Supplementary Material for Organic & Biomolecular Chemistry

Supporting Information

de novo Design and synthesis of *N*-benzylanilines as new candidates for VEGFR tyrosine kinase inhibitor

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3-Hydroxy-5-[{4-(3-phenylureido)-phenylamino}-methyl]-benzoic acid (1)

White solid: mp: 273 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H, Ar-**H**), 7.41-6.64 (m, 15H), 4.25 (s, 2H, ArC**H$_2$**NHAr); ^{13}C NMR (75 MHz, CD_3OD) δ 191.7, 170.6, 170.0, 158.9, 146.7, 143.7, 140.7, 133.3, 129.8, 129.7, 124.0, 123.6, 120.8, 120.4, 119.8, 115.8, 114.5; IR (KBr) 3327.0, 3057.0, 2841.0, 2742.6, 2584.4, 2360.7, 1697.2, 1596.9, 1519.8, 1440.7, 1317.3, 1234.4, 1155.3, 829.3 cm^{-1}; HRMS (ESI) Exact mass calc. for $C_{21}H_{19}N_3O_4$ $[M+H]^+$: 378.1454, found: 378.1452.

1-[4-(3,5-Dihydroxybenzylamino)-phenyl]-3-phenylurea (2)

White solid: mp: 157 ^{o}C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (2H, d, *J* = 8.4 Hz, CONHPh-2,6-**H**), 7.21 (2H, t, *J* = 8.4 Hz, CONHPh-3,5-**H**), 7.06 (2H, d, *J* = 6.8 Hz, NHAr-**H**NHCO), 6.94 (1H, t, *J* = 7.2 Hz, CONHPh-4-**H**), 6.57 (2H, d, *J* = 6.4 Hz, NHAr-**H**NHCO), 6.29 (2H, s, 3,5-$(HO)_2$Ar-2,6-**H**), 6.09 (1H, s, 3,5-$(OH)_2$Ar-4-**H**), 4.11 (2H, s, ArC**H$_2$**NH); ^{13}C NMR (75 MHz, CD_3OD) δ 169.4, 157.6, 153.8, 146.2, 142.4, 139.6, 139.3, 138.8, 138.2, 134.1, 123.7, 116.4, 111.8; IR (KBr) 3305.8, 3035.7, 2852.5, 1595.0, 1556.4, 1519.8, 1498.6, 1442.7, 1394.4, 1315.4, 1234.4, 1155.3, 999.1 cm^{-1}; HRMS (ESI) Exact mass calc. for $C_{20}H_{19}N_3O_3$ $[M+H]^+$: 350.1505, found: 350.1496.

N-[4-(3,5-Dihydroxy-benzylamino)-phenyl]-benzamide (3)

White solid: mp: 170 ^{o}C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (2H, d, *J* = 7.2 Hz, NHCOAr-2,6-**H**), 7.47-7.40 (3H, m, NHCOAr-**H**), 7.26 (2H, d, *J* = 8.4 Hz, NHAr-**H**-NHCO), 6.55 (2H, d, *J* = 8.0 Hz, NHAr-**H**NHCO), 6.25 (2H, s, 3,5-$(HO)_2$Ar-2,6-**H**), 6.05 (1H, s, 3,5-$(HO)_2$Ar-4-**H**), 4.10 (2H, s, ArC**H$_2$**NH); ^{13}C NMR (75 MHz, CD_3OD) δ 157.4, 155.2, 141.9, 129.2, 128.6, 128.3, 122.6, 122.4, 119.1, 118.3, 113.9, 113.5, 113.3; IR (KBr) 3301.9, 3205.5, 3064.7, 1643.2, 1608.5, 1519.8, 1456.2, 1406.0, 1313.4, 1244.0, 1163.0, 829.3 cm^{-1}; HRMS (ESI) Exact mass calc. for $C_{20}H_{18}N_2O_3$ $[M+H]^+$: 335.1396, found: 335.1391.

1-(4-Amino-phenyl)-3-phenyl-urea (11)

White solid: mp: 295 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H, CONHPh-2,6-**H**), 7.15 (t, *J* = 8.0 Hz, 2H, CONHPh-3,5-**H**), 7.14 (d, *J* = 8.0 Hz, 2H, 4-NH_2Ar**H**-NHCO), 6.93 (t, *J* = 8.0 Hz, 1H, CONHPh-4-**H**), 6.60 (d, *J* = 8.0 Hz, 2H, 4-NH_2Ar**H**-NHCO);. ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 144.8, 140.7, 131.0, 129.8, 123.6, 122.4, 120.4, 117.3; IR (KBr) 156.2, 144.8, 140.7, 131.0, 129.8, 123.6, 122.4, 117.0 cm^{-1}; MS (ESI) m/z $(M+H)^+$ 228.

5-Benzyloxy-isophthalic acid monomethyl ester (13)

White solid: mp: 250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, Ar-2-**H**), 7.90 (m, 2H, Ar-4,6-**H**), 7.48-7.36 (m, 5H, $OCH_2C_6\mathbf{H_5}$), 5.17 (s, 2H, O**C$\mathbf{H_2}$**Ph), 3.96 (s, 3H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.0, 158.8, 135.9, 132.0, 128.7, 128.3,127.6, 123.8, 121.1, 120.6, 70.5, 52.5; MS (ESI) m/z $(M+H)^+$ 287.

3-Benzyloxy-5-hydroxymethyl-benzoic acid methyl ester (14)

White solid: mp: 32 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H, Ar-6-**H**), 7.58 (s, 1H, Ar-2-**H**), 7.48-7.36 (m, 5H, $OCH_2C_6\mathbf{H_5}$), 7.23 (s, 1H, Ar-4-**H**), 5.12 (s, 2H, O**C$\mathbf{H_2}$**Ph), 4.72 (d, *J* = 6.0 Hz, 2H, Ar**C$\mathbf{H_2}$**OH), 3.92 (s, 3H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 158.8, 142.9, 136.4, 131.4, 128.5, 128.0, 127.5, 120.4, 118.2, 114.2, 70.1, 64.5, 52.15; MS (ESI) m/z $(M+H)^+$ 271.9.

3-Benzyloxy-5-formyl-benzoic acid methyl ester (15)

White solid: mp: 102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H, Ar**C**H**O**), 8.12 (s, 1H, Ar-2-**H**), 7.91 (s, 1H, Ar-6-**H**), 7.66 (s, 1H, Ar-4-**H**), 7.46-7.33 (m, 5H, $OCH_2C_6\mathbf{H_5}$), 5.16 (s, 2H, O**C$\mathbf{H_2}$**Ph), 3.95 (s, 3H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 170.6, 165.6, 159.2, 137.6, 135.7, 132.3, 128.6, 128.2, 127.4, 124.3, 122.0, 117.6,70.4, 52.4; IR (KBr) 1728.1, 1699.2, 1595.0, 1461.9, 1431.1, 1394.4, 1340.4, 1244.0, 1151.4, 1110.9, 1051.1, 867.9 cm^{-1}; MS (ESI) m/z $(M+H)^+$ 307.

3-Benzyloxy-5-formyl-benzoic acid (16)

White solid: mp: 130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H, Ar**C**H**O**), 8.12 (s, 1H, Ar-2-**H**), 7.98 (s, 1H, Ar-6-**H**),7.73 (s, 1H, Ar-4-**H**), 7.48-7.35 (m, 5H, $OCH_2C_6\mathbf{H_5}$), 5.19 (s, 2H, O**C$\mathbf{H_2}$**Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 170.6, 159.4, 138.0, 135.7, 131.6, 128.8, 127.6, 125.1, 122.7, 118.6, 70.6; IR (KBr) 3030.0, 2607.6, 2362.6, 1724.2, 1458.1, 1421.4, 1336.6, 1147.6, 1049.2, 929.6, 883.3 cm^{-1}; MS (ESI) m/z $(M+H)^+$ 256.

3-Formyl-5-hydroxy-benzoic acid (17)

White solid: mp: 193 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H, Ar**C**H**O**), 8.04 (s, 1H, Ar-2-**H**), 7.75 (s, 1H, Ar-6-**H**), 7.50 (s, 1H, Ar-4-**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 172.6, 157.4, 138.0, 135.7, 131.6, 122.7, 120.5; MS (ESI) m/z $(M+H)^+$ 166.