Supplementary Information

Synthesis of New 1,2,3-Triazolo-naphthalimide/phthalimide Conjugates via ‘Click’ Reaction: DNA Intercalation and Cytotoxic Studies

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Experimental

General methods

All reagents and solvents were obtained from commercial suppliers and were used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60-F254 (0.5 mm) aluminum plates. Visualization of the spots on TLC plates was achieved by UV light. ¹H and ¹³C NMR spectra were recorded on Varian Gemini 200 or Varian Unity 400 or Varian Inova 500 or Bruker Avance 300 MHz, making a solution of samples in CDCl₃ solvent using tetramethylsilane (TMS) as the internal standard. Chemical shifts for ¹H and ¹³C are reported in parts per million (ppm) downfield from tetramethylsilane. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). Coupling constant (J) values are reported in hertz (Hz). HRMS were determined with Agilent QTOF mass spectrometer 6540 series instrument. Wherever required, column chromatography was performed using silica gel (60-120 or 100-200) or neutral alumina. The anhydrous reactions are carried under nitrogen positive pressure using freshly distilled solvents. All evaporation of solvents was carried out under reduced pressure on Heidolph rotary evaporator below 45 °C.

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General procedure for the synthesis of 1,2,3-triazolo based naphthalimide/phthalimide conjugates (6a-x and 7a-c)

Various bromides 3a-c, 4 (1.0 mmol), NaN₃ (1.0 mmol) and N/O-linked terminal alkynes (1.0 mmol) were added to a solution of the catalyst (2.0 mol%) in water (3 mL). The reaction mixture was stirred at room temperature for 4 h, until all the starting materials disappear as observed by TLC. Later, the reaction mixture was extracted with EtOAc (2 × 10 mL) and the combined organic phase was washed with water (2 × 10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue obtained after evaporation contained the crude product and was purified by column chromatography.

2-(4-{[(3,4,5-Trimethoxyphenoxy)methyl]-1H-1,2,3-triazol-1-yl}butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6a)

White solid, yield 87%; mp 163-165 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.53 (d, J 8.36 Hz, 2H), 8.24 (d, J 7.54 Hz, 2H), 7.85 (t, J 7.54 Hz, 2H), 7.72 (s, 1H), 6.31 (s, 2H), 5.12 (s, 2H), 4.54 (t, J 7.54 Hz, 2H), 4.26 (t, J 7.54 Hz, 2H), 3.83 (s, 6H), 3.71 (s, 3H), 2.23-1.97 (m, 2H), 1.83-1.78 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 164.0, 154.6, 153.4, 153.3, 143.6, 133.8, 132.2, 131.2, 131.0, 127.8, 126.6, 122.4, 122.1, 92.3, 62.1, 60.6, 55.7, 49.5, 38.8, 27.4, 24.7; IR (KBr) ν / cm⁻¹ 2940, 1690, 1662, 1591, 1123, 779, 541; HRMS (ESI): m/z calcd. for C₂₈H₂₈O₆N₈ 517.2082, found 517.2055 [M + H]+.

2-(4-{[(5-Methyl-1,3-dioxoisindolin-2-yl)methyl]-1H-1,2,3-triazol-1-yl}butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6b)

White solid, yield 71%; mp 170-172 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.53 (d, J 6.72 Hz, 2H), 8.24 (d, J 8.36 Hz, 2H), 7.75-7.68 (m, 3H), 7.61 (s, 2H), 7.51 (d, J 7.54 Hz, 1H), 4.96 (s, 2H), 4.03 (t, J 7.54 Hz, 2H), 4.25 (t, J 7.54 Hz, 2H), 2.56 (s, 3H), 1.83-1.79 (m, 2H), 1.72-1.66 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 163.9, 134.4, 134.2, 132.3, 131.2, 127.1, 126.9, 123.7, 123.2, 49.7, 46.2, 38.9, 29.8, 27.8, 25.2, 21.8; IR (KBr) ν / cm⁻¹ 3145, 2924, 1713, 1697, 1658, 1384, 1102, 778, 613; HRMS (ESI): m/z calcd. for C₂₈H₂₈O₆N₈ 494.182228, found 494.18001 [M + H]+.

2-[(4-{(1,3-Dioxo-1H-benzo[de]isoquinoline-2(3H)-yl)butyl}-1H-1,2,3-triazolo-4-yl)methyl]-1H-benzo[de]isoquinoline-1,3(2H)-dione (6c)

White solid, yield 83%; mp 154-156 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.54 (dd, J 7.14, 15.03 Hz, 4H), 8.13 (d, J 8.13 Hz, 4H), 7.74 (t, J 7.76 Hz, 5H), 5.56 (s, 2H), 4.43 (t, J 7.14 Hz, 2H), 4.24 (t, J 7.14 Hz, 2H), 2.12-1.7 (m, 2H), 1.83-1.79 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 164.2, 164.0, 143.8, 134.2, 131.7, 131.3, 128.4, 127.3, 123.3, 122.7, 50.2, 39.9, 35.4, 27.5, 24.1; IR (KBr) ν / cm⁻¹ 3125, 2925, 2676, 1705, 1662, 960, 781, 610; HRMS (ESI): m/z calcd. for C₃₁H₂₅O₇N₈ 530.17988, found 530.18009 [M + H]+.
2-(4-(4-((5,6-Dichloro-1,3-dioxoisoindolin-2-yl)methyl)-1H-1,2,3-triazol-1-yl)butyl)-
1H-benzo[de]isoquinoline-1,3(2H)-dione (6d)

White solid, yield 86%; mp 166-168 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.36 Hz, 2H), 8.22 (d, J 7.76 Hz, 2H), 7.93-7.89 (m, 2H), 7.85 (t, J 7.74 Hz, 2H), 7.64 (s, 1H), 5.13 (s, 2H), 4.43 (t, J 7.12 Hz, 2H), 4.23 (t, J 7.12 Hz, 2H), 2.23-1.94 (m, 2H), 1.84-1.71 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 165.5, 164.1, 141.9, 138.8, 134.0, 131.3, 126.8, 124.0, 122.9, 122.2, 49.7, 39.0, 33.3, 27.7, 24.8; IR (KBr) ν / cm⁻¹ 3165, 2362, 1708, 1658, 1386, 1340, 778, 601; HRMS (ESI): m/z calcd. for C27H19O5N3Cl2 548.08869, found 548.08673 [M + H]+.

2-(4-(4-((2-Allyl-6-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)butyl)-1H-benzo[de]isoquinoline-
1,3(2H)-dione (6e)

White solid, yield 79%; mp 171-174 °C; 1H NMR (300 MHz, CDCl3) δ 8.62 (d, J 8.41 Hz, 2H), 8.24 (d, J 8.36 Hz, 2H), 7.84 (t, J 7.36 Hz, 2H), 7.66 (s, 1H), 7.02 (d, J 7.54 Hz, 1H), 6.75 (d, J 10.51 Hz, 2H), 6.11-6.00 (m, 1H), 5.24 (s, 2H), 5.02 (t, J 8.84 Hz, 2H), 4.47 (t, J 7.14 Hz, 2H), 4.2 (t, J 6.93 Hz, 2H), 3.84 (s, 3H), 3.31 (d, J 6.66 Hz, 2H), 2.0-1.9 (m, 2H), 1.73-1.64 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 164.0, 149.3, 145.9, 144.5, 137.3, 134.0, 133.6, 131.5, 131.3, 128.0, 126.8, 122.8, 122.3, 120.4, 115.6, 114.4, 112.4, 63.2, 55.7, 49.7, 39.7, 39.1, 27.7, 25.0; IR (KBr) ν / cm⁻¹ 3071, 2930, 1698, 1664, 1586, 1514, 1234, 1138, 780, 610; HRMS (ESI): m/z calcd. for C29H25O4N4 497.21593, found 497.21648 [M + H]+.

2-(4-(4-((3,4-Dihydroquinolin-1(2H)-yl)methyl)-1H-1,2,3-triazol-1-yl)butyl)-1H-benzo[de]isoquinoline-
1,3(2H)-dione (6f)

White solid, yield 76%; mp 176-179 °C; 1H NMR (300 MHz, CDCl3) δ 8.53 (d, J 6.02 Hz, 2H), 8.21 (d, J 8.36 Hz, 2H), 7.85 (t, J 7.54 Hz, 2H), 7.32 (s, 1H), 7.03-6.88 (m, 2H), 6.61-6.49 (m, 2H), 4.66 (s, 2H), 4.43 (t, J 6.72 Hz, 2H), 4.25 (t, J 7.54 Hz, 2H), 3.46 (t, J 5.23 Hz, 2H), 2.74 (t, J 6.77 Hz, 2H), 2.03-1.97 (m, 3H), 1.72-1.69 (m, 3H); 13C NMR (75 MHz, CDCl3) δ 163.7, 144.9, 144.5, 133.6, 130.8, 128.6, 126.6, 122.3, 122.0, 121.1, 115.8, 110.7, 49.0, 46.6, 38.7, 27.5, 27.3, 24.5, 21.8; IR (KBr) ν / cm⁻¹ 3128, 2928, 2357, 1693, 1651, 1586, 1112.15, 777, 748, 610; HRMS (ESI): m/z calcd. for C29H25O4N4 466.22375, found 466.22187 [M + H]+.

2-(5-(4-((3,4,5-Trimethoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-
1,3(2H)-dione (6g)

White solid, yield 84%; mp 182-184 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.14 Hz, 2H), 8.24 (d, J 8.32 Hz, 2H), 7.85 (t, J 7.77 Hz, 2H), 7.62 (s, 1H), 6.26 (s, 2H), 5.14 (s, 2H), 4.41 (t, J 7.77 Hz, 2H), 4.13 (t, J 7.7 Hz, 2H), 3.84 (s, 9H), 2.0-1.9 (m, 2H), 1.82-1.79 (m, 2H), 1.54-1.49 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 163.8, 154.5, 153.2, 143.7, 133.6, 132.1, 131.2, 130.9, 127.8, 126.6, 122.2, 92.3, 62.1, 60.6, 55.7, 49.9, 39.4, 29.4, 27.0, 23.4; IR (KBr) ν / cm⁻¹ 3132, 2934, 1698, 1656, 1590, 1129, 1059, 779, 608; HRMS (ESI): m/z calcd. for C29H30O5N4 531.2238, found 531.22111 [M + H]+.
2-(5-(4-((2-Allyl-6-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6h)

White solid, yield 85%; mp 148-150 °C; 1H NMR (300 MHz, CDCl₃) δ 8.53 (d, J 7.36 Hz, 2H), 8.21 (d, J 8.34 Hz, 2H), 7.84 (t, J 7.77 Hz, 2H), 7.61 (s, 1H), 7.04 (d, J 7.92 Hz, 1H), 6.74 (d, J 8.14 Hz, 2H), 5.92-5.89 (m, 1H), 5.22 (s, 2H), 5.0 (t, J 10.0 Hz, 2H), 4.41 (t, J 7.34 Hz, 2H), 4.11 (t, J 7.34 Hz, 2H), 3.74 (s, 3H), 3.31 (d, J 6.72 Hz, 2H), 2.0-1.9 (m, 2H), 1.82-1.79 (m, 2H), 1.51-1.48 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 163.8, 149.3, 145.6, 144.0, 137.1, 133.6, 133.3, 131.2, 130.9, 127.9, 126.5, 122.3, 120.1, 115.3, 114.1, 111.9, 63.1, 55.6, 54.3, 49.8, 39.4, 30.4, 29.5, 27.0, 23.6; IR (KBr) ν / cm⁻¹ 3137, 2954, 3591, 1669, 1654, 1590, 1225, 782, 603; HRMS (ESI): m/z calcd. for C₃₀H₂₈O₄N₄ 511.23398, found 511.23186 [M + H]⁺.

2-(5-(4-((1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6i)

White solid, yield 88%; mp 146-148 °C; 1H NMR (300 MHz, CDCl₃) δ 8.54-8.52 (m, 5H), 8.24 (d, J 7.73 Hz, 3H), 7.83-7.79 (m, 4H), 7.62 (s, 1H), 5.52 (s, 2H), 4.43 (t, J 7.36 Hz, 2H), 4.20 (t, J 7.36 Hz, 2H), 2.04-1.97 (m, 2H), 1.86-1.75 (m, 2H), 1.51-1.46 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 164.2, 164.0, 143.8, 134.2, 131.7, 131.3, 128.4, 127, 123.3, 122.7, 50.2, 39.9, 35.4, 30.0, 27.5, 24.1; IR (KBr) ν / cm⁻¹ 3152, 2934, 1701, 1656, 1591, 1385, 1234, 785, 610; HRMS (ESI): m/z calcd. for C₃₂H₂₉O₄N₅ 544.19553, found 544.19593 [M + H]⁺.

2-(5-(4-((5-Methyl-1,3-dioxoisindolin-2-yl)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6j)

White solid, yield 88%; mp 172-174 °C; 1H NMR (300 MHz, CDCl₃) δ 8.54 (d, J 6.63 Hz, 1H), 8.22 (d, J 7.74 Hz, 2H), 7.84-7.77 (m, 4H), 7.64-7.61 (m, 2H), 7.51-7.02 (m, 1H), 5.03 (s, 2H), 4.35 (t, J 7.16 Hz, 2H), 4.24 (t, J 7.34 Hz, 2H), 2.50 (s, 3H), 2.31-1.97 (m, 2H), 1.81-1.77 (m, 2H), 1.44-1.36 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 164.1, 145.1, 142.7, 134.4, 133.9, 132.2, 131.3, 126.9, 123.9, 123.2, 122.6, 122.3, 50.0, 39.7, 32.9, 29.6, 27.2, 23.9, 21.7; IR (KBr) ν / cm⁻¹ 3120, 2955, 2859, 2360, 1701, 1658, 1385, 1233, 1099, 779, 612; HRMS (ESI): m/z calcd. for C₂₉H₂₉O₄N₅ 508.19793, found 508.19525 [M + H]⁺.

2-(5-(4-((3,4-Dihydroquinolin-1(2H)-yl)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6k)

White solid, yield 73%; mp 179-181 °C; 1H NMR (300 MHz, CDCl₃) δ 8.54 (d, J 7.13 Hz, 2H), 8.26 (d, J 8.16 Hz, 2H), 7.74 (t, J 7.54 Hz, 2H), 7.35 (s, 1H), 7.03-6.96 (m, 2H), 6.64-6.59 (m, 2H), 4.61 (s, 2H), 4.32 (t, J 7.13 Hz, 2H), 4.12 (t, J 7.34 Hz, 2H), 3.43 (t, J 5.41 Hz, 2H), 2.71 (t, J 6.24 Hz, 2H), 2.03-1.96 (m, 2H), 1.84-1.77 (m, 2H), 1.45-1.38 (m, 2H), 0.96-0.89 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 164.0, 133.9, 131.4, 131.1, 129.1, 127.0, 126.8, 122.7, 122.4, 121.1, 116.2, 111.1, 50.0, 49.5, 47.1, 39.7, 31.8, 27.9, 27.2, 23.8, 22.6; IR (KBr) ν / cm⁻¹ 2922, 2352, 1666, 1219, 1163, 772; HRMS (ESI): m/z calcd. for C₂₅H₂₉O₄N₅ 480.23940, found 480.23740 [M + H]⁺.
2-((5-((1,1'-Biphenyl)-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6l)

White solid, yield 88%; mp 194-196 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.13 Hz, 2H), 8.24 (d, J 8.34 Hz, 2H), 7.71 (t, J 7.54 Hz, 2H), 7.63 (s, 1H), 7.51-7.47 (m, 2H), 7.45 (t, J 7.54 Hz, 3H), 7.32 (d, J 7.54 Hz, 2H), 7.03 (d, J 8.63 Hz, 2H), 5.25 (s, 2H), 4.43 (t, J 6.71 Hz, 2H), 4.22 (t, J 7.52 Hz, 2H), 2.03-2.00 (m, 2H), 1.84-1.79 (m, 2H), 1.53-1.46 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 163.7, 157.2, 140.2, 133.5, 131.0, 130.7, 128.3, 127.7, 127.4, 126.2, 122.0, 114.5, 49.7, 39.3, 29.4, 26.8, 23.8; IR (KBr) ν / cm⁻¹ 3317, 3142, 2930, 2364, 1694, 1667, 1590, 1387, 816, 779, 613; HRMS (ESI): m/z calcd. for C32H28O3N3 517.22342, found 517.22281 [M + H]+.

2-((5-(((4-Bromophenoxy)methyl)-1H-1,2,3-triazol-1-yl)pentyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6m)

White solid, yield 85%; mp 201-203 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.13 Hz, 2H), 8.24 (d, J 8.3 Hz, 2H), 7.73 (t, J 7.34 Hz, 2H), 7.65 (s, 1H), 7.42 (d, J 9.03 Hz, 2H), 6.92 (d, J 9.03 Hz, 2H), 5.24 (s, 2H), 4.45 (t, J 7.31 Hz, 2H), 4.22 (t, J 7.54 Hz, 2H), 2.03-1.98 (m, 2H), 1.82-1.79 (m, 2H), 1.51-1.47 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 164.2, 157.3, 143.6, 133.9, 132.3, 131.5, 131.2, 128.0, 126.9, 122.5, 116.6, 113.3, 62.2, 50.2, 39.7, 29.8, 27.2, 23.8; IR (KBr) ν / cm⁻¹ 3164, 2932, 2360, 1696, 1657, 1233, 1125, 785, 698, 611; HRMS (ESI): m/z calcd. for C26H19BrO2N3 519.10263, found 519.10432 [M + H]+.

2-(3-(((1,3-Dioxoisindolin-2-yl)methyl)-1H-1,2,3-triazol-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6n)

White solid, yield 81%; mp 206-208 °C; 1H NMR (300 MHz, CDCl3) δ 8.53 (d, J 7.13 Hz, 2H), 8.24 (d, J 8.34 Hz, 2H), 7.71-7.66 (m, 7H), 5.02 (s, 2H), 4.43 (t, J 7.34 Hz, 2H), 4.28 (t, J 6.65 Hz, 2H), 2.42-2.38 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 164.3, 157.2, 143.4, 134.6, 131.9, 131.5, 131.1, 127.4, 126.7, 122.3, 121.9, 116.4, 113.0, 61.8, 48.0, 37.1, 28.4; IR (KBr) ν / cm⁻¹ 3316, 3146, 1767, 1721, 1671, 1393, 778, 713, 609; HRMS (ESI): m/z calcd. for C26H19O3N3 466.15098, found 466.14968 [M + H]+.

2-(3-(((2-Allyl-6-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6o)

White solid, yield 76%; mp 193-195 °C; 1H NMR (300 MHz, CDCl3) δ 8.54 (d, J 8.43 Hz, 2H), 8.23 (d, J 8.34 Hz, 2H), 7.85 (s, 1H), 7.77 (t, J 7.54 Hz, 2H), 7.03 (d, J 7.54 Hz, 1H), 6.73 (d, J 10.57 Hz, 2H), 5.93-5.87 (m, 1H), 5.24 (s, 2H), 5.14 (t, J 9.04 Hz, 2H), 4.51 (t, J 7.54 Hz, 2H), 4.36 (t, J 6.74 Hz, 2H), 3.83 (s, 3H), 3.32 (d, J 6.60 Hz, 2H), 2.41-2.38 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 163.9, 149.1, 145.7, 144.1, 137.3, 134.0, 133.3, 131.1, 127.9, 126.7, 122.7, 122.1, 63.2, 55.6, 48.1, 39.6, 37.4, 28.1; IR (KBr) ν / cm⁻¹ 3317, 3132, 3076, 2361, 1702, 1654, 1624, 1350, 879, 781; HRMS (ESI): m/z calcd. for C26H26O3N4 483.20268, found 483.20158 [M + H]+.
2-(3-(4-((1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6p)

White solid, yield 79%; mp 198-200 ºC; 1H NMR (300 MHz, CDCl3) δ 8.63 (dd, J 7.17, 6.23 Hz, 4H), 8.21 (dd, J 8.12, 16.34 Hz, 4H), 7.86 (s, 1H), 7.76 (t, J 8.36 Hz, 4H), 5.52 (s, 2H), 4.43 (t, J 7.54 Hz, 2H), 4.21 (t, J 6.76 Hz, 2H), 2.34-2.21 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 163.1, 156.2, 143.1, 133.7, 131.9, 131.4, 130.1, 127.6, 127.7, 122.4, 121.9, 116.3, 113.4, 61.8, 48.5, 37.2, 28.1; IR (KBr) ν / cm⁻¹ 3020, 2400, 1527, 1218, 772, 672; HRMS (ESI): m/z calcd. for C₃₉H₂₅O₂N₅ 516.16663, found 516.16638 [M + H]⁺.

2-(3-(4-((3,4-Dihydroquinolin-1(2H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6q)

White solid, yield 74%; mp 192-195 ºC; 1H NMR (300 MHz, CDCl3) δ 8.62 (d, J 6.03 Hz, 2H), 8.24 (d, J 8.37 Hz, 2H), 7.82 (t, J 7.54 Hz, 2H), 7.03-6.97 (m, 2H), 6.62-6.57 (m, 2H), 4.64 (s, 2H), 4.41 (t, J 7.54 Hz, 2H), 4.21 (t, J 6.76 Hz, 2H), 3.33 (t, J 6.02 Hz, 2H), 2.72 (t, J 6.04 Hz, 2H), 2.34-2.29 (m, 4H), 2.0-1.9 (m, 2H, CH₂); 13C NMR (125 MHz, CDCl3) δ 163.9, 145.1, 144.5, 133.9, 131.2, 128.8, 127.8, 126.8, 126.7, 122.5, 122.0, 121.3, 115.9, 110.8, 49.3, 47.9, 46.8, 37.2, 28.6, 22.0; IR (KBr) ν / cm⁻¹ 3312, 3130, 2928, 1702, 1653, 1592, 1399, 780, 739, 609; HRMS (ESI): m/z calcd. for C₃₇H₂₅O₂N₅ 452.20810, found 452.20702 [M + H]⁺.

2-(3-(4-(((1,1'-Biphenyl)-4-yl oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6r)

White solid, yield 89%; mp 181-183 ºC; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.12 Hz, 2H), 8.24 (d, J 8.36 Hz, 2H) 7.82 (t, J 8.42 Hz, 2H), 7.64 (t, J 6.92 Hz, 3H), 7.43 (t, J 7.12 Hz, 2H), 7.32 (d, J 7.50 Hz, 2H), 7.06 (d, J 8.62 Hz, 3H), 5.22 (s, 2H), 4.54 (t, J 6.93 Hz, 2H), 4.32 (t, J 6.72 Hz, 2H), 2.49-2.44 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 163.8, 140.1, 133.8, 130.9, 128.2, 127.8, 126.5, 126.2, 121.6, 114.6, 47.9, 37.0, 28.4; IR (KBr) ν / cm⁻¹ 2924, 2355, 1219, 1162, 772; HRMS (ESI): m/z calcd. for C₃₉H₂₅O₂N₅ 489.19212, found 489.19321 [M + H]⁺.

2-(3-(4-((4-Bromophenoxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (6s)

White solid, yield 85%; mp 172-174 ºC; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.12 Hz, 2H), 8.24 (d, J 8.36 Hz, 2H), 7.82 (s, 1H), 7.77 (t, J 7.36 Hz, 2H), 7.39 (d, J 9.04 Hz, 2H), 6.92 (d, J 9.04 Hz, 2H), 5.22 (s, 2H), 4.53 (t, J 7.16 Hz, 2H), 4.36 (t, J 6.76 Hz, 2H), 2.48-2.43 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 164.0, 157.0, 143.2, 134.0, 131.9, 131.2, 131.1, 127.8, 126.7, 122.7, 121.9, 116.3, 113.0, 61.8, 48.0, 37.1, 28.6; IR (KBr) ν / cm⁻¹ 3315, 3137, 2957, 1697, 1660, 1588, 1383, 1237, 784, 611; HRMS (ESI): m/z calcd. for C₃₉H₂₅O₂N₅Br 491.07133, found 491.07221 [M + H]⁺.
2-{(6-(4-{(1,3-Dioxoisindolin-2-yl)methyl}-1H-1,2,3-triazol-1-yl)hexyl}-1H-benzo[de]isoquinoline-1,3(2H)-dione (6t)

White solid, yield 77%; mp 162-164 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.16 Hz, 2H), 8.22 (d, J 8.34 Hz, 2H), 7.83-7.79 (m, 2H), 7.77 (t, J 7.96 Hz, 2H), 7.63-7.59 (m, 2H), 7.54 (s, 1H), 5.02 (s, 2H), 4.35 (t, J 7.14 Hz, 2H), 4.15 (t, J 7.14 Hz, 2H), 1.93-1.90 (m, 2H), 1.76-1.71 (m, 2H), 1.48-1.44 (m, 4H); 13C NMR (125 MHz, CDCl3) δ 167.9, 164.3, 142.8, 134.3, 132.3, 131.8, 131.4, 128.2, 127.1, 123.6, 122.8, 50.4, 40.2, 33.3, 30.3, 27.9, 26.6, 26.2; IR (KBr) v / cm⁻¹ 3317, 3133, 2938, 1713, 1656, 1625, 1395, 931, 779, 712, 610; HRMS (ESI): m/z calcd. for C38H29O2N7 508.19793, found 508.19553 [M + H]+.

2-{((1-{6-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexyl}-1H-1,2,3-triazol-4-yl)methyl}-1H-benzo[de]isoquinoline-1,3(2H)-dione (6u)

White solid, yield 77%; mp 197-199 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (dd, J 7.34, 14.7 Hz, 4H), 8.24 (dd, J 7.77, 15.2 Hz, 4H), 7.76 (s, 1H), 7.63-7.59 (m, 4H), 5.51 (s, 2H), 4.38 (t, J 7.13 Hz, 2H), 4.14 (t, J 7.34 Hz, 2H), 1.92-1.88 (m, 2H), 1.72-1.69 (m, 4H), 1.41-1.37 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 163.7, 163.5, 133.7, 133.5, 131.2, 131.1, 130.7, 127.8, 127.6, 126.5, 122.7, 122.2, 122.1, 49.9, 39.5, 35.0, 29.7, 27.3, 25.9, 25.6; IR (KBr) v / cm⁻¹ 3315, 3142, 2928, 1694, 1656, 1626, 1355, 780, 610; HRMS (ESI): m/z calcd. for C32H27O2N7 558.21118, found 558.21118 [M + H]+.

2-{(6-(4-{(2-Allyl-6-methoxyphenoxy)methyl}-1H-1,2,3-triazol-1-yl)hexyl}-1H-benzo[de]isoquinoline-1,3(2H)-dione (6v)

White solid, yield 75%; mp 158-160 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 6.03 Hz, 2H), 8.24 (d, J 8.36 Hz, 2H), 7.82 (t, J 7.54 Hz, 2H), 7.66 (s, 1H), 7.03-6.99 (m, 1H), 6.62-6.59 (m, 2H), 6.02-5.88 (m, 1H), 5.37 (s, 2H), 5.21-5.19 (m, 2H), 4.33 (t, J 7.54 Hz, 2H), 4.11 (t, J 7.54 Hz, 2H), 3.84 (s, 3H), 3.43 (t, J 5.21 Hz, 2H), 1.98 (t, J 6.72 Hz, 2H), 1.77 (t, J 6.72 Hz, 2H), 1.41-1.39 (m, 4H); 13C NMR (75 MHz, CDCl3) δ 163.8, 149.1, 145.6, 144.1, 137.2, 133.6, 133.3, 131.2, 130.8, 127.8, 126.5, 122.2, 120.1, 115.3, 114.0, 111.9, 63.1, 55.5, 49.9, 39.7, 39.4, 28.2, 27.7, 26.0, 25.7; IR (KBr) v / cm⁻¹ 3317, 3340, 2853, 1699, 1663, 1589, 779, 610; HRMS (ESI): m/z calcd. for C31H25O4N6 525.2463, found 525.2475 [M + H]+.

2-{(6-(4-{(3,4-Dihydroquinolin-1(2H)-yl)methyl}-1H-1,2,3-triazol-1-yl)hexyl}-1H-benzo[de]isoquinoline-1,3(2H)-dione (6w)

White solid, yield 75%; mp 203-205 °C; 1H NMR (300 MHz, CDCl3) δ 8.63 (d, J 7.36 Hz, 2H), 8.24 (d, J 8.34 Hz, 2H), 7.81 (t, J 7.36 Hz, 2H), 7.44 (s, 1H), 7.02 (d, J 8.12 Hz, 1H), 6.98 (d, J 8.12 Hz, 1H), 6.71-6.69 (m, 1H, CH), 6.62-6.58 (m, 1H), 4.62 (s, 2H), 4.34 (t, J 7.12 Hz, 2H), 4.16 (t, J 7.12 Hz, 2H), 3.44 (t, J 7.36 Hz, 2H), 2.82 (t, J 7.36 Hz, 2H), 2.03-1.79 (m, 4H), 1.73-1.68 (m, 2H), 1.41-1.39 (m, 4H, CH₂); 13C NMR (75 MHz, CDCl3) δ 164.0, 133.8, 131.1, 129.1, 127.0, 126.8, 121.0, 116.2, 110.9, 50.1, 49.6, 47.2, 39.9, 29.9, 28.0, 27.6, 26.2, 26.0, 22.2; IR (KBr) v / cm⁻¹ 3685, 3020, 2400, 1519, 771, 673; HRMS (ESI): m/z calcd. for C30H30O2N5 494.25505, found 494.25309 [M + H]+.
2-{6-{4-(((1,1'-Biphenyl)-4-yl)[2H]-3,1,2,3-triazol-1-yl)hexyl}-1H)[2,3]benzo[de]isoquinoline-1,3(2H)-dione (6x)

White solid, yield 87%; mp 170-172 °C; 1H NMR (300 MHz, CDCl₃) δ 8.63 (d, J 7.12 Hz, 2H), 8.22 (d, J 8.36 Hz, 2H), 7.84 (t, J 8.16 Hz, 2H), 7.63 (s, 1H), 7.52 (t, J 8.36 Hz, 2H), 7.44 (t, J 7.16 Hz, 2H), 7.32 (d, J 7.54 Hz, 2H), 7.06 (d, J 8.67 Hz, 3H), 5.22 (s, 2H), 4.43 (s, J 7.36 Hz, 2H), 4.21 (t, J 7.36 Hz, 2H), 1.93-1.89 (m, 2H), 1.73-1.67 (m, 2H), 1.42-1.39 (m, 2H), 0.92-0.89 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 164.1, 134.0, 133.8, 131.4, 128.6, 126.8, 126.6, 122.5, 114.9, 62.1, 50.2, 39.9, 30.0, 29.6, 27.6, 26.0; IR (KBr) ν / cm⁻¹ 3314, 3153, 2927, 1697, 1655, 1625, 1386, 784, 610; HRMS (ESI): m/z calcd. for C₃₅H₂₅O₃N₄ 531.23907, found 531.23933 [M + H]^+.

2-{1-(4-(1,3-Dioxoisindolin-2-y)butyl)-1H-1,2,3-triazol-4-yl)methyl]isoindoline-1,3-dione (7a)

White solid, yield 87%; mp 148-150 °C; 1H NMR (300 MHz, CDCl₃) δ 7.83-7.79 (m, 4H), 7.62-7.57 (m, 4H), 7.62 (s, 1H), 5.02 (s, 2H), 4.43 (t, J 7.14 Hz, 2H), 3.76 (t, J 6.73 Hz, 2H), 1.93-1.89 (m, 2H), 1.73-1.69 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 168.0, 167.3, 142.4, 133.7, 131.7, 131.6, 123.1, 123.0, 122.5, 49.2, 36.7, 32.7, 27.1, 25.2; IR (KBr) ν / cm⁻¹ 3314, 2934, 2360, 1767, 1702, 1396, 1098, 714, 609; HRMS (ESI): m/z calcd. for C₂₃H₁₀O₄N₅ 430.15098, found 430.14890 [M + H]^+.

2-{4-(3,4-Dihydroquinolin-1(2H)-yl)methyl]-1H-1,2,3-triazol-4-yl]butyl]isoindoline-1,3-dione (7b)

White solid, yield 83%; mp 159-161 °C; 1H NMR (300 MHz, CDCl₃) δ 7.82-7.79 (m, 2H), 7.61-7.58 (m, 2H), 7.34 (s, 1H), 7.02-6.98 (m, 2H), 6.62-6.57 (m, 2H), 4.54 (s, 2H), 4.36 (t, J 7.54 Hz, 2H), 3.76 (t, J 6.72 Hz, 2H), 3.34 (t, J 5.24 Hz, 2H), 2.73 (t, J 6.03 Hz, 2H), 1.94-1.89 (m, 4H), 1.61-1.59 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 168.0, 145.2, 144.5, 133.8, 131.6, 128.9, 126.7, 123.0, 122.5, 121.2, 116.0, 110.9, 49.4, 49.2, 46.9, 36.6, 27.6, 27.2, 25.3, 22.0; IR (KBr) ν / cm⁻¹ 3319, 3125, 2919, 1777, 1714, 1600, 1398, 747, 718, 611; HRMS (ESI): m/z calcd. for C₂₃H₂₃O₄N₅ 416.20810, found 416.20648 [M + H]^+.

2-{4-{2-Allyl-6-methoxyphenoxy)methyl]-1H-1,2,3-triazol-1-yl]butyl]isoindoline-1,3-dione (7c)

White solid, yield 84%; mp 173-175 °C; 1H NMR (300 MHz, CDCl₃) δ 7.92-7.89 (m, 2H), 7.76 (d, J 8.36 Hz, 2H), 7.62 (s, 1H), 6.92 (d, J 8.14 Hz, 1H), 6.73 (d, J 8.14 Hz, 2H), 5.92-5.87 (m, 1H), 5.24 (s, 2H), 5.13 (t, J 7.54 Hz, 2H), 4.41 (t, J 6.72 Hz, 2H), 4.15 (t, J 6.72 Hz, 2H), 3.84 (s, 3H), 3.31 (d, J 6.64 Hz, 2H), 1.94-1.89 (m, 2H), 1.72-1.68 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 168.0, 149.1, 145.5, 144.2, 137.2, 133.7, 133.4, 131.6, 123.0, 122.4, 120.1, 115.3, 114.0, 111.9, 63.0, 55.5, 49.2, 39.5, 36.5, 27.1, 25.2; IR (KBr) ν / cm⁻¹ 3315, 3150, 2936, 1769, 1698, 1598 1398, 720, 603, 529; HRMS (ESI): m/z calcd. for C₂₉H₂₆O₄N₄ 447.20268, found 447.20145 [M + H]^+.

Cell cultures

Cells were procured from National Centre for Cell Science (NCCS), Pune, India, and stocks were maintained in the sterile laboratory conditions. Breast (MCF-7), prostate (PC-3), lung (A549) and cervical (HeLa) cancer cells and RPE1 normal cells were grown in tissue culture flasks in RPMI 1640 medium (Sigma), DMEM (Dulbecco modified Eagle medium, Sigma) or MEM (minimum essential medium, Sigma)
supplemented with 10% fetal bovine serum with IX stabilized antibiotic-antimycotic solution (Sigma) in a CO₂ incubator at 37 °C with 5% CO₂ and 90% relative humidity.

**MTT assay**

The anticancer activity was determined using MTT assay for all the new compounds. 1 × 10⁴ cells per well were seeded in 100 µL respective media, supplemented with 10% FBS in each well of 96-well microculture plates and incubated at 37 °C, for 24 h in a CO₂ incubator. Compounds, diluted to the required concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 100 µL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg mL⁻¹) was added to all the plates and incubated for 4 h. Then, the supernatant from each well was carefully decanted, formazon crystals were dissolved in 100 µL of DMSO and absorbance was recorded at 570 nm wavelength.

**Acridine orange-ethidium bromide (AO-EB) staining**

A549 cells were plated at a concentration of 1 × 10⁶ cell mL⁻¹ and treated with different concentration of compound 6c. Plates were incubated in an atmosphere of 5% CO₂ at 37 °C for 48 h. 10 µL of fluorescent dyes containing acridine orange (AO) and ethidium bromide (EB) were added into each well in equal volumes (10 µg mL⁻¹) respectively and, within 10 min, the cells were visualized under fluorescence microscope (Nikon, Inc., Japan) with excitation at 488 nm and emission at 550 nm at 200× magnification.

**DAPI staining**

Nuclear morphological changes were observed through DAPI staining. After treatment with 6c for 48 h in A549 cells, cells were washed with PBS and permeabilized with 0.1% Tween 20 for 10 min followed by staining with 1 µM DAPI. Control and treated cells were observed with fluorescence microscope (model: Nikon, Japan) with excitation at 359 nm and emission at 461 nm using DAPI filter at 200× magnification.

**Relative viscosity study**

The viscosities of the DNA-ligand complexes were determined by the Lovis 2000 M/ME Rolling-ball viscometer (Anton Paar GmbH, Graz, Austria), based on the falling ball principle. The temperature was controlled at ± 0.005 K by means of an internal Peltier thermostat. A calibrated 1.59 mm glass capillary containing a steel ball was filled with the sample for measuring the ball falling time at angles in the range from 20° to 70°. The kinematic as well as dynamic viscosities at 25 °C were estimated based on the ball falling time and densities. DNA solution was prepared in 100 mM Tris-HCl (pH 7.4) and viscosity was measured, while each derivative (5 µM) was added to CT-DNA solution (50 µM). Ethidium bromide, Hoechst 33258 and doxorubicin at 5 µM concentration were used as controls. Data was represented graphically as ((η/η₀)²/³ vs. the ratio of the concentration of the hybrid to CT-DNA, where η is the viscosity of CT-DNA in the presence of the derivative and η₀ is the viscosity of CT-DNA solution.
Molecular docking

The DNA crystal structure has been retrieved from Protein Data Bank (PDB ID: 209D). Protein preparation tool was used for the preparation of the DNA hexamer. This adds up the missing atoms and removes peripheral water molecules with a distance of more than 3 Å from the pocket. The grid is generated by picking the active site where the co-crystal is located and grid box of 10 × 10 × 10 Å was generated using Glide 7.4 (Schrödinger 2017-1). The potent hybrid was sketched (6c, 6d and 6p) by using 2D sketcher and energy minimized then subjected to ligand preparation for generation of different conformers (Schrödinger 2017-1). The different conformers thus generated were subjected to molecular docking with SP Glide 7.4 (Schrödinger 2017-1). The poses obtained were evaluated and the best ones were reported.

Copies of $^1$H and $^{13}$C NMR

![Figure S1. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6a.](image-url)
Figure S2. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6a.

Figure S3. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6b.
**Figure S4.** $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6b.

**Figure S5.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6c.
Figure S6. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6c.

Figure S7. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6d.
Figure S8. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6d.

Figure S9. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6e.
**Figure S10.** $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6e.

**Figure S11.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6f.
Figure S12. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6f.

Figure S13. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6g.
Figure S14. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6g.

Figure S15. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6h.
Figure S16. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6h.

Figure S17. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6i.
Figure S18. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6i.

Figure S19. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6j.
**Figure S20.** $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6j.

**Figure S21.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6k.
Figure S22. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6k.

Figure S23. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6l.
Figure S24. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6l.

Figure S25. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6m.
Figure S26. $^1$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6m.

Figure S27. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6n.
Figure S28. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6n.

Figure S29. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6o.
Figure S30. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6o.

Figure S31. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6p.
Figure S32. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6p.

Figure S33. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6q.
Figure S34. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6q.

Figure S35. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6r.
**Figure S36.** $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 6r.

**Figure S37.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6s.
Figure S38. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6s.

Figure S39. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6t.
Figure S40. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6t.

Figure S41. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6u.
Figure S42. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6u.

Figure S43. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6v.
**Figure S44.** $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6v.

**Figure S45.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6w.
**Figure S46.** $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6w.

**Figure S47.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 6x.
Figure S48. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 6x.

Figure S49. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 7a.
Figure S50. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 7a.

Figure S51. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 7b.
Figure S52. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 7b.

Figure S53. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 7c.
Figure S54. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 7c.