SUPPORTING INFORMATION

Eco-friendly synthesis of new olanzapine derivatives and evaluation of their anticancer potential

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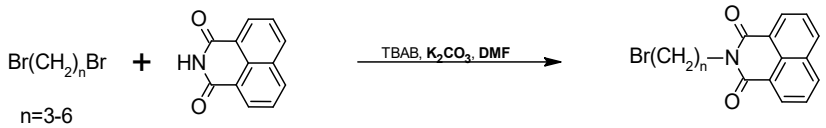
Olanzapine (2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine)

yellow solid, HPLC-MS analysis t: 3.24 min, calc. for $C_{17}H_{20}N_4S$ m/z = 312.4, found m/z = 313.2 [M+H]+; R_f 0.62 (chloroform-methanol 80:20), mp = 194°C (lit. 194 °C [1])
FT-IR (cm^{-1}) 3237, 3178, 3100, 3050, 2942, 2922, 2839, 2804, 1587, 1558, 1454, 1411, 1360, 1281, 1266, 1220, 1146, 1029, 1003, 970, 780, 760 cm^{-1}



1: n=3,
2: n=4,
3: n=5,
4: n=6

General procedure for the synthesis of 1–4 using ultrasound

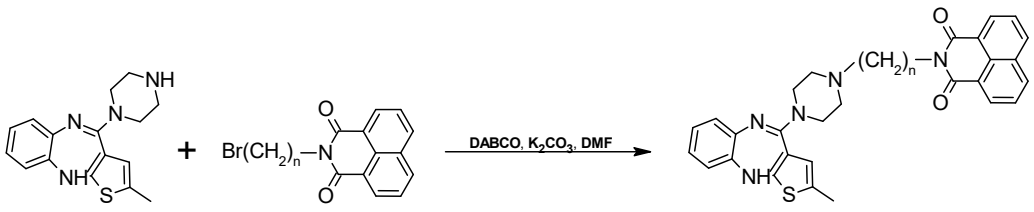
1.97 g of 1,8-naphthalimide (0.01 mol, 1 equiv), 4.14 g of potassium carbonate (0.03 mol, 3 equiv) and 0.32 g of TBAB (0.001 mol, 0.1 equiv), appropriate dibromoalkane (0.03 mol, 3 equiv) and dimethylformamide (5 mL) were placed in a round-bottomed flask, followed by in an ultrasonic bath for 1 hour (80 W, 40 KHz, 50 ˚C). After completion of the reaction, water was added and extraction was carried out with dichloromethane, after which the organic phase was evaporated to dryness. The crude products were crystallized using methanol.

***N*-(3-bromopropyl)-1,8-naphthalimide (1)**
white solid, Y = 23%, HPLC-MS analysis t: 7.92 min, calc. for $C_{15}H_{12}BrNO_2$ m/z = 318.2, found m/z = 320.0 [M+H]+, R_f = 0.90 (chloroform-methanol 90:10), mp = 137-138°C (138 – 140 °C [2]).
FT-IR (cm^{-1}): 3073, 2162, 1748, 1693, 1591, 1585, 687.

***N*-(4-bromobutyl)-1,8-naphthalimide (2)**
white solid, Y = 63%, HPLC-MS analysis t: 8.44 min, calc. for $C_{16}H_{14}BrNO_2$ m/z = 332.2, found m/z = 333.20 [M+H]+, R_f = 0.93 (chloroform-methanol 90:10), mp = 121-122°C (lit. 117-119 °C [3])
FT-IR (cm^{-1}): 3065, 1978, 1695, 1625, 1586, 687.

***N*-(4-bromopentyl)-1,8-naphthalimide (3)**
white solid, Y = 63%, HPLC-MS analysis t: 9.06 min, calc. for $C_{17}H_{16}BrNO_2$ m/z = 346.2, found m/z = 348.0 [M+H]+, R_f = 0.94 (chloroform-methanol 90:10), mp =122-123°C (lit. 121-123 °C [2])
FT-IR (cm^{-1}): 3063, 2162, 1693, 1603, 1588, 687.

***N*-(4-bromohexyl)-1,8-naphthalimide (4)**
white solid, Y = 45%, HPLC-MS analysis t: 9.40 min, calc. for $C_{18}H_{18}BrNO_2$ m/z = 360.2, found m/z = 361.2 [M+H]+, R_f = 0.90 (chloroform-methanol 90:10), mp = 96-97°C (lit. 95-96 °C [4])
FT-IR (cm^{-1})3062, 2162, 1798, 1692, 1601, 1588, 687.



DOLA

1: n=3,
2: n=4,
3: n=5,
4: n=6

5: n=3,
6: n=4,
7: n=5,
8: n=6

2-[3-[4-(2-methyl-5H-thieno[3,2-c][1,5]benzodiazepin-4-yl)piperazin-1-yl]propyl]-3a,6-dihydrobenzo[de]isoquinoline-1,3-dione (5)

yellow oil; HPLC-MS analysis t: 5.23 min, calc. for $C_{31}H_{31}N_5O_2S$ m/z = 535.7, found m/z = 536.2 [M+H]+; R_f = 0.40 (chloroform-methanol 90:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (dd, J = 7.3, 0.9 Hz, 2H), 8.45 (d, J = 8.3 Hz, 2H), 7.91 – 7.84 (m, 2H), 7.59 (s, 1H), 6.87 – 6.75 (m, 3H), 6.68 (dd, J = 7.5, 1.6 Hz, 1H), 6.30 (d, J = 1.1 Hz, 1H), 4.13 (t, J = 7.2 Hz, 2H), 3.22 (bs, 4H), 2.45 (d, J = 7.1 Hz, 6H), 2.26 (s, 3H), 1.89 – 1.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164, 159.3, 148.0, 145.2, 138.9, 137.9, 137.4, 137.5, 126.7, 129.5, 128.1, 126.6, 126.5, 125.6, 123.5, 123.6, 121.4, 117.6, 110.9, 57.4, 56,4, 50.1, 40.1, 26.6, 14.9.

2-[4-[4-(2-methyl-5H-thieno[3,2-c][1,5]benzodiazepin-4-yl)piperazin-1-yl]butyl]-3a,6-dihydrobenzo[de]isoquinoline-1,3-dione (6)

yellow oil; HPLC-MS analysis t: 5.43 min, calc. for $C_{32}H_{33}N_5O_2S$ m/z = 549.7, found m/z = 550.2 [M+H]+; R_f = 0.40 (chloroform-methanol 90:10); ^{1}H NMR (400 MHz, DMSO) δ 8.50 (d, J = 7.2 Hz, 2H), 8.45 (d, J = 8.2 Hz, 2H), 7.87 (t, J = 7.8 Hz, 2H), 7.60 (s, 1H), 6.87 – 6.76 (m, 3H), 6.72 – 6.65 (m, 1H), 6.33 (s, 1H), 4.08 (t, J = 7.2 Hz, 2H), 3.34 – 3.27 (s, 4H), 2.40 (d, J = 25.0 Hz, 6H), 1.68 (dt, J = 14.8, 7.5 Hz, 2H), 1.53 (dt, J = 14.4, 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 158.2, 148.6, 146.7, 139.3, 137.9, 137.8, 136.4, 127.5, 129.8, 128.1, 127.3, 126.1, 125.6, 124.5, 123.3, 120.4, 117.6, 110.9, 58.2, 50.1, 40.4, 40.1, 25.0, 25.4, 14.7.

2-[5-[4-(2-methyl-5H-thieno[3,2-c][1,5]benzodiazepin-4-yl)piperazin-1-yl]pentyl]-3a,6-dihydrobenzo[de]isoquinoline-1,3-dione (7)

yellow oil; HPLC-MS analysis t: 5.41 min, calc. for $C_{33}H_{35}N_5O_2S$ m/z = 563.7, found m/z = 564.3 [M+H]+; R_f = 0.30 (chloroform-methanol 90:10); ^{1}H NMR (400 MHz, DMSO) δ 8.50 (d, J = 7.3 Hz, 2H), 8.45 (d, J = 7.7 Hz, 2H), 7.90 – 7.84 (m, 2H), 7.61 (s, 1H), 6.88 – 6.76 (m, 3H), 6.69 (d, J = 7.8 Hz, 1H), 6.32 (s, J = 0.8 Hz, 1H), 4.06 (t, J = 7.3 Hz, 2H), 3.29 (bs, 4H), 2.40 (bs, 4H), 2.33 – 2.28 (m, 2H), 2.27 (s, 3H), 1.67 (dt, J = 14.8, 7.6 Hz, 2H), 1.51 (dt, J = 14.5, 7.3 Hz, 2H), 1.41 – 1.31 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165, 159.4, 148.0, 147.3, 138.9, 138.1, 137.7, 131.4, 127.5, 129.5, 128.1, 126.6, 125.9, 125.6, 124.9, 124.1, 123.2, 116.5, 110.3, 58.8, 56.3, 40.3, 29.0, 28.1, 25.4, 24.4, 14.1.

2-[6-[4-(2-methyl-5H-thieno[3,2-c][1,5]benzodiazepin-4-yl)piperazin-1-yl]hexyl]-3a,6-dihydrobenzo[de]isoquinoline-1,3-dione (8)

HPLC-MS analysis t: 5.85 min, calc. for $C_{34}H_{37}N_5O_2S$ m/z = 577.8, found m/z = 578.2 [M+H]+; R_f = 0.32 (chloroform-methanol 90:10); ^{1}H NMR (400 MHz, DMSO) δ 8.52 – 8.44 (m, 4H), 7.90 – 7.84 (m, 2H), 7.64 (s, 1H), 6.87 – 6.78 (m, 3H), 6.70 (dd, *J* = 7.3, 1.4 Hz, 1H), 6.34 (s, 1H), 4.08 – 4.02 (m, 2H), 3.34 (bs, 4H), 2.50 – 2.31 (m, 6H), 2.27 (s, *J* = 2.8 Hz, 3H), 1.69 – 1.59 (m, 2H), 1.52 – 1.42 (m, 2H), 1.36 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ163.1, 158.2, 149.2, 140.3, 138.2, 138.0, 136.9, 133.4, 129.9, 128.7, 127.7, 126.6, 125.9, 125.6, 124.8, 124.1, 123.7, 115.5, 111.6, 58.3, 57.3, 40.3, 27.3, 28.1, 26.6, 25.9, 23.4, 15.0.

Literature:

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