **7h**.

Compounds **7c, 7g** and **7k** showed moderate activity, whereas compounds **7a, 7e** and **7m** showed less sensitivity. Compound **7n** with one fluorine group on the benzoyl ring, exhibited highest IC_{50} values 425.5 µg/ml and 289.4 µg/ml against the MCF-7 cell line and KB cell line respectively by inducing maximum viability, which was least potent under identical experimental conditions. Importantly, this compound does not contain a chlorine group. The graphs of percentage of cell viability versus different concentrations of each compound against KB and MCF-7 cell lines are shown in Fig. 2.

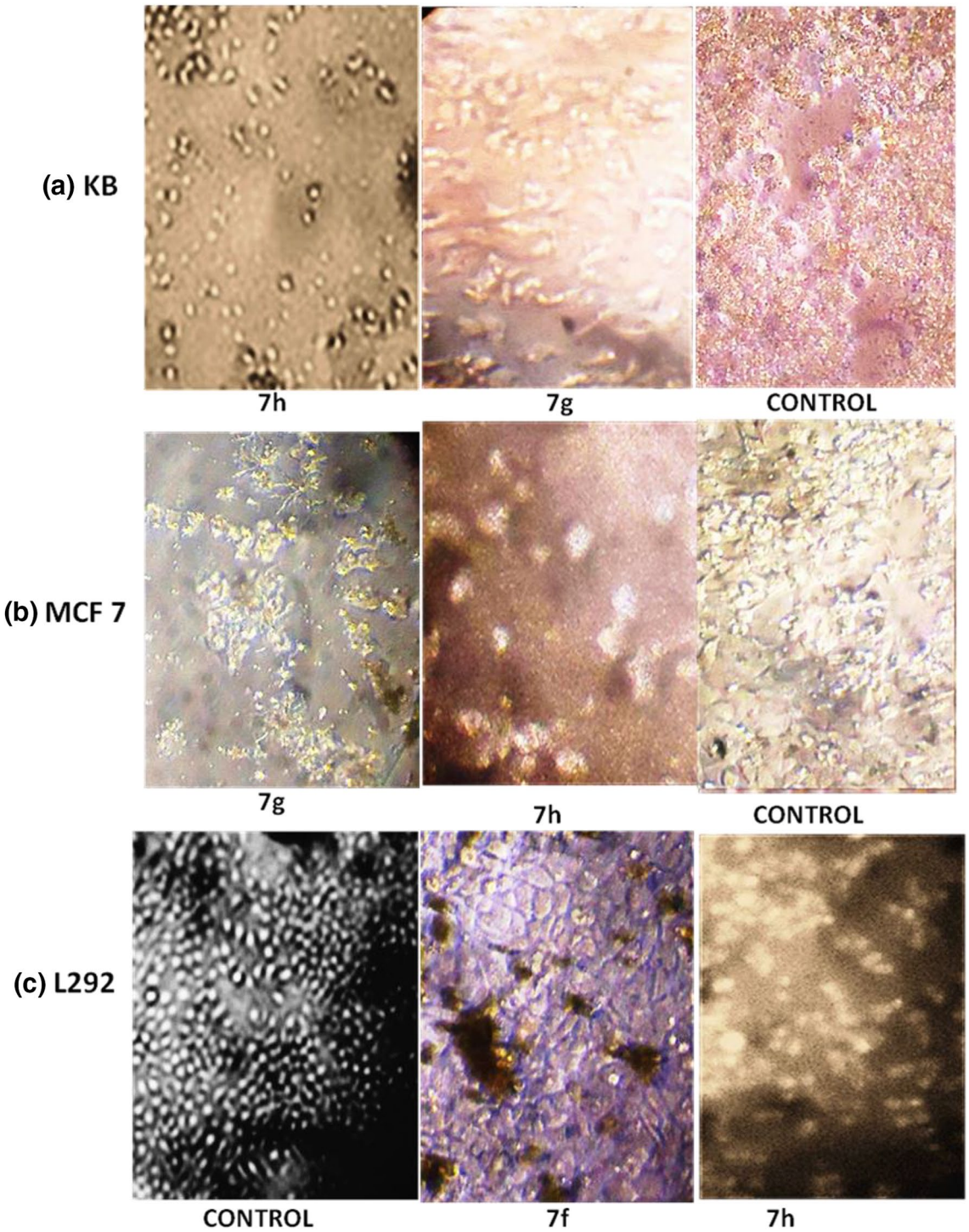


Fig. 1 Anticancer and cytotoxicity activity assay was performed by MTT assay. **a** Photographs of KB cell line at various concentrations**.** Compound **7h** at 125 µg/ml, compound **7g** at 62.5 µg/ml, control. **b** Photographs of MCF 7 cell line at various concentrations. Compound **7g** at 125 µg/ml, compound **7h** at 125 µg/ml, control. **c** Photographs of L292 cell line at various concentrations. Control, compound **7f** at 250 µg/ml, compound **7h** at 250 µg/ml

Table 1 IC_{50} value of compounds in µg/ml

Compound	MCF-7		KB	
	µg/ml	µM	µg/ml	µM
7a	423.5	1.001	149.5	0.353
7b	163.5	0.384	133.6	0.314
7c	176.0	0.386	128.8	0.283
7d	122.4	0.267	169.6	0.371
7e	209.3	0.46	127.7	0.280
7f	113.8	0.241	127.0	0.268
7g	119.8	0.254	139.0	0.295
7h	112.6	0.238	126.7	0.267
7i	174.8	0.368	132.5	0.278
7j	176.4	0.369	163.5	0.342
7k	148.3	0.246	131.3	0.218
7l	174.8	0.289	282.6	0.468
7m	412.5	0.935	155.6	0.352
7n	425.4	0.960	289.4	0.653
Paclitaxel	298.86	0.35	273.25	0.32

4.1.3 In-vitro cytotoxicity assay

Cytotoxicity assay of the selected compounds on the viability of normal cell lines was satisfactory. The selected compounds are screened based on their better activities on the above discussed in vitro MTT assay against MCF-7 cell line and KB cell line. The synthesized compounds **7f, 7g** and **7h** were most active and hence toxicity towards the normal cell line (L292) was evaluated by MTT assay. From the experimental data (Table 2), it is revealed that, all the selected compounds were non-toxic to the normal cells at higher concentration with IC_{50} value > 193 µg/ml. These compounds showed the anti-cancer activity at IC_{50} values 113.8–119.8 µg/ml and 126.7–139 µg/ml against the MCF-7 cell line and KB cell line respectively. Minimum toxicity is the major advantage of the synthesized benzophenone derivatives.

Table 2 IC_{50} values of oxadiazole analogs against normal cell line

Compounds	Cytotoxicity (IC_{50}) against normal cells (µg/ml)
7f	201.3 ± 1.4
7g	193.3 ± 1.7
7h	256.7 ± 0.6
PC	298.6 ± 0.5

Data represented in mean ± SD of three experiments. Positive control: cisplatin

Compound **7h** acts as an eminent compound by exhibiting an excellent efficacy in vitro anti-cancer experiment. Structurally, compound **7h** has morpholine group (six membered ring) attached to oxadiazole through two CH_2 groups, methyl substituent at ortho-position of the phenoxy ring and chlorine group at ortho-position of

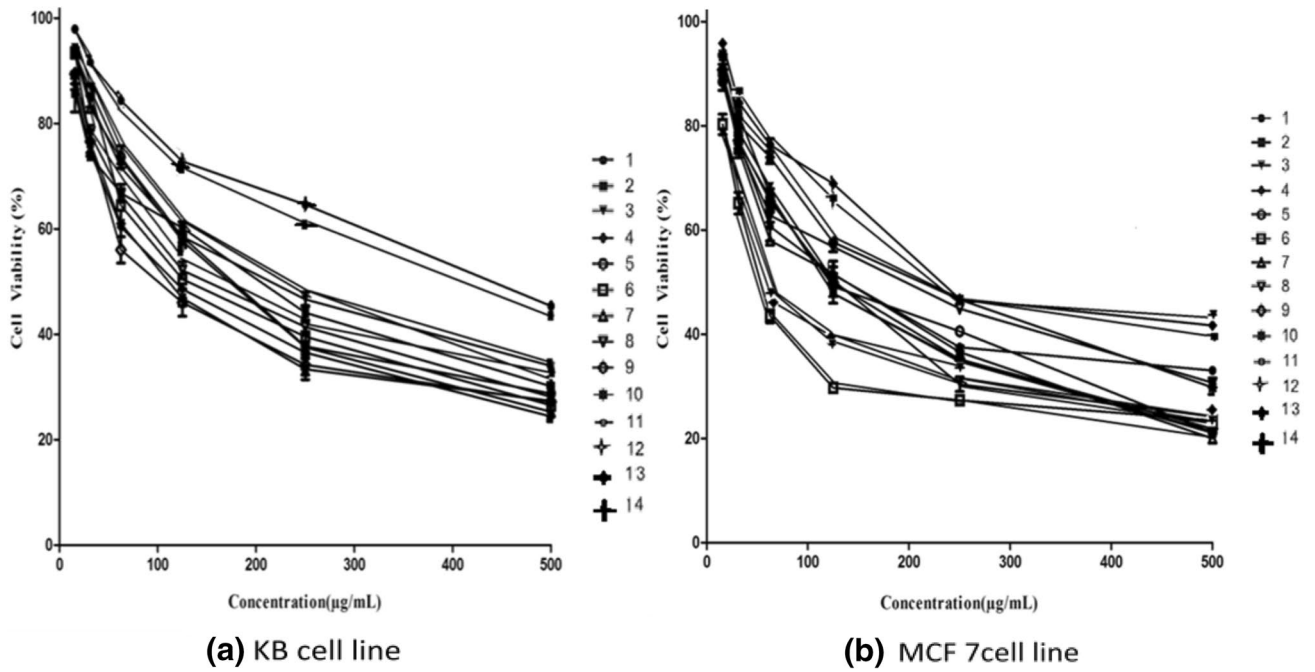


Fig. 2 **a** Graph of MTT Assay of the synthesized compounds of anti-cancer activity on KB cell line. **b** Graph of MTT Assay of the synthesized compounds of Anti-cancer activity on MCF 7 cell line

benzoyl ring which showed a significant cytotoxic effect, with enhancement in the IC_{50} values, as verified by an MTT assay.

5 Conclusion

In the present study, we synthesized analogs of oxadiazolyl benzophenone **(7a–n)** which vary in the number and position of the methyl and halogen groups on the benzophenone moiety, which were then evaluated for their *anti cancer* activity. IC_{50} values for anticancer activity were 112.6 and 126.7 µg/ml, against the MCF-7 cell line and KB cell line respectively by MTT assay method. In the series of the synthesized compounds, compound containing the electron withdrawing group, along with sufficient hetero atom rich compound showed more activity. In general, the activity of the compound is influenced by the chemical structure, size & shape, molecular arrangements, and electron donating/withdrawing groups, etc.

The structure–activity relationship study reveals that, the compounds with morpholine moiety, exhibited better activity than piperidine scaffolds. All the compounds having morpholine group with chlorine substitution at 2-position on benzoyl ring showed superior potency. Incorporation of morpholine and piperidine nuclei to the benzophenone skeleton has enhanced the bioactivity of the synthesized compounds to be recognized as a drug. Structure–activity relation interrelates the biological potency and chemical scaffold of the molecule.

5.1 Statistical analysis

The values of antioxidant activity are expressed as mean ± standard deviation. The inhibition zone was measured from the antimicrobial activity of compound and analyzed using one way analysis of variance (ANOVA) followed by Tukey's test at $p < 0.05$. The software Origin Pro 9.0 was employed for the statistical analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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