SUPPORTING INFORMATION

Investigation of triazole linked indole and oxindole glycoconjugates as potential anticancer agents: Novel Akt/PKB signaling pathway inhibitors

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Content

Experimental Section:

Chemistry

General. All melting points were determined on a stuart digital SMP-30 melting point apparatus. IR spectra were recorded on a Perkin Elmer, FT-IR spectrometer using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on either Bruker AVANCE-I 300 MHz NMR spectrometer, Bruker AVANCE-II 300 MHz and Inova 500 and recorded in $CDCl_3$, DMSO-d_6 or DMSO-d_6 + $CDCl_3$ solvents. Chemical shift were reported in parts per million (ppm) with respect to internal standard tetramethylsilane (TMS). Mass spectra were obtained on Agilent technologies LC/HRMS-TOF spectrometer. TLC experiments were performed on 0.2 mm Merck pre-coated silica gel 60 F_{254} aluminium sheets and the spots were visualized under a UV lamp or by exposure in iodine vapors. Column chromatography was performed using silica gel (60-120mesh) and the column was usually eluted with EtOAc/hexane.

General experimental procedure for the synthesis of 3-alkenyl oxindoles ***E*-7(a-j)** and ***Z*-7(a-j)**

To a stirred solution of oxindole **6** (1 equiv) in ethanol was added aldehyde (1 equiv) and piperidine (0.01 equiv) and refluxed for 3h. Completion of the reaction was checked by TLC (*n*-hexane/EtOAc; 7:3). Ethanol was evaporated and the crude product ***7(a-j)*** was taken up in EtOAc and was washed successively with water and brine. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to isolate pure ***E*-7(a-j)** and ***Z*-7(a-j)** in moderate to good yields.

General experimental procedure for the synthesis of **4(a-k)**, ***E*-8(a-j)** and ***Z*-8(a-j)**

To a stirred solution of 3-substituted indole/oxindole **[3(a-k)**, ***E*-7(a-j)** and ***Z*-7(a-j)]** (1 equiv) in acetonitrile was added propargyl bromide (1.5 equiv, 80% in toluene) and potassium carbonate (5 equiv) and was refluxed for 6h. Completion of the reaction was checked by TLC (*n*-hexane/EtOAc 8:2). Acetonitrile was evaporated and the crude product was taken up in EtOAc and was washed successively with water and brine. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to isolate pure *N*-propargylated products **[4(a-k)**, ***E*-8(a-j)** and ***Z*-8(a-j)]** in good to excellent yields.

General experimental procedure for the synthesis of **5(a-k)**, ***E*-9(a-j)** and ***Z*-9(a-j)**

To a stirred solution of *N*-propargylated 3-substituted indole/oxindole **[4(a-k)**, ***E*-8(a-j)** and ***Z*-8(a-j)]** (1 equiv) in solvent (*t*-butanol/water; 1:1) was added CuI (0.01 equiv) and *β*-D-glucopyranosyl azide (1 equiv) and was heated at 40 ^{O}C for 48h. Completion of the reaction was checked by TLC (*n*-hexane/EtOAc 5:5). *t*-Butanol was evaporated and the crude product was taken up in EtOAc and was washed successively with water and dil. ammonia solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to isolate pure indole/oxindole triazole linked glycoconjugate **[5(a-k)**, ***E*-9(a-j)** and ***Z*-9(a-j)]** in good to excellent yields.

5-(acetoxymethyl)-6-(4-((3-formyl-1H-inden-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5a)***

Off white solid; yield: 82%; mp 139-140 °C. IR (KBr): 1730, 1754, 1665, 1366, 1226, 1063, 787 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 9.96 (s, 1H), 8.45 (s, 1H), 8.32 (s, 1H), 8.12 (d, J =7.3 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.31 (p, J = 6.9, 13.5 Hz, 2H), 6.18-6.14 (m, 1H), 5.58-5.49 (m, 4H), 5.25-5.19 (m, 1H), 4.34-4.31 (m, 1H), 4.16-4.03 (m, 2H), 2.02-1.95 (m, 9H), 1.74 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 184.0 (CHO), 169.5 (CO), 169.0 (CO), 168.7 (CO), 168.0 (CO), 142.3 (Ar), 138.9 (Ar), 136.5 (Ar), 124.6 (Ar), 123.4 (Ar), 122.3 (Ar), 121.9 (Ar), 121.2 (Ar), 117.7 (Ar), 110.1 (Ar), 84.4 (CH), 73.8 (CH), 71.9 (CH), 69.9 (CH), 67.2 (CH), 61.1 (CH_2), 41.5 (CH_2), 20.0 (CH_3), 19.9 (CH_3), 19.9 (CH_3), 19.4 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{29}N_4O_{10}$ $[M+H]^+$ 557.1878; found 557.1880.

5-(acetoxymethyl)-6-(4-((3-formyl-5-methoxy-1H-inden-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5b)***

Off white solid; yield: 79%; mp 162-164 °C. IR (KBr): 1732, 1660, 1532, 1366, 1226, 1039, 807 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 9.93 (s, 1H), 8.02 (s, 1H), 7.74 (d, J = 2.26 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.40 (s, J = 8.8 Hz, 1H), 6.96 (dd, J = 2.4 Hz, 1H), 6.09-6.05 (m, 1H), 5.52-5.46 (m, 4H), 5.26-5.19 (m, 1H), 4.29-4.07 (m, 3H), 3.86 (s, 3H), 2.07-1.99 (m, 9H), 1.78 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 183.8 (CHO), 169.5 (CO), 169.0 (CO), 168.6 (CO), 168.0 (CO), 156.0 (Ar), 142.2 (Ar), 138.3 (Ar), 131.3 (Ar), 125.5 (Ar), 121.3 (Ar), 117.5 (Ar), 113.5 (Ar), 110.6 (Ar), 102.9 (Ar), 84.6 (CH), 74.0 (CH), 71.7 (CH), 69.8 (CH), 67.0 (CH), 60.9 (CH_2), 55.0 (OCH_3), 41.7 (CH_2), 19.9

(CH_3), 19.7 (CH_3), 19.3 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{31}N_4O_{11}$ $[M+H]^+$ 587.1984; found 587.1992.

(E)-5-(acetoxymethyl)-6-(4-((3-((hydroxyimino)methyl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5c)***

White solid; yield: 83%; mp 167-169 °C. IR (KBr): 3483, 1735, 1544, 1483, 1367, 1253, 1037, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 10.22 (s, 1H), 8.28 (s, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 4.7 Hz, 1H), 7.56-7.52 (m, 1H), 7.28-7.15 (m, 2H), 6.04 (d, *J* = 4.5 Hz, 1H), 5.51-5.39 (m, 4H), 5.25-5.17 (m, 1H), 4.29-4.20 (m, 1H), 4.15-4.05 (m, 2H), , 2.07-1.97 (m, 9H), 1.77 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.9 (CO), 169.3 (CO), 168.8 (CO), 168.2 (CO), 143.9 (C-C=N), 143.4 (Ar), 136.3 (Ar), 129.6 (Ar), 124.9 (Ar), 122.5 (Ar), 121.8 (Ar), 121.4 (Ar), 120.3 (Ar), 109.7 (Ar), 109.4 (Ar), 84.5 (CH), 73.9 (CH), 72.1 (CH), 69.9 (CH), 67.2 (CH), 61.1 (CH_2), 41.1 (CH_2), 20.2 (CH_3), 20.0 (CH_3), 20.0 (CH_3), 19.5 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{30}N_5O_{10}$ $[M+H]^+$ 572.1987; found 572.1995.

5-(acetoxymethyl)-6-(4-((3-acetyl-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5d)***

Off white solid; yield: 88%; mp 171–173 °C. IR (KBr): 1753, 1638, 1529, 1368, 1211, 1120, 1045, 927, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.31 (s, 1H), 7.95-7.84 (m, 2H), 7.47-7.38 (m, 1H), 7.26 (s, 2H), 6.00-5.90 (m, 1H), 5.48-5.37 (m, 4H), 5.19 (s, 1H), 4.26-4.01 (m, 3H), 2.51 (s, 3H), 2.05-1.93 (m, 9H), 1.60-1.68 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 192.0 (CO_{Ac}), 169.5 (CO), 169.0 (CO), 168.7 (CO), 167.9 (CO), 142.6 (Ar), 136.1 (Ar), 136.0 (Ar), 125.7 (Ar), 122.6 (Ar), 122.4 (Ar), 121.8 (Ar), 121.5 (Ar), 116.2 (Ar), 110.2 (Ar), 84.0 (CH), 73.4 (CH), 71.9 (CH), 70.0 (CH), 67.3 (CH), 62.1 (CH), 61.2 (CH_2), 41.2 (CH_2), 20.1 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.5 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{31}N_4O_{10}$ $[M+H]^+$ 571.2035; found 571.2042.

5-(acetoxymethyl)-6-(4-((3-nitro-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5e)***

Off white solid; yield: 85%; mp 160–162 °C. IR (KBr): 1753, 1369, 1307, 1229, 1049, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.11-8.05 (m, 2H), 7.40-7.36 (m, 1H), 7.24-7.18 (s, 3H), 5.82 (d, *J* = 8.6 Hz, 1H), 5.34 (s, 2 H), 5.29 (t, *J* = 6.4 Hz, 2H), 5.08 (t, *J* = 9.6 Hz, 1H), 4.12-4.05 (m, 1H), 3.96-3.88 (m, 2H), 1.88-1.82 (m, 9H), 1.60 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.8 (CO), 169.2 (CO), 168.8 (CO), 168.2 (CO),

141.7 (Ar), 134.6 (Ar), 130.7 (Ar), 128.3 (Ar), 124.0 (Ar), 123.7 (Ar), 122.2 (Ar), 120.4 (Ar), 119.9 (Ar), 110.8 (Ar), 84.6 (CH), 74.0 (CH), 71.9 (CH), 69.9 (CH), 67.2 (CH), 61.1 (CH_2), 41.8 (CH_2), 20.1 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.4 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{28}N_5O_{11}$ $[M+H]^+$ 574.1780; found 574.1780.

(E)-5-(acetoxymethyl)-6-(4-((3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5f)***

Yellow solid; yield: 90%; mp 168–170 °C. IR (KBr): 1742, 1654, 1588, 1467, 1376, 1285, 1208, 1035, 777, 441 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.41-8.33 (m, 1H), 8.07-7.90 (m, 5H), 7.63-7.51 (m, 5H), 7.26-7.23 (m, 2H), 6.31-6.28 (m, 1H), 5.60-5.48 (m, 4H), 5.19 (t, J = 9.6 Hz, 1H), 4.31-4.28 (m, 1H), 4.15-4.00 (m, 2H), 1.99-1.93 (m, 9 H), 1.68 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 188.7 (COPh), 169.5 (CO), 169.1 (CO), 168.8 (CO), 168.1 (CO), 142.9 (Ar), 138.3 (Ar), 137.8 (Ar), 136.9 (Ar), 134.5 (Ar), 131.9 (Ar), 128.2 (Ar), 127.8 (Ar), 125.8 (Ar), 122.6 (Ar), 122.5 (Ar), 121.2 (Ar), 120.1 (Ar), 116.0 (Ar), 112.3 (Ar), 110.7 (Ar), 83.8 (CH), 73.3 (CH), 71.9 (CH), 70.0 (CH), 67.3 (CH), 61.4 (CH_2), 41.1 (CH_2), 20.1 (CH_3), 20.1 (CH_3), 20.0 (CH_3), 19.5 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{35}N_4O_{10}$ $[M+H]^+$ 659.2348; found 659.2358.

(E)-5-(acetoxymethyl)-6-(4-((3-(3-(anthracen-9-yl)-3-oxoprop-1-en-1-yl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5g)***

Yellow solid; yield: 82%; mp 141–143 °C. IR (KBr): 1749, 1640, 1521, 1366, 1214, 1148, 1035, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.54 (d, J = 10.0 Hz, 1H), 8.09-7.80 (m, 6H), 7.52-7.23 (m, 10H), 5.97-5.88 (m, 1H), 5.44-5.30 (m, 4H), 5.22-5.13 (m, 1H), 4.27-4.00 (m, 3H), 2.07-1.95 (m, 9H), 1.67-1.95 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 198.5 (COnaph), 169.4 (CO), 168.9 (CO), 168.6 (CO), 167.8 (CO), 142.3 (Ar), 141.8 (Ar), 136.9 (Ar), 134.9 (Ar), 130.4 (Ar), 128.1 (Ar), 127.5 (Ar), 127.1 (Ar), 125.9 (Ar), 125.2 (Ar), 125.0 (Ar), 124.8 (Ar), 123.7 (Ar), 122.7 (Ar), 122.3 (Ar), 121.4 (Ar), 120.0 (Ar), 111.6 (Ar), 110.6 (Ar), 83.9 (CH), 73.3 (CH), 71.8 (CH), 69.9 (CH), 67.2 (CH), 61.1 (CH_2), 41.0 (CH_2), 20.1 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.2 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{42}H_{39}N_4O_{10}$ $[M+H]^+$ 759.2661; found 759.2682.

(E)-5-(acetoxymethyl)-6-(4-((3-(3-oxo-3-(pyridin-3-yl)prop-1-en-1-yl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,4-triyl triacetate ***(5h)***

Orange solid; yield: 78%; mp 127–129 °C. IR (KBr): 1740, 1661, 1584, 1557, 1383, 1219, 1038, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.37 (d, J = 7.5 Hz, 1H), 8.17 (s, 1H), 8.12-8.05 (m, 1H), 7.01-7.97 (m, 1H), 7.91 (s, 1H), 7.77 (s, 1H), 7.58—7.49 (m, 4H), 7.33-7.29 (m, 2H), 6.18 (d, J = 8.3 Hz, 1H), 5.60-5.50 (m, 4H), 5.26-5.19 (m, 1H), 4.27-4.05 (m, 3H), 2.05-1.97 (m, 9H), 1.75 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 188.1 (COpy), 169.7 (CO), 169.1 (CO), 168.7 (CO), 168.1 (CO), 151.9 (Ar), 148.8 (Ar), 142.6 (Ar), 138.9 (Ar), 136.9 (Ar), 135.1 (Ar), 134.0 (Ar), 125.8 (Ar), 122.8 (Ar), 121.4 (Ar), 119.9 (Ar), 115.7 (Ar), 112.5 (Ar), 110.3 (Ar), 84.4 (CH), 73.8 (CH), 71.9 (CH), 69.9 (CH), 67.1 (CH), 61.1 (CH_2), 41.3 (CH_2), 20.1 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.5 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{33}H_{34}N_5O_{10}$ $[M+H]^+$ 660.2300; found 660.2308.

(E)-2-(acetoxymethyl)-6-(4-((3-((2-oxoindolin-3-ylidene)methyl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate ***(5i)***

Yellow solid; yield: 88%; mp 251-253 °C. IR (KBr): 3421, 2925, 1751, 1686, 1466, 1364, 1223, 1165, 1038, 738 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 10.68 (d, J = 16.4 Hz, 1H), 9.91 (s, 0.5H), 9.52 (s, 0.5H), 8.46 (s, 1H), 8.36-8.30 (m, 1H), 8.17-8.05 (m, 1H), 7.87-7.46 (m, 3H), 7.31-7.11 (m, 2H), 6.98-6.86 (m, 1H), 6.33 (d, J = 8.1 Hz, 1H), 5.70-5.50 (m, 4H), 5.19-5.12 (m, 1H), 4.31 (s, 1H), 4.14-4.01 (m, 2H), 2.01-1.90 (m, 9H), 1.67 (s 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.6 (CO), 169.2 (CO), 169.0 (CO), 168.1 (CO), 168.1 (CO), 143.0 (Ar), 142.7 (Ar), 140.2 (Ar), 139.2 (Ar), 136.6 (Ar), 135.4 (Ar), 129.7 (Ar), 124.6 (Ar), 123.4 (Ar), 122.7 (Ar), 122.3 (Ar), 120.9 (Ar), 119.1 (Ar), 117.3 (Ar), 117.1 (Ar), 110.9 (Ar), 110.7 (Ar), 108.8 (Ar), 83.8 (CH), 73.2 (CH), 71.9 (CH), 70.0 (CH), 67.3 (CH), 61.5 (CH_2), 52.2 (CH_2), 20.3 (CH_3), 20.1 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{33}N_5O_{10}$ $[M+H]^+$ 672.2306; found 672.2284.

(E)-2-(acetoxymethyl)-6-(4-((3-((6-fluoro-2-oxoindolin-3-ylidene)methyl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate ***(5j)***

Yellow solid; yield: 80%; mp 262-254 °C. IR (KBr): 2923, 1742, 1682, 1661, 1595, 1482, 1355, 1221, 1189, 1045, 847, 782 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 10.52 (s, 1H), 9.54 (s, 1H), 8.49 (s, 1H), 8.26-8.23 (m, 1H), 8.19 (s, 1H), 7.87 (dd, J = 2.1 Hz, 1H), 7.69-7.58 (m, 1H), 7.28-7.25 (m, 2H), 6.96-6.81 (m, 1H), 6.34 (d, J = 9.1 Hz, 1H), 5.73-5.48 (m, 4H), 5.16 (t, J = 9.7 Hz, 1H), 4.33 (m, 1H), 4.11-4.02 (m, 2H), 2.00-1.94 (m, 9H), 1.68 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.9 (CO), 169.4 (CO), 169.2 (CO), 168.2 (CO), 167.9 (CO), 156.9 (Ar), 143.1 (Ar), 136.5 (Ar), 135.5 (Ar), 132.7 (Ar), 128.9

(Ar), 128.0 (Ar), 127.0 (Ar), 122.7 (Ar), 121.2 (Ar), 119.0 (Ar), 118.8 (Ar), 110.9 (Ar), 110.8 (Ar), 109.8 (Ar), 109.4 (Ar), 106.2 (Ar), 106.0 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.4 (CH), 61.6 (CH_2), 41.5 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 20.1 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{33}FN_5O_{10}$ $[M+H]^+$ 690.2206; found 690.2216.

*(E)-2-(acetoxymethyl)-6-(4-((3-((6-fluoro-2-oxoindolin-3-ylidene)methyl)-5-methoxy-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**5k**)*

Yellow solid; yield: 85%; mp 267-269 °C. IR (KBr): 2926, 1745, 1662, 1595, 1478, 1353, 1227, 1168, 1042, 807, 767 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 10.49 (s, 1H), 9.50 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 7.90-7.87 (m, 1H), 7.79 (d, J = 1.9 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 6.93-6.78 (m, 2H), 6.34 (d, J = 9.3 Hz, 1H), 5.68-5.47 (m, 4H), 5.18 (t, J = 9.7 Hz, 1H), 4.34-4.30 (m, 1H), 4.09-4.04 (m, 2H), 3.87 (s, 3H), 2.00-1.94 (m, 9H), 1.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.9 (CO), 169.4 (CO), 169.2 (CO), 168.2 (CO), 167.9 (CO), 156.9 (Ar), 155.4 (Ar), 143.1 (Ar), 136.8 (Ar), 135.2 (Ar), 130.5 (Ar), 129.8 (Ar), 128.3 (Ar), 127.2 (Ar), 122.7 (Ar), 118.3 (Ar), 112.4 (Ar), 118.8 (Ar), 109.4 (Ar), 106.1 (Ar), 105.9 (Ar), 101.1 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.3 (CH), 61.6 (CH_2), 55.6 (OCH_3), 41.7 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 20.1 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{35}H_{35}FN_5O_{11}$ $[M+H]^+$ 720.2312; found 720.2325.

(E)-2-(acetoxymethyl)-6-(4-((3-benzylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9a)**

Yellow solid; yield: 79%; mp 162-165 °C. IR (KBr): 3134, 2956, 1752, 1613, 1471, 1375, 1225, 1093, 1040, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.34-8.25 (m, 2H), 7.97 (s, 1H), 7.67-7.54 (m, 2H), 7.50-7.41 (m, 3H), 7.29 (t, J = 6.9 Hz, 1H), 7.11-6.96 (m, 2H), 6.06 (d, J = 5.8 Hz, 1H), 5.53-5.40 (m, 2H), 5.26-5.13 (m, 1H), 5.11 (m, 2H), 4.30-4.18 (m, 1H), 4.17-4.11 (m, 2H), 2.10-1.94 (m, 9H), 1.75 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.7 (CO), 169.1 (CO), 168.6 (CO), 167.8 (CO), 167.2 (CO), 142.7 (Ar), 142.0 (Ar), 136.7 (Ar), 134.0 (Ar), 129.2 (Ar), 129.1 (Ar), 128.6 (Ar), 128.0 (Ar), 126.2 (Ar), 122.0 (Ar), 121.4 (Ar), 121.2 (Ar), 120.3 (Ar), 108.7 (Ar), 84.4 (CH), 73.8 (CH), 71.9 (CH), 69.6 (CH), 67.0 (CH), 60.9 (CH_2), 34.6 (CH_2), 20.0 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 19.4 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{32}H_{32}N_4O_{10}$ $[M+H]^+$ 633.2191; found 633.2186.

(Z)-2-(acetoxymethyl)-6-(4-((3-benzylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9a)**

Yellow solid; yield: 82%; mp 133-135 °C. IR (KBr): 3068, 2928, 1750, 1607, 1466, 1368, 1224, 1103, 1039, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.55-8.47 (m, 2H), 8.33-8.25 (m, 2H), 8.17-8.04 (m, 3H), 7.93 (t, J = 7.5 Hz, 1H), 7.72-7.48 (m, 2H), 6.62-6.54 (m, 1H), 6.11-6.05 (m, 2H), 5.91-5.82 (m, 1H), 5.79 (s, 2H), 4.97-4.67 (m, 2H), 4.62 (s, 1H), 2.76-2.62 (m, 9H), 2.45 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.7 (CO), 169.2 (CO), 169.0 (CO), 168.1 (CO), 166.8 (CO), 142.6 (Ar), 142.5 (Ar), 136.7 (Ar), 135.5 (Ar), 134.1 (Ar), 129.1 (Ar), 128.6 (Ar), 122.4 (Ar), 122.0 (Ar), 121.6 (Ar), 120.2 (Ar), 119.2 (Ar), 117.2 (Ar), 109.3 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.4 (CH), 61.6 (CH_2), 34.5 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{32}H_{32}N_4O_{10}$ $[M+H]^+$ 633.2191; found 633.2189.

(E)-2-(acetoxymethyl)-6-(4-((3-(4-methylbenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9b)**

Yellow solid; yield: 84%; mp 201-205 °C. IR (KBr): 2918, 1755, 1605, 1467, 1368, 1224, 1103, 1037, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.30 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.81 (s, 1H), 7.63-7.53 (m, 2H), 7.33-7.18 (m, 3H), 7.08-6.83 (m, 2H), 6.16-6.07 (m, 1H), 5.59-5.43 (m, 2H), 5.26-5.16 (m, 1H), 5.11 (s, 2H), 4.29-4.02 (m, 3H), 2.45 (s, 3H), 2.07-1.95 (m, 9H), 1.76 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.6 (CO), 169.1 (CO), 168.9 (CO), 168.0 (CO), 166.9 (CO), 142.6 (Ar), 142.3 (Ar), 139.6 (Ar), 136.8 (Ar), 132.0 (Ar), 131.2 (Ar), 129.5 (Ar), 129.1 (Ar), 125.5 (Ar), 122.3 (Ar), 121.9 (Ar), 121.4 (Ar), 120.3 (Ar), 109.1 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.3 (CH), 61.5 (CH_2), 34.5 (CH_2), 21.0 (CH_3), 20.3 (CH_3), 20.1 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{33}H_{34}N_4O_{10}$ $[M+H]^+$ 647.2348; found 647.2349.

(Z)-2-(acetoxymethyl)-6-(4-((3-(4-methylbenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9b)**

Yellow solid; yield: 81%; mp 180-182 °C. IR (KBr): 3140, 2955, 1755, 1605, 1467, 1368, 1226, 1102, 1038, 749 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.45 (s, 1H), 7.75 (s, 1H), 7.65-7.60 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.08 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.33 (d, J = 9.1 Hz, 1H), 5.69 (t, J = 9.4 Hz, 1H), 5.55 (t, J = 9.4 Hz, 1H), 5.19 (t, J = 9.7 Hz, 1H), 5.10 (q, J = 15.8 Hz, 2H), 4.35-4.31 (m, 1H), 4.14-3.98 (m, 2H), 2.41 (s, 3H), 2.03-1.92 (m, 9H), 1.71 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.9 (CO), 169.4 (CO), 169.2 (CO), 168.2 (CO), 166.9 (CO), 142.8 (Ar), 142.4 (Ar),

139.8 (Ar), 137.0 (Ar), 131.2 (Ar), 129.7 (Ar), 129.4 (Ar), 129.3 (Ar), 125.5 (Ar), 122.4 (Ar), 121.9 (Ar), 121.7 (Ar), 120.3 (Ar), 109.3 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 70.0 (CH), 67.4 (CH), 61.6 (CH_2), 34.5 (CH_2), 21.0 (CH_3), 20.4 (CH_3), 20.2 (CH_3), 20.1 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{33}H_{34}N_4O_{10}$ $[M+H]^+$ 647.2348; found 647.2344.

(Z)-2-(acetoxymethyl)-6-(4-((3-(3,4-dimethoxybenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9c)**

Yellow solid; yield: 75%; mp 205-207 °C. IR (KBr): 2925, 1750, 1606, 1467, 1369, 1224, 1141, 1037, 748 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.02-7.73 (m, 2H), 7.68-7.47 (m, 1H), 7.43-7.15 (m, 3H), 7.13-6.84 (m, 3H), 6.08-5.95 (m, 1H), 5.57-5.39 (m, 2H), 5.31-5.00 (m, 3H), 4.35-3.82 (m, 9H), 2.14-1.94 (m, 9H), 1.85 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.9 (CO), 169.1 (CO), 168.9 (CO), 168.0 (CO), 167.1 (CO), 150.3 (Ar), 148.4 (Ar), 142.7 (Ar), 142.2 (Ar), 137.2 (Ar), 129.2 (Ar), 126.4 (Ar), 124.2 (Ar), 123.1 (Ar), 122.3 (Ar), 121.9 (Ar), 121.4 (Ar), 120.5 (Ar), 112.6 (Ar), 111.3 (Ar), 109.1 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.3 (CH), 61.5 (CH_2), 55.4 (OCH_3), 55.4 (OCH_3), 34.5 (CH_2), 20.3 (CH_3), 20.1 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{36}N_4O_{12}$ $[M+H]^+$ 693.2402; found 693.2397.

2-(acetoxymethyl)-6-(4-(((E)-2-oxo-3-((E)-3-phenylallylidene)indolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9d)**

Yellow solid; yield: 83%; mp 201-204 °C. IR (KBr): 2927, 1752, 1604, 1466, 1369, 1226, 1165, 1038, 748 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.58-8.45 (m, 1H), 8.43 (s, 1H), 7.72-7.57 (m, 4H), 7.49-7.35 (m, 3H), 7.30-7.17 (m, 2H), 7.06-6.91 (m, 2H), 6.33 (d, J = 9.0 Hz, 1H), 5.68 (t, J = 9.4 Hz, 1H), 5.54 (t, J = 9.4 Hz, 1H), 5.19 (t, J = 9.8 Hz, 1H), 5.09-4.97 (m, 2H), 4.37-4.25 (m, 1H), 4.15-3.97 (m, 2H), 2.06-1.89 (m, 9H), 1.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.9 (CO), 169.5 (CO), 169.3 (CO), 168.3 (CO), 166.0 (CO), 143.0 (Ar), 142.8 (Ar), 140.7 (Ar), 136.3 (Ar), 136.0 (Ar), 129.5 (Ar), 129.1 (Ar), 128.7 (Ar), 127.4 (Ar), 123.9 (Ar), 123.8 (Ar), 122.7 (Ar), 122.5 (Ar), 121.8 (Ar), 119.7 (Ar), 108.9 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 70.0 (CH), 67.4 (CH), 61.7 (CH_2), 34.1 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 20.1 (CH_3), 19.7 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{34}N_4O_{10}$ $[M+H]^+$ 659.2348; found 659.2358.

2-(acetoxymethyl)-6-(4-(((Z)-2-oxo-3-((E)-3-phenylallylidene)indolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9d)**

Yellow solid; yield: 80%; mp 189-192 °C. IR (KBr): 2927, 1751, 1701, 1606, 1466, 1369, 1225, 1142, 1038, 748 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.42 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.85-7.76 (m, 3H), 7.50-7.38 (m, 5H), 7.30-7.22 (m, 1H), 7.14-6.94 (m, 2H), 6.34 (d, J = 9.0 Hz, 1H), 5.67 (t, J = 9.2 Hz, 1H), 5.56 (t, J = 9.4 Hz, 1H), 5.19 (t, J = 9.8 Hz, 1H), 5.05 (d, J = 3.2 Hz, 2H), 4.37-4.28 (m, 1H), 4.15-3.99 (m, 2H), 2.05-1.89 (m, 9H), 1.71 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.0 (CO), 169.5 (CO), 169.3 (CO), 168.3 (CO), 167.0 (CO), 145.3 (Ar), 143.0 (Ar), 141.8 (Ar), 135.7 (Ar), 135.6 (Ar), 129.8 (Ar), 128.9 (Ar), 128.1 (Ar), 127.4 (Ar), 124.3 (Ar), 124.0 (Ar), 123.0 (Ar), 122.5 (Ar), 122.1 (Ar), 121.4 (Ar), 109.0 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 70.0 (CH), 67.4 (CH), 61.7 (CH_2), 34.5 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 20.2 (CH_3), 19.7 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{34}N_4O_{10}$ $[M+H]^+$ 659.2348; found 659.2357.

(E)-2-(acetoxymethyl)-6-(4-((3-(4-(dimethylamino)benzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9e)**

Yellow solid; yield: 77%; mp 171-174 °C. IR (KBr): 3243, 2940, 1753, 1605, 1481, 1372, 1104, 933, 750 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.62 (s, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.56 (s, 1H), 7.34-7.16 (m, 2H), 7.07 (t, J = 7.1 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.44 (d, J = 9.0 Hz, 1H), 5.75-5.45 (m, 3H), 5.22 (t, J = 9.6 Hz, 1H), 4.42-4.28 (m, 1H), 4.18-3.98 (m, 3H), 3.11 (s, 6H), 2.05-1.86 (m, 9H), 1.81 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.7 (CO), 169.2 (CO), 169.0 (CO), 168.0 (CO), 167.6 (CO), 151.3 (Ar), 142.9 (Ar), 141.6 (Ar), 138.5 (Ar), 138.3 (Ar), 134.8 (Ar), 131.9 (Ar), 128.2 (Ar), 122.3 (Ar), 121.3 (Ar), 120.8 (Ar), 111.3 (Ar), 110.8 (Ar), 108.8 (Ar), 83.7 (CH), 73.3 (CH), 72.1 (CH), 69.9 (CH), 67.4 (CH), 61.5 (CH_2), 39.5 (CH_2), 34.5 (CH_3), 20.3 (CH_3), 20.2 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{37}N_5O_{10}$ $[M+H]^+$ 676.2613; found 676.2605.

(Z)-2-(acetoxymethyl)-6-(4-((3-(4-(dimethylamino)benzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9e)**

Yellow solid; yield: 82%; mp 181-185 °C. IR (KBr): 3245, 2922, 1752, 1699, 1592, 1368, 1225, 1165, 1101, 1037 924, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.49 (d, J = 8.6 Hz, 1H), 7.95-7.57 (m, 4H), 7.26-7.09 (m, 1H), 7.07-6.87 (m, 2H), 6.80-6.66 (m, 2H), 6.04-5.92 (m, 1H), 5.54-5.39 (m, 2H), 5.30-4.99 (m, 3H), 4.32-4.16 (m, 1H), 4.17-4.00 (m, 2H), 3.17 (s, 6H), 2.13-1.89 (m, 9H), 1.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.7 (CO), 169.2 (CO), 169.0 (CO), 168.0 (CO), 167.6 (CO), 151.3 (Ar), 142.9

(Ar), 141.5 (Ar), 138.3 (Ar), 134.8 (Ar), 131.8 (Ar), 128.2 (Ar), 124.9 (Ar), 122.3 (Ar), 121.2 (Ar), 120.8 (Ar), 111.2 (Ar), 110.7 (Ar), 108.8 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.3 (CH), 61.5 (CH_2), 39.5 (CH_2), 34.5 (CH_3), 20.3 (CH_3), 20.2 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{37}N_5O_{10}$ $[M+H]^+$ 676.2613; found 676.2604.

(E)-2-(acetoxymethyl)-6-(4-((3-(naphthalen-2-ylmethylene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9f)**

Yellow solid; yield: 79%; mp 185-189 °C. IR (KBr): 3057, 2929, 1751, 1697, 1604, 1466, 1367, 1218, 1102, 1034, 746 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.95 (s, 1H), 8.65 (d, J = 8.1 Hz, 1H), 8.48 (s, 1H), 8.14-7.90 (m, 4H), 7.86 (d, J = 6.7 Hz, 1H), 7.67-7.54 (m, 2H), 7.32 (t, J = 7.9 Hz, 1H), 7.13-6.94 (m, 2H), 6.36 (d, J = 9.0 Hz, 1H), 5.70-5.43 (m, 2H), 5.21-5.01 (m, 3H), 4.38-4.26 (m, 1H), 4.14-3.98 (m, 2H), 2.05-1.87 (m, 9H), 1.71 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.7 (CO), 169.1 (CO), 168.6 (CO), 167.9 (CO), 167.3 (CO), 142.7 (Ar), 142.1 (Ar), 136.7 (Ar), 133.0 (Ar), 132.3 (Ar), 131.5 (Ar), 129.3 (Ar), 128.7 (Ar), 127.7 (Ar), 127.2 (Ar), 126.7 (Ar), 126.3 (Ar), 126.2 (Ar), 125.6 (Ar), 122.0 (Ar), 121.4 (Ar), 121.3 (Ar), 120.4 (Ar), 108.7 (Ar), 84.4 (CH), 73.8 (CH), 71.9 (CH), 69.7 (CH), 67.0 (CH), 61.0 (CH_2), 34.6 (CH_2), 20.1 (CH_3), 19.9 (CH_3), 19.9 (CH_3), 19.4 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{36}H_{34}N_4O_{10}$ $[M+H]^+$ 683.2348; found 683.2361.

(Z)-2-(acetoxymethyl)-6-(4-((3-(naphthalen-2-ylmethylene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9f)**

Yellow solid; yield: 78%; mp 194-198 °C. IR (KBr): 3057, 2926, 1697, 1604, 1466, 1367, 1218, 1102, 1034, 746 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.47 (s, 1H), 8.34 (s, 1H), 8.11-7.90 (m, 4H), 7.87 (d, J = 8.1 Hz, 1H), 7.68-7.52 (m, 3H), 7.33 (t, J = 7.9 Hz, 1H), 7.09-6.85 (m, 2H), 6.36 (d, J = 8.8 Hz, 1H), 5.69 (t, J = 9.0 Hz, 1H), 5.56 (t, J = 9.4 Hz, 1H), 5.21-4.98 (m, 3H), 4.39 (m, 1H), 4.16-3.99 (m, 2H), 2.08-1.88 (m, 9H), 1.74 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 170.0 (CO), 169.5 (CO), 169.3 (CO), 168.3 (CO), 166.9 (CO), 142.8 (Ar), 142.7 (Ar), 136.8 (Ar), 133.2 (Ar), 132.5 (Ar), 131.8 (Ar), 130.0 (Ar), 129.3 (Ar), 128.4 (Ar), 128.2 (Ar), 127.7 (Ar), 127.4 (Ar), 126.8 (Ar), 126.5 (Ar), 126.2 (Ar), 122.5 (Ar), 122.1 (Ar), 121.9 (Ar), 120.3 (Ar), 109.5 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 70.0 (CH), 67.4 (CH), 61.7 (CH_2), 34.6 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 20.2 (CH_3),

19.7 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{36}H_{34}N_4O_{10}$ $[M+H]^+$ 683.2348; found 683.2358

(E)-2-(acetoxymethyl)-6-(4-((2-oxo-3-(pyridin-2-ylmethylene)indolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9g)**

Yellow solid; yield: 75%; mp 162–164 °C. IR (KBr): 3067, 2925, 1752, 1691, 1375, 1355, 1254, 1223, 1044, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 9.10 (d, J = 7.1 Hz, 1H), 8.92 (d, J = 4.4 Hz, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 7.99-7.90 (m, 1H), 7.63-7.54 (m, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 7.07-7.03 (m, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.32 (d, J = 8.0 Hz, 1H), 5.65 (t, J = 9.4 Hz, 1H), 5.56-5.48 (m, 1H), 5.17-5.09 (m, 1H), 5.08 (d, J = 7.4 Hz, 1H), 5.00 (s, 1H), 4.37-4.30 (m, 1H), 4.13-3.99 (m, 2H), 2.03-1.91 (m, 9H), 1.70 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.9 (CO), 169.4 (CO), 169.2 (CO), 168.2 (CO), 167.6 (CO), 157.7 (Ar), 152.9 (Ar), 142.1 (Ar), 137.9 (Ar), 137.2 (Ar), 134.6 (Ar), 128.6 (Ar), 124.3 (Ar), 123.3 (Ar), 122.8 (Ar), 122.4 (Ar), 121.8 (Ar), 117.5 (Ar), 111.0 (Ar), 108.8 (Ar), 83.7 (CH), 73.2 (CH), 71.9 (CH), 70.0 (CH), 67.4 (CH), 61.6 (CH_2), 34.8 (CH_2), 20.4 (CH_3), 20.2 (CH_3), 20.1 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{31}H_{31}N_5O_{10}$ $[M+H]^+$ 634.2144; found 634.2138.

(E)-2-(acetoxymethyl)-6-(4-((2-oxo-3-(thiophen-2-ylmethylene)indolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9h)**

Yellow solid; yield: 76%; mp 205-207 °C. IR (KBr): 3110, 2924, 1750, 1696, 1467, 1368, 1227, 1103, 1038, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 8.01-7.73 (m, 3H), 7.69-7.52 (m, 2H), 7.30-7.15 (m, 2H), 7.11-6.97 (m, 2H), 5.99-5.90 (m, 1H), 5.47-5.38 (m, 2H), 5.24-5.07 (m, 3H), 4.30-4.18 (m, 1H), 4.13-4.10 (m, 2H), 2.08-1.93 (m, 9H), 1.78 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.5 (CO), 169.0 (CO), 168.8 (CO), 167.9 (CO), 167.5 (CO), 140.0 (Ar), 137.4 (Ar), 137.0 (Ar), 136.7 (Ar), 133.8 (Ar), 128.4 (Ar), 127.9 (Ar), 127.1 (Ar), 123.2 (Ar), 122.1 (Ar), 121.4 (Ar), 120.1 (Ar), 118.7 (Ar), 108.5 (Ar), 83.7 (CH), 73.3 (CH), 72.0 (CH), 69.8 (CH), 67.2 (CH), 61.3 (CH_2), 34.2 (CH_2), 20.2 (CH_3), 20.1 (CH_3), 20.0 (CH_3), 19.5 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{30}H_{30}N_4O_{10}S$ $[M+H]^+$ 639.1755; found 639.1751.

(Z)-2-(acetoxymethyl)-6-(4-((2-oxo-3-(thiophen-2-ylmethylene)indolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9h)**

Yellow solid; yield: 75%; mp 192-195 °C. IR (KBr): 3070, 2924, 1750, 1697, 1467, 1368, 1227, 1103, 1038, 738 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.27 (d, J = 7.7 Hz, 1H), 7.98 (s, 1H), 7.90-7.82 (m, 1H), 7.72-7.53 (m, 2H), 7.35-7.14 (m, 2H), 7.11-6.96 (m, 2H), 6.08 (d, J = 7.3 Hz, 1H), 5.58-5.39 (m, 2H), 5.30-5.12 (m, 3H), 4.31-4.03 (m, 3H), 2.10-1.91 (m, 9H), 1.79 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.7 (CO), 169.2 (CO), 169.0 (CO), 168.0 (CO), 167.5 (CO), 142.2 (Ar), 137.7 (Ar), 137.1 (Ar), 136.7 (Ar), 136.0 (Ar), 130.0 (Ar), 129.4 (Ar), 122.8 (Ar), 122.3 (Ar), 121.7 (Ar), 121.5 (Ar), 120.1 (Ar), 118.6 (Ar), 109.1 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 69.9 (CH), 67.3 (CH), 61.5 (CH_2), 34.6 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 20.0 (CH_3), 19.6 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{30}H_{30}N_4O_{10}S$ $[M+H]^+$ 639.1755; found 639.1753.

(E)-2-(acetoxymethyl)-6-(4-((3-(furan-2-ylmethylene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9i)**

Yellow solid; yield: 88%; mp 210-212 °C. IR (KBr): 3068, 2925, 1753, 1690, 1369, 1355, 1224, 1169, 1044, 742 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.41 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.01 (s, 1H), 7.82-7.77 (m, 2H), 7.38-7.15 (m, 1H), 7.09-6.92 (m, 2H), 6.80 (s, 1H), 6.37 (d, J = 9.0 Hz, 1H), 5.69 (t, J = 9.2 Hz, 1H), 5.53 (t, J = 9.2 Hz, 1H), 5.20-4.97 (m, 3H), 4.38 (s, 1H), 4.16-3.97 (m, 2H), 2.08-1.84 (m, 9H), 1.73 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.0 (CO), 169.5 (CO), 169.3 (CO), 168.3 (CO), 164.8 (CO), 150.7 (Ar), 146.6 (Ar), 143.0 (Ar), 140.3 (Ar), 128.6 (Ar), 123.1 (Ar), 122.5 (Ar), 121.9 (Ar), 121.7 (Ar), 121.0 (Ar), 119.6 (Ar), 119.3 (Ar), 113.7 (Ar), 108.8 (Ar), 83.7 (CH), 73.2 (CH), 72.1 (CH), 70.0 (CH), 67.4 (CH), 61.7 (CH_2), 34.4 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 20.1 (CH_3), 19.7 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{30}H_{30}N_4O_{11}$ $[M+H]^+$ 623.1984; found 623.1988.

(Z)-2-(acetoxymethyl)-6-(4-((3-(furan-2-ylmethylene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9i)**

Yellow solid; yield: 81%; mp 197-200 °C. IR (KBr): 3117, 2926, 1752, 1690, 1465, 1367, 1229, 1105, 1050, 751 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.46-8.38 (s, 2H), 8.20 (d, J = 1.3 Hz, 1H), 7.48 (s, 1H), 7.35-7.22 (m, 2H), 7.11-6.95 (m, 2H), 6.84-6.80 (m, 1H), 6.33 (d, J = 9.0 Hz, 1H), 5.66 (t, J = 9.4 Hz, 1H), 5.55 (t, J = 9.4 Hz, 1H), 5.18 (t, J = 9.8 Hz, 1H), 5.07 (d, J = 2.6 Hz, 2H), 4.36-4.27 (m, 1H), 4.10-4.00 (m, 2H), 2.02-1.90 (m, 9H), 1.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.9 (CO), 169.5 (CO), 169.3 (CO), 168.3 (CO), 167.6 (CO), 150.4 (Ar), 147.5 (Ar), 142.9 (Ar), 142.2 (Ar), 129.4 (Ar), 124.2 (Ar),

122.5 (Ar), 122.0 (Ar), 121.5 (Ar), 120.7 (Ar), 120.1 (Ar), 113.6 (Ar), 108.9 (Ar), 83.7 (CH), 73.2 (CH), 72.0 (CH), 70.0 (CH), 67.4 (CH), 61.7 (CH_2), 34.6 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 20.1 (CH_3), 19.7 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{30}H_{30}N_4O_{11}$ $[M+H]^+$ 623.1984; found 623.1987.

(E)-2-(acetoxymethyl)-6-(4-((3-butylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*E*-9j)**

Off white solid; yield: 76%; mp 176-178 °C. IR (KBr): 3087, 2926, 1754, 1710, 1609, 1467, 1377, 1220, 1105, 1039, 743 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.99-7.83 (m, 1H), 7.62-7.48 (m, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.13-6.97 (m, 2H), 6.07-5.95 (m, 1H), 5.54-5.41 (m, 2H), 5.28-5.17 (m, 1H), 5.11 (s, 2H), 4.34-4.04 (m, 3H), 2.73-2.64 (m, 1H), 2.13-1.95 (m, 9H), 1.81-1.63 (m, 5H), 1.12-0.86 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 168.1 (CO), 167.6 (CO), 167.3 (CO), 166.4 (CO), 164.7 (CO), 141.1 (Ar), 140.2 (Ar), 140.0 (Ar), 127.0 (Ar), 125.4 (Ar), 121.5 (Ar), 120.6 (Ar), 120.2 (Ar), 119.9 (Ar), 107.2 (Ar), 82.3 (CH), 71.8 (CH), 70.5 (CH), 68.4 (CH), 65.8 (CH), 59.9 (CH_2), 32.9 (CH_2), 29.0 (CH_2), 19.9 (CH_2), 18.7 (CH_3), 18.6 (CH_3), 18.5 (CH_3), 18.0 (CH_3), 12.1 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{34}N_4O_{10}$ $[M+H]^+$ 599.2348; found 599.2347.

(Z)-2-(acetoxymethyl)-6-(4-((3-butylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(*Z*-9j)**

Off white solid; yield: 83%; mp 153-155 °C. IR (KBr): 3088, 2926, 1752, 1609, 1376, 1220, 1105, 1034, 743 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.41 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.30-7.18 (m, 1H), 7.08-6.87 (m, 2H), 6.35 (d, *J* = 9.0 Hz, 1H), 5.67 (t, *J* = 9.4 Hz, 1H), 5.55 (t, *J* = 9.4 Hz, 1H), 5.21 (t, *J* = 9.8 Hz, 1H), 5.04 (d, *J* = 5.0 Hz, 2H),4.38-4.26 (m, 1H), 4.16-3.98 (m, 2H), 2.72 (q, *J* = 7.5 Hz, 1H), 2.06-1.90 (m, 9H), 1.73-1.51 (m, 5H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.91-0.79 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 169.5 (CO), 169.0 (CO), 168.8 (CO), 167.9 (CO), 166.2 (CO), 142.6 (Ar), 141.7 (Ar), 141.5 (Ar), 128.5 (Ar), 126.9 (Ar), 123.0 (Ar), 122.1 (Ar), 121.7 (Ar), 121.4 (Ar), 108.7 (Ar), 83.8 (CH), 73.3 (CH), 72.0 (CH), 69.9 (CH), 67.3 (CH), 61.4 (CH_2), 34.3 (CH_2), 30.5 (CH_2), 21.3 (CH_2), 20.2 (CH_3), 20.1 (CH_3), 19.9 (CH_3), 19.5 (CH_3), 13.5 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{34}N_4O_{10}$ $[M+H]^+$ 599.2348; found 599.2347.

Biological evaluation

Cytotoxicity activity of compounds:

The cytotoxic effect of the series of compounds synthesized was ascertained against selected cancer cell lines of interest. The cytotoxicity was determined using a Sulforhodamine assay (SRB Assay). The cell lines of interest were DU145 (Prostrate cancer), A549 (Lung cancer), HeLa (cervical cancer), MCF-7 (Breast cancer) and NIH/3T3 (Fibroblast) cell lines. Initially, the individual cell line of interest was seeded in flat bottom 96-well plate (6000 cells/100μL) in a medium containing 10% serum and incubated in an incubator continuously supplied with 5% CO_2. When the cells had adhered to the surface of the well after 20 h, the cells were treated with the all compounds respectively at varying concentrations, thereby making the final concentration of compound 0 to 100 μM in each well. Each compound was tested in triplicate. DMSO and doxorubicin (a standard control anti-cancer drug) were taken as vehicle and positive controls respectively. After treatment the cells were incubated for another 48 h in an incubator maintained at 37^{o}C with a constant supply of 5% CO_2. After the period of 48 h, 10% TCA solution was added to the cells and incubated for 1 h at 4^{o}C thereby fixing the cells. After fixation the plate was rinsed with MQ water and air dried; 0.057% SRB solution was added to each well to stain the cells and the plate was kept at RT for approximately 30 min before the excess stain was rinsed off using 1% acetic acid. The plates were then air dried and the absorbance was measured at 510 nm. To measure the absorbance, 100μL of 10mMTrisBase was added to each well to solubilize the SRB. From the O.D. values obtained, the percentage cytoxicity was measured against DMSO.

Change in Morphology:

Based on the cytoxicity values of the compounds **5f** and ***E*-9b** on DU145 cells, the effect of these compounds on the cells was tested in a dose dependent manner. The cells were seeded in a 24 well plate as previously described. After 20 h, when the cells had adhered to the surface of wells, the cells were treated with compounds **5f** and ***E*-9b** at different concentrations respectively. The plates were then incubated for 48 h in humidified 5% CO_2 incubator at 37^{o}C. After the period of 48 h of incubation the morphology of cells was seen using Olympus Xi71 microscope.

Colony Formation (Soft Agar) Assay:

To test the long term effect of **5f** and ***E*-9b** on the colony forming ability of cells, a colony formation assay was conducted. The assay conducted was a soft agar assay as reported previously with minor modifications. For the assay, base agar was prepared by mixing 1% of agarose (Bacto Agar: Becton, Dickinson, Sparks, MD) with 2 × DMEM along with 20% FBS and 2X antibiotics in 6-well plates to achieve a final concentration of 0.5% of agar in 1X growth medium containing 10% serum. After solidification of the base agar, 2.5×10^4cells were mixed with cultivation medium containing compound at varying concentrations (0-25μM) and mixed with agar solution to obtain a final concentration of 0.35% agar. This solution was spread on the base agar previously solidified. The plate was incubated for 10 days with periodic replenishment every 3 days with medium and compound. Over the period of incubation, plates were monitored regularly for appearance of colonies. After 10 days of incubation the plates were stained with 0.005% crystal violet solution until colonies turned purple in colour. The excessive stain was washed off using MQ water and the colonies were photographed and counted using a Olympus Xi71 microscope.

Cell Cycle Analysis (FACS):

Cell cycle arrest caused by compounds **5f** and ***E*-9b** was determined by staining the cells with propidium iodide. The cells were seeded in a 6 well plate as previously mentioned. After 20 h, the cells were treated with compounds **5f** and ***E*-9b** respectively at increasing concentrations (0-25μM). After 48 h of incubation the cells were harvested and processed by fixing in 70% ethanol at -20°C overnight. For analysis using Flow cytometry, the cells were stained with propidium iodide. This was achieved by resuspending the cells in PI solution (RNase -0.1 mg/mL, Triton X-100-0.05%, PI-50 μg/mL) and incubating for 1 h in dark at room temperature. The excess PI solution was washed away by washings with PBS buffer. The resultant PI uptake was analyzed by fluorescence activated cell sorting (FACS Calibur System; BD Bio- science, Erembodegem, Belgium) in a FL-2 fluorescence detector (10000 events were recorded for each condition). Flow cytometry data was analyzed using FCS express 4 software (De Novo Software, Los Angeles, CA).

Determination of activation of caspase -3, caspase-9 and caspase-8:

The DU145 cells were treated with compounds **5f** and ***E*-9b** and incubated for 48 h, following which, the cell were harvested and lysates were prepared. The cell lystes thus obtained were analysed for the activation of caspases using fluorogenic substrates. Ac-DEVD AMC, Ac-

DEVD AFC and Ac-VETD-AMC were used as substrates for caspase-3, caspase-9 and caspase-8 respectively. The lysates were incubated with the respective substrate in 20mM HEPES (pH 7.5), 0.1% CHAPS, 2mM EDTA and 5 mM DTT at 37 °C for 2 h. The release of AFC and AMC was analyzed by a fluorimeter using an excitation/emission wavelength of 400/505 nm (for AFC) and 380/460 nm (for AMC) which is directly proportional to increase in caspase activity. The observed fluorescence values were normalized with total protein concentration estimated by Bradford method and the relative caspase activities were calculated as the ratio of values between DMSO and compound treated cells. Doxorubicin (10 μM) was taken as a positive control.

Western Blotting:

In order to assess the effect of the compounds **5f** and ***E*-9b**, DU145 cells were seeded and treated with the compounds respectively at varying concentrations and incubated in a 5% CO_2 incubator for 48 h. Upon the completion of the incubation period, the cells were harvested in chilled PBS and washed thrice with PBS. The cells were then lysed using a complete lysis buffer (8M urea, 2M thiourea, 4% CHAPS, 4mM Tris base, and 65mM DTT) containing inhibitors against protease and phosphatase. The protein concentration was determined using Bradford method. The protein extracts thus obtained were separated on a 12% SDS-PAGE gel and transferred electrophoretically onto a nitrocellulose membrane. The membrane was then incubated in a blocking solution (3% BSA in TBST solution) to reduce non-specific binding for 1 hour following which the membrane was then incubated in primary antibody solution of interest at a dilution of 1:1000 respectively. Antibodies against specific protein targets of interest were purchased from Cell Signaling Technology (Frankfurt, Germany), if not otherwise specified. After overnight incubation in 4 ^{o}C, the cells were washed thrice at an interval of 5 mins each with TBST (20 mM Tris, 138 mM NaCl, pH 7.6 and 0.1% Tween 20) buffer. For detection, blots were incubated with secondary antibody conjugated to horseradish peroxidise [anti-(mouse IgG) or anti-(rabbit IgG), diluted 1: 10,000 in TBST or 1:5000 respectively] for 1 h at room temperature.

After three washes with TBST buffer, the reaction was developed by chemiluminescence using an ECL (Biorad) substrate.