A UNIQUE AND SIMPLE PREPARATIVE METHOD FOR α-ARYL PIPECOLINIC ACID ESTERS VIA BASE-INDUCED SOMMELET–HAUSER REARRANGEMENT

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Supporting Information

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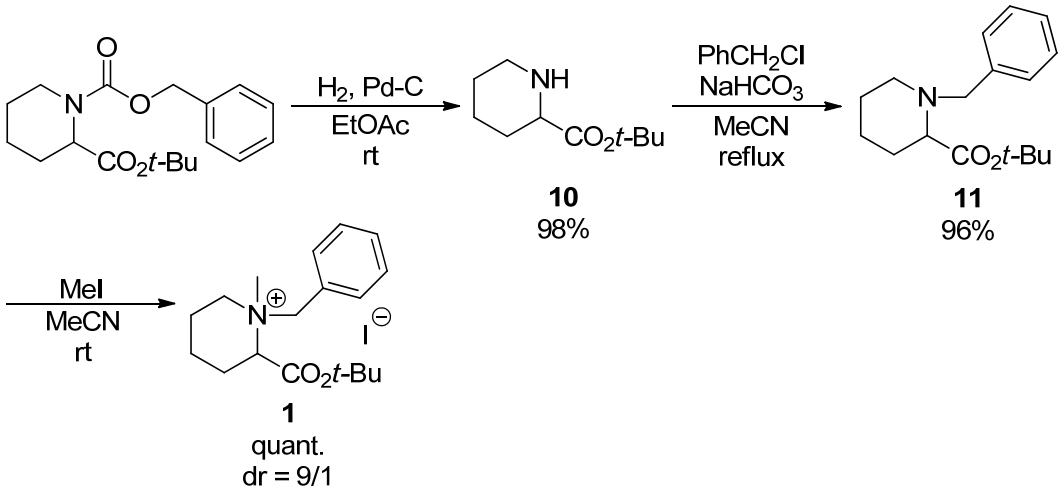
Preparation and characterization of 1 and 3

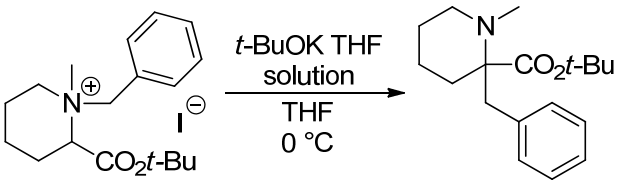
1-Benzyl-2-(*tert*-butoxycarbonyl)-1-methylpiperidinium iodide (1)



(Step 1) Cbz-pipecolinic acid[1] (1.26 g, 9.94 mmol) and palladium on activated carbon (loading: 10 wt.%, 84 mg) in ethyl acetate (20 mL) was stirred for 3.5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated to obtain *tert*-butyl piperidine-2-carboxylate (**10**) (716 mg, 98% yield) as a colorless oil. (Step 2) A mixture of **10** (260 mg, 1.40 mmol), benzyl chloride (0.18 mL, 1.6 mmol), and sodium hydrogen carbonate (0.35 g, 4.2 mmol) in acetonitrile (7 mL) was refluxed for 12 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 15/1 to 10/1 as the eluent) to give *tert*-butyl 1-benzylpiperidine-2-carboxylate (**11**) (372 mg, 96% yield) as a colorless oil. (Step 3) A solution of **11** (175 mg, 0.635 mmol) and iodomethane (0.12 mL, 1.9 mmol) in acetonitrile (1.3 mL) was stirred for 48 h at room temperature. Evaporation of the volatiles and purification of the residue by chromatography on silica gel (dichloromethane/methanol = 20/1 to 10/1 as the eluent) gave **1** (274 mg, quant., dr = 9/1) as a pale yellow solid; IR (KBr) 3442, 2974, 2945, 2873, 1731, 1621, 1458, 1395, 1370, 1304, 1236, 1151, 1085, 1054, 1028, 987, 920, 891, 858, 838, 775, 749, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, J = 7.2 Hz, Ph), 7.59-7.44 (3H, m, Ph), 5.31 (0.9H, d, J = 12.8 Hz, CH_2Ph), 5.17 (0.1H, d, J = 12.8 Hz, CH_2Ph), 5.08 (0.9H, d, J = 12.8 Hz, CH_2Ph), 5.01 (0.1H, d, J = 12.8 Hz, CH_2Ph), 4.67 (1H, dd, J = 11.6, 3.2 Hz, CHCO), 4.23 (1H, dd, J = 11.6, 11.6 Hz, NCH_2), 3.70 (1H, d, J = 11.6 Hz, NCH_2), 3.41 (0.3H, s, NCH_3), 3.39 (2.7H, s, NCH_3), 2.35 (1H, d, J = 14.8 Hz, CH_2), 2.20-1.82 (5H, m, CH_2), 1.58 (0.9H, s, *t*-Bu), 1.55 (8.1H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 133.4, 130.9, 129.2, 126.1, 85.5, 68.1, 67.2, 60.7, 42.7, 27.9, 24.6, 20.3, 19.6; HRMS–ESI (m/z): $[M–I]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2117.

(1) M. J. Genin; W. B. Gleason; R. L. Johnson, *J. Org. Chem.*, 1993, **58**, 860.

***tert*-Butyl 2-benzyl-1-methylpiperidine-2-carboxylate (3)**



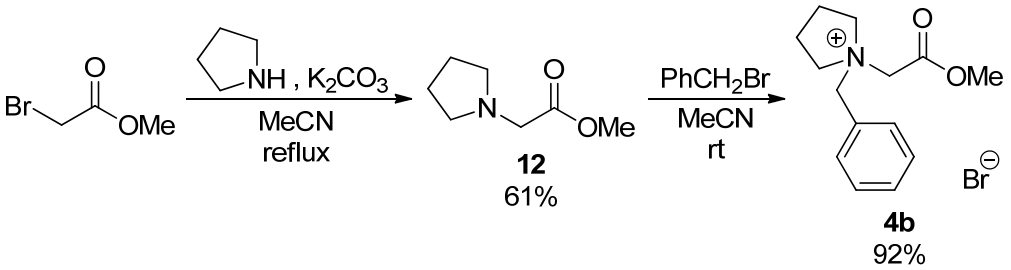
1
dr = 9/1

3
75%

A 1.0 M THF solution of potassium *tert*-butoxide (0.30 mL, 0.30 mmol) was added to a solution of **1** (104 mg, 0.249 mmol) in THF (2.5 mL) at 0 °C. The mixture was stirred for 3 h at the same temperature under an argon atmosphere. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 10/1 to 5/1 as the eluent) gave **3** (54.3 mg, 75% yield) as a pale yellow oil; IR (film) 3087, 3063, 3028, 2975, 2934, 2867, 2806, 2718, 1715, 1605, 1496, 1455, 1392, 1367, 1291, 1249, 1147, 1103, 1033, 995, 905, 848, 775, 752, 734, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.17 (5H, m, Ph), 3.28 (1H, d, J = 13.4 Hz, CH_2Ph), 2.82 (1H, d, J = 13.4 Hz, CH_2Ph), 2.73-2.58 (2H, m, NCH_2), 2.63 (3H, s, NCH_3), 1.76-1.66 (1H, m, CH_2), 1.59-1.50 (4H, m, CH_2), 1.48 (9H, s, *t*-Bu), 1.37-1.24 (1H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.1, 130.7, 127.7, 126.3, 81.0, 66.2, 52.1, 42.9, 39.7, 33.0, 28.4, 25.6, 21.3; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2112.

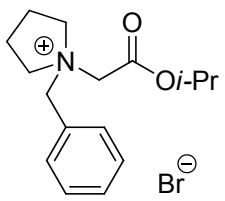
Preparation and characterization of 4

1-Benzyl-1-(2-methoxy-2-oxoethyl)pyrrolidinium bromide (4b)

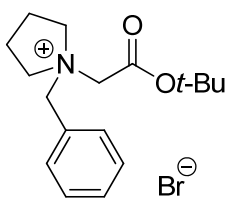


(Step 1) A mixture of methyl bromoacetate (0.76 mL, 8.0 mmol), pyrrolidine (0.73 mL, 8.7 mmol), and potassium carbonate (3.32 g, 24.0 mmol) in acetonitrile (15 mL) was refluxed for 20 h. The resulting mixture was cooled at room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10/1 as the eluent) to obtain methyl 2-(pyrrolidin-1-yl)acetate (**12**) (0.70 g, 61% yield) as a pale yellow oil. (Step 2) A solution of **12** (0.70 g, 4.9 mmol) and benzyl bromide (0.70 mL, 5.9 mmol) in acetonitrile (10 mL) was stirred for 17 h at room temperature. Evaporation of the volatiles and purification of the residue by chromatography on silica gel (dichloromethane/methanol = 5/1 as the eluent) gave **4b** (1.42 g, 92% yield) as a white solid; IR (KBr) 3035, 2964, 2905, 1759, 1496, 1456, 1441, 1396, 1373, 1350, 1307, 1206, 1183, 1121, 1098, 1072, 1036, 1019, 999, 937, 901, 870, 818, 773, 730, 709 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.56-7.51 (1H, m, Ph), 7.51-7.46 (4H, m, Ph), 4.99 (2H, s, CH_2Ph), 4.72 (2H, s, CH_2CO), 4.29-4.22 (2H, m, pyrrolidinyl-NCH_2), 4.09-4.01 (2H, m, pyrrolidinyl-NCH_2), 3.86 (3H, s, OCH_3), 2.43-2.34 (2H, m, pyrrolidinyl-CH_2), 2.26-2.18 (2H, m, pyrrolidinyl-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 132.4, 131.2, 129.7, 127.2, 63.0, 62.1, 57.8, 53.3, 21.4; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{14}H_{20}NO_2$: 234.1489. Found: 234.1489.

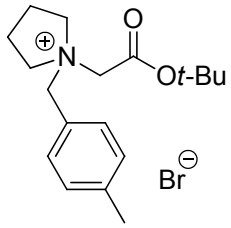
1-Benzyl-1-(2-isopropoxy-2-oxoethyl)pyrrolidinium bromide (4c): prepared in a 92% yield (overall) by the same procedure with **4b** using isopropyl chloroacetate instead of methyl bromoacetate; white solid; IR (film) 3066, 2968, 2938, 1741, 1496, 1453, 1396, 1374, 1342, 1317, 1280, 1252, 1215, 1145, 1105, 1065, 1043, 1023, 978, 935, 910, 896, 859, 815, 775, 760, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.44 (5H, m, Ph), 5.17 (1H, septet, J = 6.4 Hz, OCH), 5.00 (2H, s, CH_2Ph), 4.44 (2H, s, CH_2CO), 4.27-4.05 (4H, m, pyrrolidinyl-NCH_2), 2.42-2.23 (4H, m, pyrrolidinyl-CH_2), 1.34 (6H, d, J = 6.4 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 132.3, 131.1, 129.6, 127.4, 71.4, 62.9, 62.4, 57.7, 21.6, 21.4; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{16}H_{24}NO_2$: 262.1802. Found: 262.1799.



1-Benzyl-1-(2-*tert*-butoxy-2-oxoethyl)pyrrolidinium bromide (4d): prepared in a 84% yield (overall) by the same procedure with **4b** using *tert*-butyl chloroacetate instead of methyl bromoacetate; white solid; IR (film) 3033, 2975, 2899, 2835, 2774, 1737, 1611, 1458, 1424, 1398, 1368, 1300, 1236, 1157, 1051, 1019, 966, 900, 852, 807, 757, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.44 (5H, m, Ph), 5.00 (2H, s, CH_2Ph), 4.28 (2H, s, CH_2CO), 4.20-4.06 (4H, m, pyrrolidinyl-NCH_2), 2.40-2.25 (4H, m, pyrrolidinyl-CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 132.2, 131.0, 129.5, 127.5, 85.4, 62.7, 62.3, 57.8, 27.9, 21.3; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. Found: 276.1955.

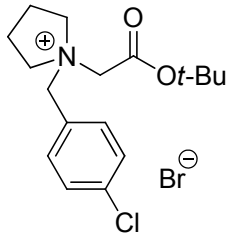


1-(2-*tert*-Butoxy-2-oxoethyl)-1-(4-methylbenzyl)pyrrolidinium bromide (4e): prepared in a 95% yield



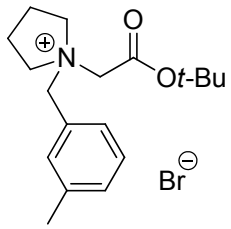
(overall) by the same procedure with **4b** using *tert*-butyl chloroacetate and 4-methylbenzyl bromide instead of methyl bromoacetate and benzyl bromide; white solid; IR (KBr) 2975, 2927, 1736, 1614, 1517, 1457, 1425, 1397, 1369, 1305, 1244, 1154, 1074, 1047, 1026, 983, 961, 899, 866, 822, 776, 750, 720, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.2 Hz, ArH), 7.28 (2H, d, *J* = 8.2 Hz, ArH), 4.86 (2H, s, CH_2Ar), 4.29 (2H, s, CH_2CO), 4.26-4.17 (2H, m, pyrrolidinyl-NCH_2), 4.11-4.01 (2H, m, pyrrolidinyl-NCH_2), 2.43-2.19 (4H, m, pyrrolidinyl-CH_2), 2.41 (3H, s, $ArCH_3$), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 141.4, 132.0, 130.2, 124.3, 85.3, 62.4, 62.1, 57.7, 27.9, 21.25, 21.23; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2114.

1-(2-*tert*-Butoxy-2-oxoethyl)-1-(4-chlorobenzyl)pyrrolidinium bromide (4f): prepared in a 86% yield



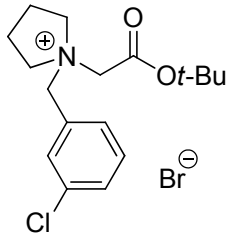
(overall) by the same procedure with **4b** using *tert*-butyl chloroacetate and 4-chlorobenzyl bromide instead of methyl bromoacetate and benzyl bromide; white solid; IR (KBr) 3058, 3016, 2977, 2918, 1729, 1595, 1491, 1471, 1455, 1425, 1395, 1367, 1337, 1311, 1290, 1252, 1155, 1121, 1082, 1053, 1013, 983, 968, 899, 867, 843, 823, 755, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, ddd, *J* = 8.4, 2.2, 2.2 Hz, ArH), 7.46 (2H, ddd, *J* = 8.4, 2.2, 2.2 Hz, ArH), 5.11 (2H, s, CH_2Ar), 4.26 (2H, s, CH_2CO), 4.12 (4H, br, pyrrolidinyl-NCH_2), 2.35-2.23 (4H, m, pyrrolidinyl-CH_2), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 137.4, 133.7, 129.7, 126.1, 85.6, 62.4, 62.3, 57.8, 27.9, 21.5; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{17}H_{25}NO_2Cl$: 310.1568. Found: 310.1563.

1-(2-*tert*-Butoxy-2-oxoethyl)-1-(3-methylbenzyl)pyrrolidinium bromide (4g): prepared in a 90% yield



(overall) by the same procedure with **4b** using *tert*-butyl chloroacetate and 3-methylbenzyl bromide instead of methyl bromoacetate and benzyl bromide; white solid; IR (film) 2977, 1738, 1609, 1590, 1460, 1425, 1395, 1370, 1307, 1247, 1155, 1122, 1083, 1034, 967, 926, 887, 867, 841, 807, 770, 751, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (2H, m, ArH), 7.28-7.21 (2H, m, ArH), 4.89 (2H, s, CH_2Ar), 4.27 (2H, s, CH_2CO), 4.22-4.05 (4H, m, pyrrolidinyl-NCH_2), 2.44-2.23 (4H, m, pyrrolidinyl-CH_2), 2.40 (3H, s, $ArCH_3$), 1.56 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 139.5, 132.6, 131.8, 129.4, 129.3, 127.3, 85.4, 62.5, 62.3, 57.7, 28.0, 21.3, 21.2; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2113.

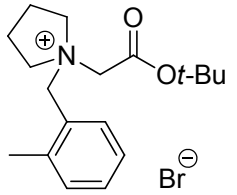
1-(2-*tert*-Butoxy-2-oxoethyl)-1-(3-chlorobenzyl)pyrrolidinium bromide (4h): prepared in a 80% yield



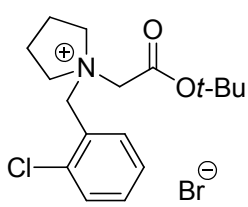
(overall) by the same procedure with **4b** using *tert*-butyl chloroacetate and 3-chlorobenzyl bromide instead of methyl bromoacetate and benzyl bromide; white solid; IR (KBr) 3060, 2971, 2906, 1739, 1572, 1476, 1459, 1438, 1392, 1370, 1306, 1293, 1250, 1219, 1152, 1124, 1082, 1061, 1021, 977, 936, 899, 881, 866, 832, 798, 769, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, ddd, *J* = 7.8, 1.6, 1.6 Hz, ArH), 7.51 (1H, ddd, *J* = 7.8, 2.0, 1.6 Hz, ArH), 7.47-7.41 (2H, m, ArH), 5.08 (2H, s, CH_2Ar),

4.26-4.07 (4H, m, pyrrolidinyl-NCH_2), 4.24 (2H, s, CH_2CO), 2.41-2.28 (4H, m, pyrrolidinyl-CH_2), 1.56 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 135.4, 131.9, 131.2, 130.9, 130.7, 129.5, 85.8, 62.7, 62.1, 57.7, 27.9, 21.3; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{17}H_{25}NO_2Cl$: 310.1568. Found: 310.1567.

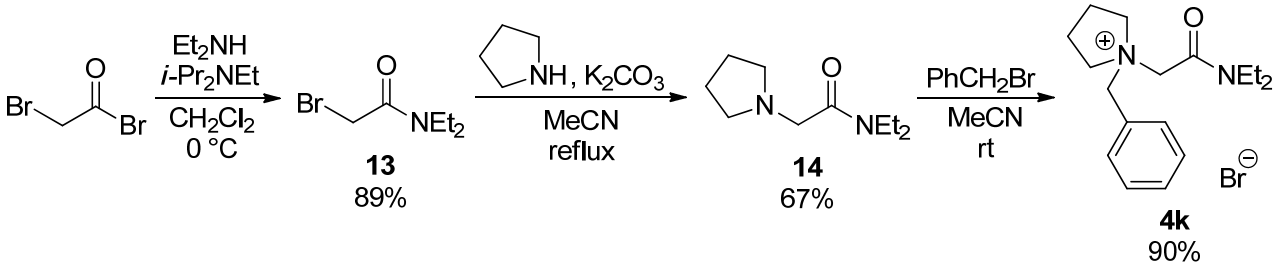
1-(2-*tert*-Butoxy-2-oxoethyl)-1-(2-methylbenzyl)pyrrolidinium bromide (4i): prepared in a 95% yield (overall) by the same procedure with **4b** using *tert*-butyl chloroacetate and 2-methylbenzyl bromide instead of methyl bromoacetate and benzyl bromide; white solid; IR (KBr) 3065, 2979, 2943, 2905, 2755, 1735, 1624, 1457, 1437, 1399, 1369, 1274, 1239, 1152, 1067, 1028, 1015, 962, 933, 918, 894, 825, 760, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 7.4 Hz, ArH), 7.41 (1H, dd, *J* = 7.4, 7.4 Hz, ArH), 7.32 (1H, d, *J* = 7.4 Hz, ArH), 7.29 (1H, dd, *J* = 7.4, 7.4 Hz, ArH), 5.17 (2H, s, CH_2Ar), 4.58 (2H, s, CH_2CO), 4.41-4.31 (2H, m, pyrrolidinyl-NCH_2), 3.77-3.65 (2H, m, pyrrolidinyl-NCH_2), 2.52 (3H, s, $ArCH_3$), 2.34-2.08 (4H, m, pyrrolidinyl-CH_2), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 140.0, 134.5, 132.0, 131.0, 126.8, 125.8, 85.6, 60.6, 60.5, 58.0, 28.0, 20.9, 20.2; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2104.



1-(2-*tert*-Butoxy-2-oxoethyl)-1-(2-chlorobenzyl)pyrrolidinium bromide (4j): Prepared in a 84% yield (overall) by the same procedure with **4b** using *tert*-butyl chloroacetate and 2-chlorobenzyl bromide instead of methyl bromoacetate and benzyl bromide; white solid; IR (KBr) 3054, 2978, 2937, 2908, 2768, 1734, 1594, 1477, 1436, 1399, 1368, 1286, 1265, 1233, 1153, 1119, 1061, 1025, 969, 939, 914, 835, 813, 779, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, dd, *J* = 7.6, 1.6 Hz, ArH), 7.53 (1H, dd, *J* = 7.6, 1.6 Hz, ArH), 7.49 (1H, ddd, *J* = 7.6, 7.6, 1.6 Hz, ArH), 7.43 (1H, ddd, *J* = 7.6, 7.6, 1.6 Hz, ArH), 5.28 (2H, s, CH_2Ar), 4.56 (2H, s, CH_2CO), 4.40-4.28 (2H, m, pyrrolidinyl-NCH_2), 4.01-3.88 (2H, m, pyrrolidinyl-NCH_2), 2.38-2.18 (4H, m, pyrrolidinyl-CH_2), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 136.6, 136.0, 132.6, 130.8, 128.0, 126.0, 85.6, 61.9, 59.7, 58.5, 28.0, 21.2; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{17}H_{25}NO_2Cl$: 310.1568. Found: 310.1558.



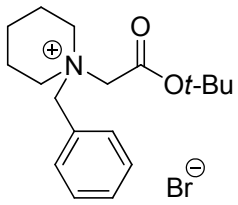
1-Benzyl-1-(2-(diethylamino)-2-oxoethyl)pyrrolidinium bromide (4k)



(Step 1) A solution of diethylamine (0.59 mL, 5.7 mmol) and *N*,*N*-diisopropylethylamine (0.99 mL, 5.7 mmol) in dichloromethane (17 mL) was treated with bromoacetyl bromide (0.50 mL, 5.7 mmol) at 0 °C. The mixture was stirred for 1.5 h at the same temperature and diluted with water. Extractive workup and evaporation of the volatiles gave *N*,*N*-diethyl-2-bromoacetamide (**13**) (0.99 g, 89% yield) as a yellow oil. (Step 2) A mixture of **13** (0.99 g, 5.1 mmol), pyrrolidine (0.47 mL, 5.6 mmol), and potassium carbonate (2.11 g, 15.3 mmol) in acetonitrile (10 mL) was refluxed for 18 h. The resulting mixture was cooled at room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on

silica gel (dichloromethane/methanol = 5/1 as the eluent) to obtain *N*,*N*-diethyl-2-(pyrrolidin-1-yl)acetamide (**14**) (0.63 g, 67% yield) as a pale yellow oil. (Step 3) A solution of **14** (0.62 g, 3.4 mmol) and benzyl bromide (0.48 mL, 4.0 mmol) in acetonitrile (6.7 mL) was stirred for 20 h at room temperature. Evaporation of the volatiles and purification of the residue by chromatography on silica gel (dichloromethane/methanol = 5/1 as the eluent) gave **4k** (1.09 g, 90% yield) as a white solid; IR (KBr) 3034, 2973, 2930, 2824, 1654, 1471, 1419, 1385, 1359, 1305, 1275, 1249, 1215, 1183, 1150, 1122, 1090, 1052, 1025, 935, 901, 841, 826, 784, 766, 734, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, tt, *J* = 7.2, 1.2 Hz, Ph), 7.50-7.44 (2H, m, Ph), 7.43-7.38 (2H, m, Ph), 4.90 (2H, s, C*H*$_2$Ph), 4.73 (2H, s, CH_2CO), 4.41-4.28 (2H, m, pyrrolidinyl-NCH_2), 4.02-3.90 (2H, m, pyrrolidinyl-NCH_2), 3.44 (2H, q, *J* = 7.2 Hz, N(C*H*$_2$$CH_3$)$_2$), 3.40 (2H, q, *J* = 7.2 Hz, N(C*H*$_2$$CH_3$)$_2$), 2.52-2.38 (2H, m, pyrrolidinyl-CH_2), 2.25-2.11 (2H, m, pyrrolidinyl-CH_2), 1.22 (3H, t, *J* = 7.2 Hz, N(CH_2C*H*$_3$)$_2$), 1.11 (3H, t, *J* = 7.2 Hz, N(CH_2C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 132.3, 131.1, 129.5, 127.8, 62.6, 62.1, 58.8, 42.1, 41.1, 21.3, 14.1, 12.9; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{17}H_{27}N_2O$: 275.2118. Found: 275.2114.

1-Benzyl-1-(2-*tert*-butoxy-2-oxoethyl)piperidinium bromide (4l)[2]: Prepared in a 85% yield (overall) by the same procedure with **4a** using *tert*-butyl bromoacetate and piperidine instead of methyl bromoacetate and pyrrolidine; white solid; IR (KBr) 3427, 2964, 2940, 1747, 1463, 1404, 1385, 1367, 1291, 1252, 1232, 1192, 1154, 1063, 1043, 1012, 969, 954, 931, 869, 851, 799, 773, 747, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.43 (5H, m, Ph), 5.23 (2H, s, C*H*$_2$Ph), 4.20 (2H, s, CH_2CO), 4.18-4.09 (2H, m, piperidinyl-NCH_2), 3.99 (2H, ddd, *J* = 12.4, 9.0, 3.2 Hz, piperidinyl-NCH_2), 2.14-1.77 (6H, m, piperidinyl-CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 132.8, 130.8, 129.3, 126.5, 85.5, 63.2, 58.3, 54.9, 27.9, 20.3, 20.0; HRMS–ESI (*m*/*z*): $[M–Br]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2106.



(2) E. Tayama, R. Sato, K. Takedachi, H. Iwamoto, and E. Hasegawa, *Tetrahedron*, 2012, **68**, 4710.

Preparation and characterization of 5

The compounds **5b**–**5k** were prepared by the procedure described in the manuscript.

Methyl 2-phenyl-2-(pyrrolidin-1-yl)acetate (5a): prepared by the literature[2]; pale yellow oil; IR (film) 3063, 3029, 2967, 2877, 2792, 1748, 1494, 1454, 1434, 1366, 1325, 1261, 1209, 1163, 1073, 1018, 908, 888, 851, 782, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.43 (2H, m, Ph), 7.38-7.25 (3H, m, Ph), 3.93 (1H, s, CHCO), 3.67 (3H, s, OCH_3), 2.62-2.51 (2H, m, NCH_2), 2.49-2.38 (2H, m, NCH_2), 1.87-1.74 (4H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 137.2, 128.4, 128.3, 128.1, 73.7, 52.4, 52.0, 23.2; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{18}NO_2$: 220.1332. Found: 220.1329.

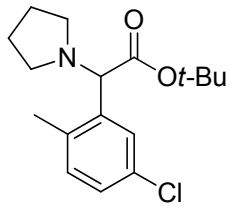
Methyl 2-(pyrrolidin-1-yl)-2-(*o*-tolyl)acetate (5b): colorless oil; IR (film) 3020, 2953, 2874, 2787, 1750, 1484, 1460, 1433, 1366, 1330, 1259, 1193, 1154, 1038, 1017, 997, 907, 893, 770, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.57 (1H, m, ArH), 7.23-7.11 (3H, m, ArH), 4.26 (1H, s, CHCO), 3.66 (3H, s, OCH_3), 2.62-2.42 (4H, m, NCH_2), 2.45 (3H, s, $ArCH_3$), 1.87-1.74 (4H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.4, 135.6, 130.4, 128.3, 127.7, 126.3, 69.0, 52.4, 51.9, 23.4, 19.8; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{20}NO_2$: 234.1489. Found: 234.1488.

Isopropyl 2-(pyrrolidin-1-yl)-2-(*o*-tolyl)acetate (5c): colorless oil; IR (film) 3063, 3021, 2974, 2875, 2786, 1742, 1603, 1485, 1462, 1371, 1315, 1266, 1165, 1107, 1038, 981, 946, 907, 823, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, dd, J = 7.6, 1.6 Hz, ArH), 7.23-7.11 (3H, m, ArH), 5.00 (1H, septet, J = 6.2 Hz, OCH), 4.21 (1H, s, CHCO), 2.57 (2H, br, NCH_2), 2.51 (2H, br, NCH_2), 2.45 (3H, s, $ArCH_3$), 1.80 (4H, br, CH_2), 1.22 (3H, d, J = 6.2 Hz, $CH(CH_3)_2$), 1.10 (3H, d, J = 6.2 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 136.3, 136.0, 130.3, 128.3, 127.4, 126.2, 69.3, 68.0, 52.3, 23.4, 21.7, 21.4, 19.8; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$: 262.1802. Found: 262.1794.

***tert*-Butyl 2-(pyrrolidin-1-yl)-2-(*o*-tolyl)acetate (5d)**: colorless oil; IR (film) 3051, 2972, 2874, 2785, 2722, 1741, 1603, 1483, 1459, 1391, 1367, 1334, 1253, 1214, 1146, 1038, 977, 940, 906, 845, 815, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, dd, J = 7.4, 1.2 Hz, ArH), 7.20-7.09 (3H, m, ArH), 4.12 (1H, s, CHCO), 2.63-2.53 (2H, m, NCH_2), 2.53-2.44 (2H, m, NCH_2), 2.43 (3H, s, $ArCH_3$), 1.83-1.71 (4H, m, CH_2), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 136.3, 135.9, 130.0, 128.0, 127.1, 125.9, 80.5, 69.5, 52.0, 27.7, 23.3, 19.6; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. Found: 276.1955.

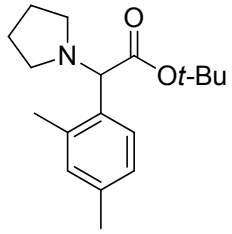
***tert*-Butyl 2-(2,5-dimethylphenyl)-2-(pyrrolidin-1-yl)acetate (5e)**: colorless oil; IR (film) 2971, 2873, 2784, 2725, 1741, 1614, 1502, 1456, 1391, 1367, 1332, 1253, 1213, 1144, 1038, 1000, 976, 944, 906, 850, 809, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, s, ArH), 7.02 (1H, d, J = 7.8 Hz, ArH), 6.96 (1H, d, J = 7.8 Hz, ArH), 4.08 (1H, s, CHCO), 2.57 (2H, br, NCH_2), 2.49 (2H, br, NCH_2), 2.38 (3H, s, $ArCH_3$), 2.30 (3H, s, $ArCH_3$), 1.80 (4H, br, CH_2), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 136.1, 135.5, 132.9, 130.0, 128.6, 128.0, 80.7, 69.7, 52.3, 27.9, 23.4, 20.9, 19.3; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2105.

***tert*-Butyl 2-(5-chloro-2-methylphenyl)-2-(pyrrolidin-1-yl)acetate (5f)**: colorless oil; IR (film) 2972, 2875,



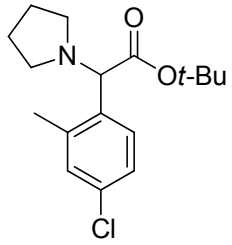
2790, 1741, 1595, 1572, 1482, 1457, 1392, 1367, 1332, 1296, 1254, 1214, 1145, 1079, 1037, 997, 978, 945, 905, 846, 810, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* = 2.2 Hz, ArH), 7.13 (1H, dd, *J* = 8.0, 2.2 Hz, ArH), 7.06 (1H, d, *J* = 8.0 Hz, ArH), 4.06 (1H, s, CHCO), 2.55 (2H, br, NCH_2), 2.50 (2H, br, NCH_2), 2.38 (3H, s, $ArCH_3$), 1.80 (4H, br, CH_2), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 138.3, 134.5, 131.9, 131.4, 128.2, 127.4, 81.2, 69.7, 52.2, 27.9, 23.4, 19.2; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}NO_2Cl$: 310.1568. Found: 310.1558.

***tert*-Butyl 2-(2,4-dimethylphenyl)-2-(pyrrolidin-1-yl)acetate (5g)**: colorless oil; IR (film) 2971, 2874,



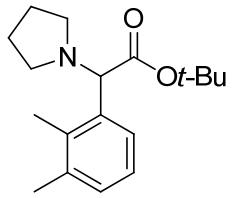
2784, 1741, 1613, 1499, 1456, 1391, 1367, 1333, 1248, 1215, 1143, 1037, 978, 945, 904, 842, 823, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 8.0 Hz, ArH), 6.99 (1H, d, *J* = 8.0 Hz, ArH), 6.95 (1H, s, ArH), 4.07 (1H, s, CHCO), 2.61-2.52 (2H, m, NCH_2), 2.52-2.42 (2H, m, NCH_2), 2.39 (3H, s, $ArCH_3$), 2.28 (3H, s, $ArCH_3$), 1.83-1.71 (4H, m, CH_2), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 136.7, 135.9, 133.4, 130.9, 128.1, 126.8, 80.7, 69.4, 52.2, 27.9, 23.4, 21.0, 19.7; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2106.

***tert*-Butyl 2-(4-chloro-2-methylphenyl)-2-(pyrrolidin-1-yl)acetate (5h)**: colorless oil; IR (film) 2972, 2875,



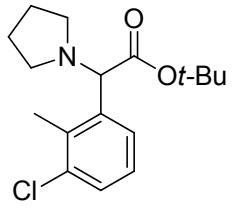
2788, 1741, 1596, 1569, 1480, 1454, 1392, 1367, 1332, 1296, 1253, 1216, 1145, 1104, 1036, 978, 942, 905, 884, 866, 853, 822, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, dd, *J* = 8.2, 1.4 Hz, ArH), 7.18-7.11 (2H, m, ArH), 4.05 (1H, s, CHCO), 2.60-2.50 (2H, m, NCH_2), 2.50-2.42 (2H, m, NCH_2), 2.40 (3H, s, $ArCH_3$), 1.84-1.71 (4H, m, CH_2), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.0, 135.0, 132.8, 130.0, 129.7, 126.2, 81.1, 69.2, 52.1, 27.8, 23.4, 19.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}NO_2Cl$: 310.1568. Found: 310.1567.

***tert*-Butyl 2-(2,3-dimethylphenyl)-2-(pyrrolidin-1-yl)acetate (5i)**: colorless oil; IR (film) 3066, 2970, 2874,



2784, 2722, 1740, 1587, 1461, 1390, 1367, 1330, 1295, 1251, 1213, 1144, 1092, 1037, 977, 944, 908, 849, 826, 813, 773, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (1H, m, ArH), 7.11-7.03 (2H, m, ArH), 4.21 (1H, s, CHCO), 2.62-2.44 (4H, m, NCH_2), 2.33 (3H, s, $ArCH_3$), 2.29 (3H, s, $ArCH_3$), 1.84-1.71 (4H, m, CH_2), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 136.5, 136.2, 134.9, 129.0, 126.2, 125.4, 80.8, 69.8, 52.1, 27.9, 23.5, 21.0, 15.1; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2110.

***tert*-Butyl 2-(3-chloro-2-methylphenyl)-2-(pyrrolidin-1-yl)acetate (5j)**: colorless oil; IR (film) 3064, 2971,

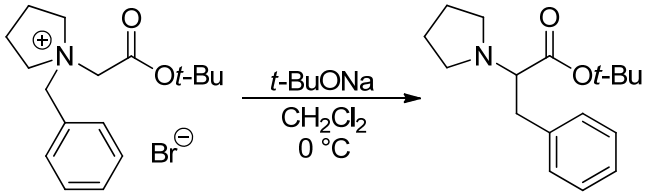


2874, 2789, 2722, 1741, 1571, 1453, 1391, 1367, 1330, 1294, 1253, 1213, 1149, 1080, 1013, 978, 944, 908, 876, 845, 774, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 7.8, 1.2 Hz, ArH), 7.28 (1H, dd, *J* = 7.8, 1.2 Hz, ArH), 7.12 (1H, dd, *J* = 7.8, 7.8 Hz, ArH), 4.17 (1H, s, CHCO), 2.61-2.44 (4H, m, NCH_2), 2.49 (3H, s, $ArCH_3$), 1.84-1.72 (4H, m, CH_2), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6,

138.5, 134.8, 134.3, 128.4, 127.0, 126.7, 81.2, 70.1, 52.0, 27.9, 23.5, 16.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}NO_2Cl$: 310.1568. Found: 310.1565.

***N*,*N*-Diethyl-2-(pyrrolidin-1-yl)-2-(*o*-tolyl)acetamide (5k)**: colorless oil; IR (film) 3061, 2966, 2933, 2872, 1647, 1458, 1427, 1378, 1361, 1264, 1220, 1125, 1097, 1054, 1035, 947, 901, 849, 733, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.45 (1H, m, ArH), 7.19-7.13 (3H, m, ArH), 4.55 (1H, s, CHCO), 3.50 (1H, dq, *J* = 13.5, 7.0 Hz, $N(CH_2CH_3)_2$), 3.27 (1H, dq, *J* = 14.8, 7.0 Hz, $N(CH_2CH_3)_2$), 3.18 (1H, dq, *J* = 13.5, 7.0 Hz, $N(CH_2CH_3)_2$), 2.99 (1H, dq, *J* = 14.8, 7.0 Hz, $N(CH_2CH_3)_2$), 2.76-2.66 (2H, m, pyrrolidinyl-NCH_2), 2.66-2.57 (2H, m, pyrrolidinyl-NCH_2), 2.44 (3H, s, $ArCH_3$), 1.81-1.70 (4H, m, pyrrolidinyl-CH_2), 1.08 (3H, t, *J* = 7.0 Hz, $N(CH_2CH_3)_2$), 0.89 (3H, t, *J* = 7.0 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 136.3, 135.8, 130.4, 128.6, 127.4, 126.1, 64.9, 50.9, 40.8, 40.2, 23.7, 19.5, 13.8, 12.6; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{27}N_2O$: 275.2118. Found: 275.2109.

***tert*-Butyl 3-phenyl-2-(pyrrolidin-1-yl)propanoate (5d')**



4d **5d'** 72%

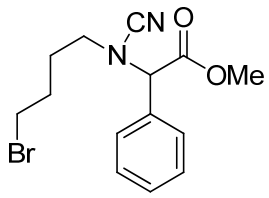
Sodium *tert*-butoxide (53 mg, 0.55 mmol) was added to a solution of **4d** (177 mg, 0.497 mmol) in dichloromethane (5 mL) at room temperature and the mixture was stirred for 3 h at the same temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 5/1 to 2/1 as the eluent) gave **5d'** (98.4 mg, 72% yield) as a colorless oil; IR (film) 3063, 3029, 2971, 2932, 2875, 2812, 1723, 1604, 1495, 1479, 1455, 1391, 1367, 1294, 1253, 1218, 1147, 1078, 1054, 1031, 982, 904, 873, 847, 742, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.15 (5H, m, Ph), 3.34 (1H, dd, *J* = 9.8, 5.8 Hz, CHCO), 3.04 (1H, dd, *J* = 13.3, 5.8 Hz, CH_2Ph), 3.00 (1H, dd, *J* = 13.3, 9.8 Hz, CH_2Ph), 2.85-2.75 (2H, m, NCH_2), 2.73-2.64 (2H, m, NCH_2), 1.86-1.73 (4H, m, pyrrolidinyl-CH_2), 1.27 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 137.9, 129.2, 128.0, 126.2, 80.6, 68.6, 50.3, 38.0, 27.9, 23.4; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. Found: 276.1953.

***tert*-Butyl 3-phenyl-2-(piperidin-1-yl)propanoate (5l)**: prepared by the same procedure with **5d'** using **4l** as a substrate; pale yellow oil; IR (film) 3062, 3028, 2974, 2933, 2853, 2808, 2753, 1722, 1603, 1495, 1453, 1390, 1367, 1255, 1224, 1204, 1145, 1116, 1053, 1033, 995, 959, 910, 847, 798, 740, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.14 (5H, m, Ph), 3.30 (1H, dd, *J* = 10.2, 5.6 Hz, CHCO), 3.04 (1H, dd, *J* = 13.4, 10.2 Hz, CH_2Ph), 2.88 (1H, dd, *J* = 13.4, 5.6 Hz, CH_2Ph), 2.71 (2H, ddd, *J* = 11.1, 7.4, 3.6 Hz, NCH_2), 2.56

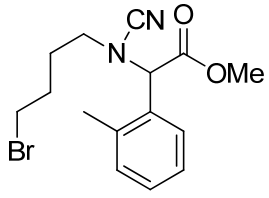
(2H, ddd, J = 11.1, 7.4, 3.6 Hz, NCH_2), 1.66-1.40 (6H, m, pyrrolidinyl-CH_2), 1.33 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.5, 129.3, 128.0, 126.1, 80.7, 70.6, 50.9, 36.1, 28.1, 26.5, 24.6; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2108.

Characterization of 6

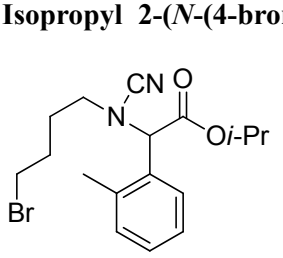
Methyl 2-(*N*-(4-bromobutyl)cyanamido)-2-phenylacetate (6a)[2]: pale yellow oil; IR (film) 3034, 2953, 2886, 2212, 1746, 1495, 1454, 1436, 1391, 1345, 1258, 1212, 1176, 1116, 1078, 1032, 1005, 992, 925, 868, 836, 773, 735, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (3H, m, Ph), 7.39-7.33 (2H, m, Ph), 4.80 (1H, s, CHCO), 3.82 (3H, s, OCH_3), 3.41 (1H, dt, *J* = 11.6, 6.4 Hz, CH_2), 3.38 (1H, dt, *J* = 11.6, 6.4 Hz, CH_2), 3.13 (1H, dt, *J* = 13.0, 6.8 Hz, CH_2), 3.09 (1H, dt, *J* = 13.0, 6.8 Hz, CH_2), 1.97-1.80 (4H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 132.3, 129.7, 129.1, 128.6, 115.2, 66.5, 52.8, 49.9, 32.6, 29.2, 26.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{17}N_2O_2BrNa$: 347.0366. Found: 347.0358.



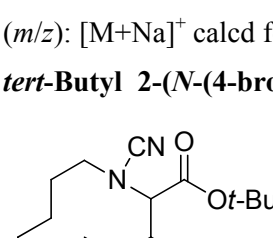
Methyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(*o*-tolyl)acetate (6b): colorless oil; IR (film) 3023, 2952, 2885, 2212, 1743, 1605, 1492, 1460, 1436, 1374, 1346, 1256, 1211, 1174, 1116, 1074, 1044, 995, 918, 864, 835, 808, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (2H, m, ArH), 7.24 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz, ArH), 7.16 (1H, dd, *J* = 7.6, 1.4 Hz, ArH), 5.01 (1H, s, CHCO), 3.82 (3H, s, OCH_3), 3.37 (1H, dt, *J* = 9.8, 6.6 Hz, CH_2), 3.35 (1H, dt, *J* = 9.8, 6.6 Hz, CH_2), 3.11 (2H, t, *J* = 6.8 Hz, CH_2), 2.43 (3H, s, $ArCH_3$), 1.95-1.76 (4H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.4, 131.2, 130.7, 129.9, 128.2, 126.6, 115.3, 63.8, 52.8, 49.5, 32.6, 29.3, 26.3, 19.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{19}N_2O_2BrNa$: 361.0522. Found: 361.0520.



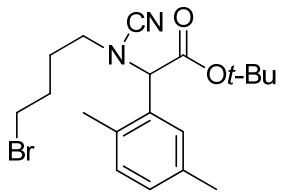
Isopropyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(*o*-tolyl)acetate (6c): white solid; IR (film) 2984, 2935, 2885, 2214, 1739, 1479, 1460, 1372, 1339, 1318, 1268, 1213, 1190, 1101, 1073, 1052, 959, 906, 865, 817, 798, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (2H, m, ArH), 7.23 (1H, ddd, *J* = 7.2, 7.2, 1.4 Hz, ArH), 7.18 (1H, dd, *J* = 7.2, 1.4 Hz, ArH), 5.19 (1H, septet, *J* = 6.4 Hz, OCH), 4.94 (1H, s, CHCO), 3.37 (1H, dt, *J* = 12.2, 6.4 Hz, CH_2), 3.34 (1H, dt, *J* = 12.2, 6.4 Hz, CH_2), 3.12 (1H, dt, *J* = 12.8, 6.4 Hz, CH_2), 3.08 (1H, dt, *J* = 12.8, 6.4 Hz, CH_2), 2.43 (3H, s, $ArCH_3$), 1.94-1.75 (4H, m, CH_2), 1.31 (3H, d, *J* = 6.4 Hz, $CH(CH_3)_2$), 1.23 (3H, d, *J* = 6.4 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 137.5, 131.2, 130.9, 129.7, 128.1, 126.5, 115.5, 70.2, 63.9, 49.4, 32.6, 29.4, 26.3, 21.8, 21.5, 19.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{23}N_2O_2BrNa$: 389.0835. Found: 389.0835.



***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(*o*-tolyl)acetate (6d)**: white solid; IR (film) 3067, 2977, 2935, 2880, 2212, 1738, 1605, 1491, 1460, 1393, 1369, 1342, 1255, 1221, 1155, 1074, 1041, 955, 881, 861, 826, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (4H, m, ArH), 4.84 (1H, s, CHCO), 3.37 (1H, dt, *J* = 12.6, 6.4 Hz, CH_2), 3.35 (1H, dt, *J* = 12.6, 6.4 Hz, CH_2), 3.10 (2H, t, *J* = 6.8 Hz, CH_2), 2.42 (3H, s, $ArCH_3$), 1.94-1.77 (4H, m, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 137.5, 131.3, 131.1, 129.6, 128.0, 126.4, 115.6, 83.4, 64.1, 49.6, 32.6, 29.4, 27.9, 26.3, 19.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{25}N_2O_2BrNa$: 403.0992. Found: 403.0990.

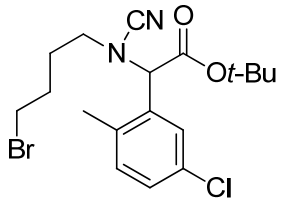


***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(2,5-dimethylphenyl)acetate (6e)**: white solid; IR (KBr)



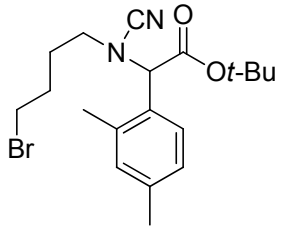
2979, 2946, 2886, 2212, 1733, 1505, 1452, 1392, 1366, 1336, 1311, 1227, 1158, 1119, 1072, 1050, 1002, 957, 927, 870, 833, 809, 781, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 8.2 Hz, ArH), 7.10 (1H, d, *J* = 8.2 Hz, ArH), 7.02 (1H, s, ArH), 4.81 (1H, s, CHCO), 3.38 (1H, dt, *J* = 12.8, 6.4 Hz, CH_2), 3.35 (1H, dt, *J* = 12.8, 6.4 Hz, CH_2), 3.11 (1H, dt, *J* = 13.0, 6.8 Hz, CH_2), 3.07 (1H, dt, *J* = 13.0, 6.8 Hz, CH_2), 2.36 (3H, s, $ArCH_3$), 2.31 (3H, s, $ArCH_3$), 1.95-1.77 (4H, m, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 135.9, 134.3, 131.04, 130.95, 130.2, 128.7, 115.7, 83.3, 64.1, 49.5, 32.7, 29.4, 27.9, 26.3, 21.0, 18.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{27}N_2O_2BrNa$: 417.1148. Found: 417.1144.

***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(5-chloro-2-methylphenyl)acetate (6f)**: white solid; IR



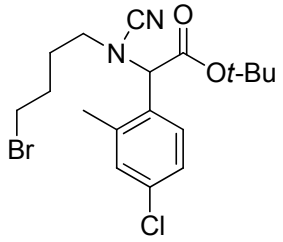
(KBr) 2969, 2944, 2886, 2211, 1730, 1489, 1450, 1395, 1369, 1252, 1229, 1158, 1121, 1089, 1072, 1045, 1001, 957, 917, 891, 868, 827, 810, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, dd, *J* = 8.2, 2.0 Hz, ArH), 7.22 (1H, d, *J* = 2.0 Hz, ArH), 7.20 (1H, d, *J* = 8.2 Hz, ArH), 4.78 (1H, s, CHCO), 3.39 (2H, t, *J* = 6.4 Hz, CH_2), 3.12 (1H, dt, *J* = 12.6, 6.8 Hz, CH_2), 3.07 (1H, dt, *J* = 12.6, 6.8 Hz, CH_2), 2.38 (3H, s, $ArCH_3$), 1.96-1.78 (4H, m, CH_2), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 136.0, 133.0, 132.4, 132.1, 129.6, 128.2, 115.2, 84.0, 63.9, 49.7, 32.6, 29.4, 27.9, 26.3, 18.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_2BrClNa$: 437.0602. Found: 437.0596.

***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(2,4-dimethylphenyl)acetate (6g)**: white solid; IR (KBr)



2970, 2933, 2212, 1736, 1613, 1504, 1452, 1393, 1368, 1345, 1291, 1257, 1230, 1156, 1113, 1068, 1044, 951, 928, 890, 851, 835, 805, 785, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, d, *J* = 8.0 Hz, ArH), 7.07 (1H, s, ArH), 7.03 (1H, d, *J* = 8.0 Hz, ArH), 4.80 (1H, s, CHCO), 3.38 (1H, dt, *J* = 11.4, 6.4 Hz, CH_2), 3.35 (1H, dt, *J* = 11.4, 6.4 Hz, CH_2), 3.08 (2H, t, *J* = 6.8 Hz, CH_2), 2.37 (3H, s, $ArCH_3$), 2.32 (3H, s, $ArCH_3$), 1.95-1.75 (4H, m, CH_2), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 139.5, 137.2, 131.9, 128.3, 127.9, 127.1, 115.7, 83.3, 63.9, 49.5, 32.7, 29.4, 27.9, 26.3, 21.1, 19.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{27}N_2O_2BrNa$: 417.1148. Found: 417.1147.

***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(4-chloro-2-methylphenyl)acetate (6h)**: white solid; IR



(KBr) 2980, 2934, 2211, 1736, 1597, 1568, 1485, 1446, 1394, 1369, 1346, 1255, 1222, 1156, 1118, 1075, 1045, 1007, 956, 875, 848, 804, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 2.0 Hz, ArH), 7.22 (1H, dd, *J* = 8.4, 2.0 Hz, ArH), 7.19 (1H, d, *J* = 8.4 Hz, ArH), 4.75 (1H, s, CHCO), 3.41 (1H, dt, *J* = 11.2, 6.4 Hz, CH_2), 3.38 (1H, dt, *J* = 11.2, 6.4 Hz, CH_2), 3.12 (1H, dt, *J* = 12.8, 6.4 Hz, CH_2), 3.08 (1H, dt, *J* = 12.8, 6.4 Hz, CH_2), 2.39 (3H, s, $ArCH_3$), 1.97-1.79 (4H, m, CH_2), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 139.4, 135.4, 131.1, 129.9, 129.3, 126.6, 115.2, 83.8, 63.4, 50.0, 32.6, 29.4, 27.9, 26.3, 19.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_2BrClNa$: 437.0602. Found: 437.0588.

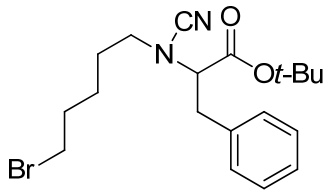
***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(2,3-dimethylphenyl)acetate (6i)**: white solid; IR (KBr) 2976, 2950, 2898, 2212, 1730, 1588, 1456, 1394, 1368, 1354, 1314, 1232, 1154, 1116, 1094, 1071, 1017, 989, 954, 906, 879, 832, 813, 777, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, d, *J* = 7.6 Hz, ArH), 7.12 (1H, dd, *J* = 7.6, 7.6 Hz, ArH), 7.07 (1H, d, *J* = 7.6 Hz, ArH), 4.90 (1H, s, CHCO), 3.35 (2H, t, *J* = 6.4 Hz, CH_2), 3.090 (1H, t, *J* = 6.6 Hz, CH_2), 3.086 (1H, t, *J* = 6.6 Hz, CH_2), 2.33 (3H, s, $ArCH_3$), 2.29 (3H, s, $ArCH_3$), 1.94-1.76 (4H, m, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 137.9, 136.1, 131.3, 131.1, 125.9, 125.8, 115.7, 83.4, 64.6, 49.3, 32.6, 29.4, 28.0, 26.4, 20.9, 15.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{27}N_2O_2BrNa$: 417.1148. Found: 417.1140.

***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(3-chloro-2-methylphenyl)acetate (6j)**: white solid; IR (KBr) 3065, 2975, 2897, 2213, 1732, 1572, 1445, 1395, 1369, 1355, 1314, 1232, 1154, 1115, 1069, 1019, 953, 878, 828, 813, 779, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (1H, m, ArH), 7.21-7.14 (2H, m, ArH), 4.83 (1H, s, CHCO), 3.45-3.34 (2H, m, CH_2), 3.18-3.05 (2H, m, CH_2), 2.45 (3H, s, $ArCH_3$), 1.98-1.80 (4H, m, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 135.8, 135.7, 133.3, 130.7, 127.0, 126.7, 115.2, 83.8, 64.5, 50.1, 32.6, 29.4, 27.9, 26.3, 16.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_2BrClNa$: 437.0602. Found: 437.0591.

2-(*N*-(4-Bromobutyl)cyanamido)-*N*,*N*-diethyl-2-(*o*-tolyl)acetamide (6k): white solid; IR (KBr) 3028, 2972, 2937, 2875, 2205, 1643, 1464, 1435, 1380, 1348, 1322, 1279, 1257, 1216, 1135, 1105, 1068, 1038, 980, 953, 880, 862, 824, 776, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (4H, m, ArH), 5.02-4.97 (1H, m, CHCO), 3.63 (1H, dq, *J* = 13.6, 7.0 Hz, $N(CH_2CH_3)_2$), 3.43-3.31 (2H, m, CH_2), 3.25 (1H, dq, *J* = 13.6, 7.0 Hz, $N(CH_2CH_3)_2$), 3.19-3.06 (2H, m, CH_2), 2.95 (1H, dq, *J* = 14.9, 7.0 Hz, $N(CH_2CH_3)_2$), 2.86 (1H, dq, *J* = 14.9, 7.0 Hz, $N(CH_2CH_3)_2$), 2.45 (3H, s, $ArCH_3$), 1.96-1.71 (4H, m, CH_2), 1.16 (3H, t, *J* = 7.0 Hz, $N(CH_2CH_3)_2$), 0.95 (3H, t, *J* = 7.0 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 136.9, 131.2, 131.0, 129.8, 128.7, 126.7, 116.3, 62.6, 49.6, 41.2, 40.4, 32.8, 29.5, 26.4, 19.2, 13.7, 12.6; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{27}N_3OBr$: 380.1332. Found: 380.1327.

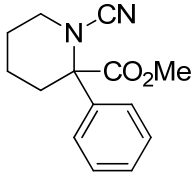
***tert*-Butyl 2-(*N*-(4-bromobutyl)cyanamido)-3-phenylpropanoate (6d')**: white solid; IR (film) 3063, 3029, 2976, 2933, 2873, 2211, 1735, 1604, 1496, 1454, 1393, 1369, 1278, 1256, 1153, 1078, 1031, 957, 909, 841, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (5H, m, Ph), 3.51 (1H, dd, *J* = 10.6, 5.0 Hz, CHCO), 3.27-3.02 (5H, m, CH_2), 2.84 (1H, dt, *J* = 12.4, 6.4 Hz, CH_2), 1.71-1.45 (4H, m, CH_2), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.2, 129.0, 128.6, 127.2, 115.1, 83.2, 65.2, 51.5, 36.5, 32.6, 28.8, 27.9, 26.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{25}N_2O_2BrNa$: 403.0992. Found: 403.0984.

***tert*-Butyl 2-(*N*-(5-bromopentyl)cyanamido)-3-phenylpropanoate (6l)**: white solid; IR (film) 3063, 3029, 2977, 2935, 2867, 2211, 1731, 1604, 1496, 1454, 1393, 1369, 1279, 1256, 1212, 1152, 1079, 1031, 962, 909, 842, 750, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m, Ph), 3.52 (1H, dd, *J* = 10.4, 4.8 Hz, CHCO), 3.31-3.19 (3H, m, CH_2), 3.12-3.02 (2H, m, CH_2), 2.79 (1H, dt, *J* = 12.8, 6.8 Hz, CH_2), 1.78-1.60 (2H, m, CH_2), 1.58-1.37 (2H, m, CH_2), 1.49 (9H, s, *t*-Bu), 1.34-1.12 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.2, 129.0, 128.5, 127.0, 115.1, 83.0, 65.2, 52.1, 36.4, 33.0, 32.0, 27.8, 26.6, 24.6; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{27}N_2O_2BrNa$: 417.1148. Found: 417.1138.



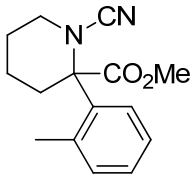
Characterization of 7

Methyl 1-cyano-2-phenylpiperidine-2-carboxylate (7a): white solid; IR (film) 3061, 3031, 2951, 2866,



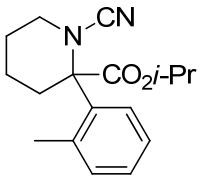
2214, 1739, 1493, 1447, 1373, 1296, 1243, 1196, 1152, 1125, 1108, 1086, 1059, 1035, 1011, 981, 936, 866, 822, 756, 731, 698 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.42-7.34 (5H, m, Ph), 3.91 (3H, s, OCH_3), 3.55-3.50 (1H, m, NCH_2), 3.37-3.31 (1H, m, NCH_2), 2.51 (1H, ddd, *J* = 13.7, 3.5, 3.5 Hz, CH_2), 1.94 (1H, ddd, *J* = 13.7, 13.7, 3.5 Hz, CH_2), 1.88-1.82 (1H, m, CH_2), 1.77-1.69 (2H, m, CH_2), 1.45-1.37 (1H, m, CH_2); ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.0, 137.8, 129.2, 128.9, 126.5, 116.7, 70.5, 53.0, 49.7, 35.1, 23.8, 21.4; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{16}N_2O_2Na$: 267.1104. Found: 267.1101.

Methyl 1-cyano-2-(*o*-tolyl)piperidine-2-carboxylate (7b): white solid; IR (film) 3062, 3020, 2952, 2867,



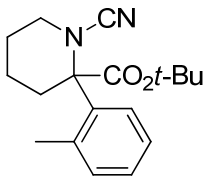
2213, 1738, 1490, 1451, 1372, 1336, 1308, 1288, 1239, 1188, 1152, 1129, 1108, 1082, 1057, 1009, 981, 959, 938, 869, 820, 760, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.12 (4H, m, ArH), 3.87 (3H, s, OCH_3), 3.56-3.44 (2H, m, NCH_2), 2.58 (3H, s, $ArCH_3$), 2.45 (1H, ddd, *J* = 13.8, 3.6, 3.6 Hz, CH_2), 2.21 (1H, ddd, *J* = 13.8, 13.8, 3.6 Hz, CH_2), 1.94-1.85 (1H, m, CH_2), 1.83-1.68 (2H, m, CH_2), 1.52-1.39 (1H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.0, 135.4, 133.2, 129.0, 127.2, 126.2, 116.6, 70.4, 52.9, 49.3, 32.1, 23.4, 21.1, 20.6; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{18}N_2O_2Na$: 281.1260. Found: 281.1259.

Isopropyl 1-cyano-2-(*o*-tolyl)piperidine-2-carboxylate (7c): white solid; IR (film) 3065, 3023, 2963, 2934,



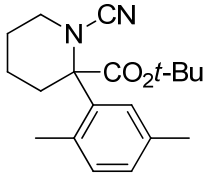
2860, 2211, 1732, 1576, 1464, 1376, 1339, 1284, 1244, 1180, 1152, 1107, 1060, 1047, 1008, 976, 949, 919, 894, 863, 838, 822, 782, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.13(4H, m, ArH), 5.23 (1H, septet, *J* = 6.0 Hz, OCH), 3.56-3.41 (2H, m, NCH_2), 2.61 (3H, s, $ArCH_3$), 2.43 (1H, ddd, *J* = 13.6, 3.8, 3.8 Hz, CH_2), 2.18 (1H, ddd, *J* = 13.6, 13.6, 3.8 Hz, CH_2), 1.93-1.84 (1H, m, CH_2), 1.83-1.69 (2H, m, CH_2), 1.54-1.40 (1H, m, CH_2), 1.33 (3H, d, *J* = 6.0 Hz, $CH(CH_3)_2$), 1.31 (3H, d, *J* = 6.0 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 137.0, 135.6, 133.2, 128.8, 127.2, 126.1, 116.8, 70.2, 49.3, 32.0, 23.5, 21.8, 21.6, 21.1, 20.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{22}N_2O_2Na$: 309.1573. Found: 309.1568.

***tert*-Butyl 1-cyano-2-(*o*-tolyl)piperidine-2-carboxylate (7d)**: white solid; IR (film) 3061, 2964, 2928, 2862,



2210, 1730, 1454, 1392, 1367, 1332, 1286, 1250, 1143, 1112, 1085, 1060, 1006, 971, 944, 865, 837, 755, 746, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.13 (4H, m, ArH), 3.55-3.39 (2H, m, NCH_2), 2.62 (3H, s, $ArCH_3$), 2.40 (1H, ddd, *J* = 13.6, 3.6, 3.6 Hz, CH_2), 2.13 (1H, ddd, *J* = 13.6, 13.6, 3.6 Hz, CH_2), 1.92-1.83 (1H, m, CH_2), 1.82-1.69 (2H, m, CH_2), 1.62-1.42 (1H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 137.0, 136.0, 133.2, 128.7, 127.2, 126.0, 117.0, 83.4, 70.6, 49.4, 32.0, 27.9, 23.5, 21.2, 20.9; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_2Na$: 323.1730. Found: 323.1727.

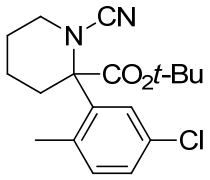
***tert*-Butyl 1-cyano-2-(2,5-dimethylphenyl)piperidine-2-carboxylate (7e)**: white solid; IR (KBr) 2964,



2931, 2860, 2210, 1730, 1498, 1480, 1451, 1390, 1368, 1340, 1330, 1283, 1249, 1194, 1146, 1113, 1087, 1057, 1013, 996, 948, 884, 848, 806, 791, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, d, *J* = 7.7 Hz, ArH), 7.04 (1H, d, *J* = 7.7 Hz, ArH), 7.00 (1H, s, ArH), 3.55-3.47 (1H, m, NCH_2), 3.45-3.34 (1H, m, NCH_2), 2.58 (3H, s, $ArCH_3$), 2.37

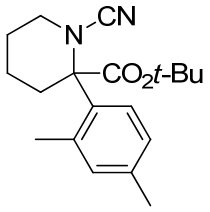
(1H, ddd, J = 13.6, 3.6, 3.6 Hz, CH_2), 2.28 (3H, s, $ArCH_3$), 2.12 (1H, ddd, J = 13.6, 13.6, 3.6 Hz, CH_2), 1.90-1.81 (1H, m, CH_2), 1.78-1.69 (2H, m, CH_2), 1.58 (9H, s, *t*-Bu), 1.54-1.40 (1H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.7, 135.2, 133.7, 133.2, 129.4, 128.1, 117.1, 83.3, 70.7, 49.4, 31.8, 27.9, 23.5, 21.2, 21.1, 20.4; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{26}N_2O_2Na$: 337.1886. Found: 337.1884.

***tert*-Butyl 2-(5-chloro-2-methylphenyl)-1-cyanopiperidine-2-carboxylate (7f)**: white solid; IR (KBr) 3012,



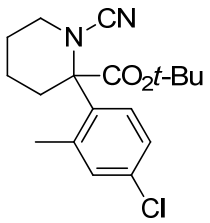
2951, 2872, 2214, 1731, 1597, 1561, 1473, 1452, 1387, 1368, 1284, 1248, 1145, 1123, 1076, 1033, 1013, 955, 892, 856, 836, 775, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, s, ArH), 7.21 (1H, dd, J = 6.2, 2.4 Hz, ArH), 7.15 (1H, dd, J = 6.2, 2.4 Hz, ArH), 3.55-3.42 (2H, m, NCH_2), 2.58 (3H, s, $ArCH_3$), 2.39 (1H, ddd, J = 13.6, 3.8, 3.8 Hz, CH_2), 2.08 (1H, ddd, J = 13.6, 13.6, 3.8 Hz, CH_2), 1.93-1.84 (1H, m, CH_2), 1.79-1.69 (2H, m, CH_2), 1.61-1.41 (1H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 137.6, 135.6, 134.3, 131.6, 128.6, 127.6, 116.6, 83.8, 70.1, 49.3, 31.8, 27.9, 23.4, 21.0, 20.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{23}N_2O_2ClNa$: 357.1340. Found: 357.1334

***tert*-Butyl 1-cyano-2-(2,4-dimethylphenyl)piperidine-2-carboxylate (7g)**: white solid; IR (film) 2933,



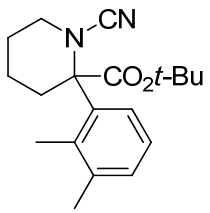
2866, 2213, 1727, 1615, 1571, 1502, 1453, 1392, 1369, 1336, 1307, 1285, 1249, 1149, 1056, 1005, 966, 894, 869, 845, 833, 808, 779, 728, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, J = 8.2 Hz, ArH), 7.03 (1H, s, ArH), 6.96 (1H, d, J = 8.2 Hz, ArH), 3.54-3.38 (2H, m, NCH_2), 2.58 (3H, s, $ArCH_3$), 2.38 (1H, ddd, J = 13.4, 3.6, 3.6 Hz, CH_2), 2.28 (3H, s, $ArCH_3$), 2.12 (1H, ddd, J = 13.4, 13.4, 3.6 Hz, CH_2), 1.91-1.81 (1H, m, CH_2), 1.81-1.68 (2H, m, CH_2), 1.61-1.40 (1H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 138.4, 136.8, 134.1, 133.1, 127.2, 126.7, 117.1, 83.2, 70.4, 49.3, 31.6, 28.0, 23.5, 21.2, 20.8, 20.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{26}N_2O_2Na$: 337.1886. Found: 337.1886.

***tert*-Butyl 2-(4-chloro-2-methylphenyl)-1-cyanopiperidine-2-carboxylate (7h)**: white solid; IR (film)



2973, 2930, 2864, 2209, 1734, 1597, 1566, 1486, 1454, 1392, 1368, 1333, 1286, 1249, 1142, 1114, 1086, 1053, 1006, 947, 876, 845, 833, 790, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (1H, s, ArH), 7.19-7.11 (2H, m, ArH), 3.54-3.43 (2H, m, NCH_2), 2.59 (3H, s, $ArCH_3$), 2.39 (1H, ddd, J = 13.5, 3.8, 3.8 Hz, CH_2), 2.08 (1H, ddd, J = 13.5, 13.5, 3.8 Hz, CH_2), 1.93-1.83 (1H, m, CH_2), 1.78-1.68 (2H, m, CH_2), 1.61-1.42 (1H, m, CH_2), 1.53 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 139.2, 134.6, 134.4, 132.9, 128.6, 126.1, 116.7, 83.6, 70.0, 49.3, 32.1, 27.9, 23.4, 21.0, 20.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{23}N_2O_2ClNa$: 357.1340. Found: 357.1337.

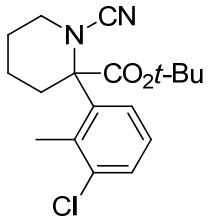
***tert*-Butyl 1-cyano-2-(2,3-dimethylphenyl)piperidine-2-carboxylate (7i)**: white solid; IR (KBr) 2964,



2927, 2861, 2210, 1728, 1452, 1390, 1368, 1332, 1285, 1258, 1247, 1146, 1109, 1077, 1052, 1003, 967, 868, 842, 820, 773, 739, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17-7.13 (1H, m, ArH), 7.11-7.04 (2H, m, ArH), 3.57-3.43 (2H, m, NCH_2), 2.51 (3H, s, $ArCH_3$), 2.40 (1H, ddd, J = 13.6, 3.5, 3.5 Hz, CH_2), 2.28 (3H, s, $ArCH_3$), 2.16 (1H, ddd, J = 13.6, 13.6, 3.5 Hz, CH_2), 1.92-1.82 (1H, m, CH_2), 1.82-1.68 (2H, m, CH_2), 1.62-1.43

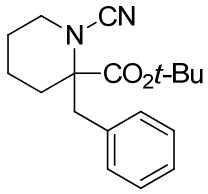
(1H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 139.1, 135.87, 135.86, 130.6, 125.4, 125.2, 117.0, 83.2, 70.7, 49.4, 32.2, 27.9, 23.5, 21.2, 21.1, 16.6; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{26}N_2O_2Na$: 337.1886. Found: 337.1878.

***tert*-Butyl 2-(3-chloro-2-methylphenyl)-1-cyanopiperidine-2-carboxylate (7j)**: white solid; IR (KBr) 2964,



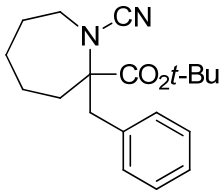
2927, 2862, 2209, 1728, 1435, 1390, 1368, 1332, 1287, 1256, 1150, 1105, 1076, 1051, 1027, 1002, 968, 866, 833, 773, 727, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, dd, *J* = 8.0, 1.6 Hz, ArH), 7.17 (1H, dd, *J* = 8.0, 1.6 Hz, ArH), 7.12 (1H, dd, *J* = 8.0, 8.0 Hz, ArH), 3.57-3.45 (2H, m, NCH_2), 2.65 (3H, s, $ArCH_3$), 2.40 (1H, ddd, *J* = 13.7, 3.8, 3.8 Hz, CH_2), 2.12 (1H, ddd, *J* = 13.7, 13.7, 3.8 Hz, CH_2), 1.94-1.85 (1H, m, CH_2), 1.84-1.69 (2H, m ,CH_2), 1.62-1.44 (1H, m, CH_2), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 138.0, 137.3, 135.5, 130.0, 126.6, 125.9, 116.6, 83.7, 70.4, 49.4, 32.2, 27.9, 23.3, 21.0, 17.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{23}N_2O_2ClNa$: 357.1340. Found: 357.1330.

***tert*-Butyl 2-benzyl-1-cyanopiperidine-2-carboxylate (7d')**: colorless oil; IR (film) 3063, 3031, 2937, 2864,



2209, 1728, 1604, 1497, 1453, 1393, 1369, 1292, 1252, 1216, 1152, 1123, 1102, 1062, 1032, 999, 981, 896, 844, 778, 755, 737, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, Ph), 3.43-3.35 (1H, m, NCH_2), 3.27-3.16 (1H, m, NCH_2), 3.22 (1H, d, *J* = 13.8 Hz, C*H*$_2$Ph), 3.16 (1H, d, *J* = 13.8 Hz, C*H*$_2$Ph), 2.13-2.01 (1H, m, CH_2), 1.72-1.48 (2H, m, CH_2), 1.52 (9H, s, *t*-Bu), 1.48-1.34 (1H, m, CH_2), 1.34-1.18 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 134.0, 130.8, 128.1, 127.1, 117.0, 83.0, 66.0, 49.5, 43.2, 30.8, 27.9, 23.7, 20.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_2Na$: 323.1730. Found: 323.1726.

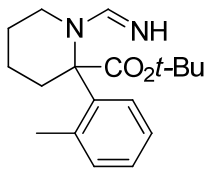
***tert*-Butyl 2-benzyl-1-cyanoazepane-2-carboxylate (7l)**: colorless oil; IR (film) 3062, 3030, 2930, 2859,



2207, 1727, 1604, 1496, 1454, 1392, 1369, 1274, 1257, 1229, 1159, 1086, 1031, 993, 967, 846, 774, 756, 733, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (5H, m, Ph), 3.30-3.15 (3H, m, C*H*$_2$Ph and NCH_2), 2.86 (1H, ddd, *J* = 15.2, 5.9, 4.8 Hz, NCH_2), 2.01 (1H, dd, *J* = 15.2, 8.4 Hz, CH_2), 1.78-1.36 (6H, m, CH_2), 1.53 (9H, s, *t*-Bu), 1.34-1.22 (1H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.8, 130.7, 128.2, 127.1, 117.8, 82.9, 69.4, 51.6, 42.2, 33.2, 29.8, 28.6, 27.9, 23.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{26}N_2O_2Na$: 337.1886. Found: 337.1881.

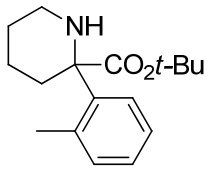
Characterization of 8d, 9d, and 2

***tert*-Butyl 1-(iminomethyl)-2-(*o*-tolyl)piperidine-2-carboxylate (8d):** white solid; IR (KBr) 3427, 3287, 3057,



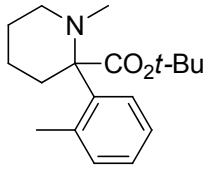
2978, 2947, 2869, 2822, 1725, 1620, 1454, 1392, 1356, 1285, 1244, 1150, 1125, 1005, 973, 956, 897, 845, 820, 778, 756, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, s, CH=N), 7.24-7.11 (3H, m, ArH), 7.08 (1H, dd, *J* = 8.2, 1.2 Hz, ArH), 4.45-4.35 (1H, m, NH), 2.58-2.45 (1H, m, NCH_2), 2.50 (3H, s, $ArCH_3$), 2.37-2.29 (1H, m, NCH_2), 2.00 (1H, ddd, *J* = 13.3, 13.3, 3.8 Hz, CH_2), 1.86-1.76 (2H, m, CH_2), 1.73-1.46 (2H, m, CH_2), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 161.3, 138.5, 136.0, 133.3, 127.7, 127.3, 126.1, 82.7, 71.9, 40.3, 33.3, 27.9, 23.3, 22.0, 21.7; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{27}N_2O_2$: 303.2067. Found: 303.2063.

***tert*-Butyl 2-(*o*-tolyl)piperidine-2-carboxylate (9d):** colorless oil; IR (film) 3427, 3333, 3059, 2932, 2867, 2827,



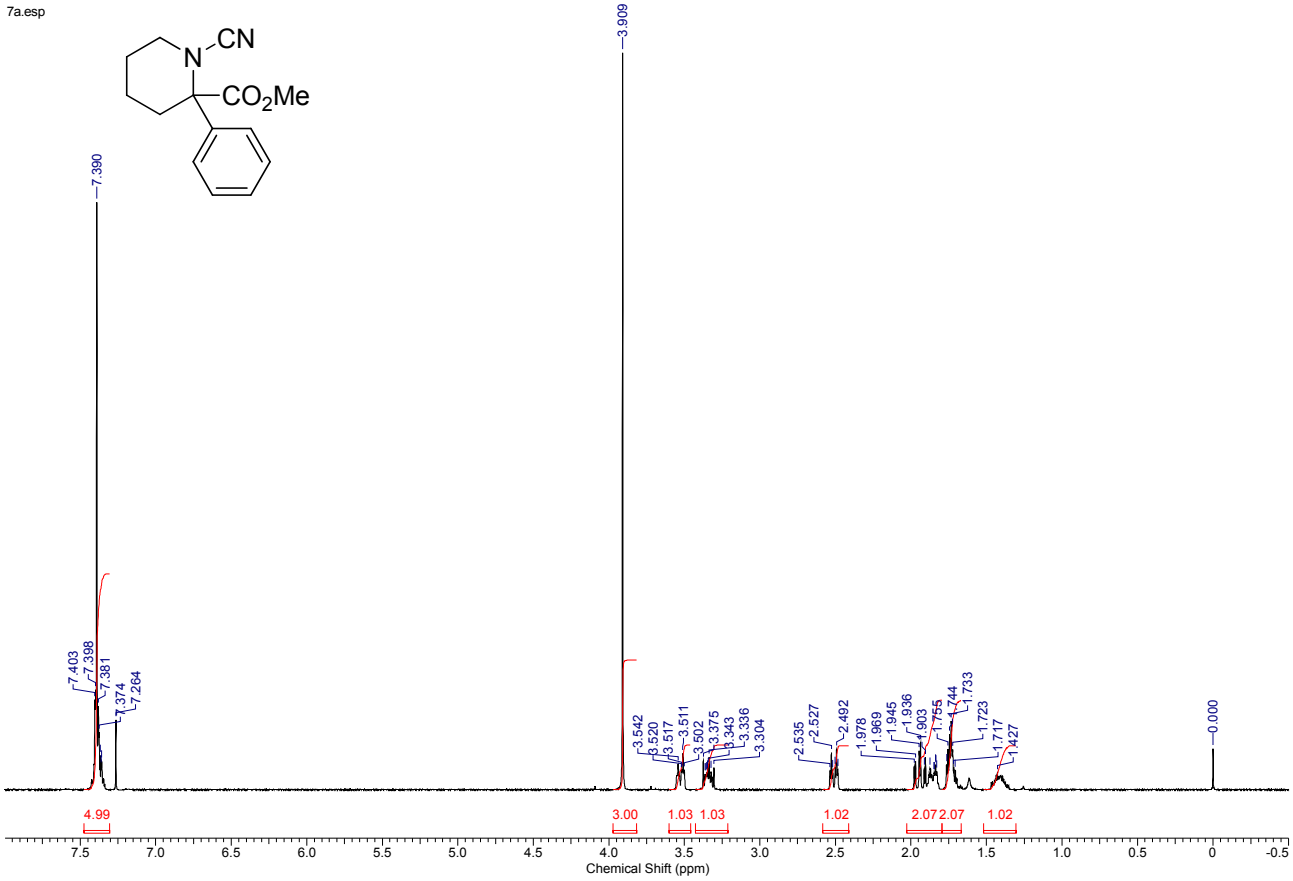
2783, 2690, 1724, 1601, 1479, 1453, 1391, 1366, 1239, 1161, 1121, 1059, 1030, 969, 930, 898, 838, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.57 (1H, m, ArH), 7.18-7.06 (3H, m, ArH), 2.89 (1H, dddd, *J* = 12.2, 4.5, 4.5, 0.8 Hz, NCH_2), 2.82 (1H, ddd, *J* = 12.2, 9.5, 3.6 Hz, NCH_2), 2.47 (3H, s, $ArCH_3$), 2.32-2.21 (1H, m, CH_2), 2.18 (1H, br, NH), 1.90-1.67 (3H, m, CH_2), 1.63-1.47 (2H, m, CH_2), 1.44 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 142.0, 136.0, 132.2, 126.8, 126.2, 125.6, 80.9, 65.7, 42.7, 32.9, 27.9, 25.4, 21.7, 21.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. Found: 276.1958.

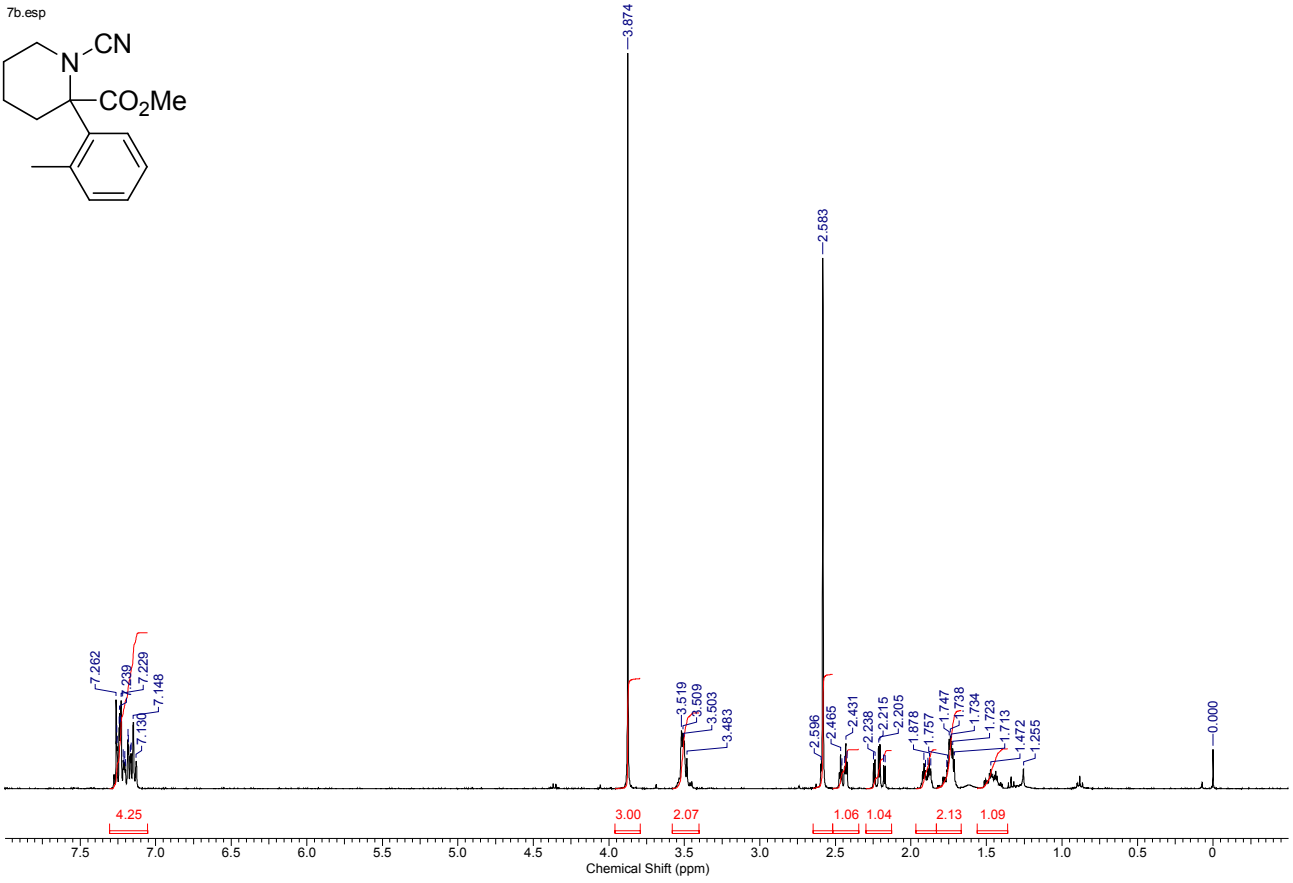
***tert*-Butyl 1-methyl-2-(*o*-tolyl)piperidine-2-carboxylate (2):** colorless oil; IR (film) 3059, 2974, 2928, 2804,



2719, 1716, 1477, 1453, 1391, 1366, 1291, 1238, 1212, 1158, 1135, 1099, 1056, 1033, 1004, 956, 894, 847, 773, 754, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, br, ArH), 7.15-7.06 (3H, m, ArH), 2.79 (1H, d, *J* = 11.2 Hz, NCH_2), 2.66 (1H, dd, *J* = 11.2, 11.2 Hz, NCH_2), 2.55 (3H, br, $ArCH_3$), 2.30 (3H, s, NCH_3), 2.16 (1H, d, *J* = 11.2 Hz, CH_2), 1.85-1.50 (5H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 141.7, 136.6, 132.4, 127.1, 126.5, 125.4, 81.2, 72.3, 50.8, 40.9, 34.5, 28.4, 25.4, 22.1, 21.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2113.

Copies of representative ^{1}H NMR spectra





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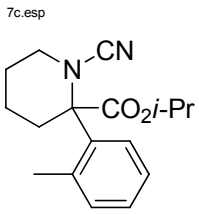
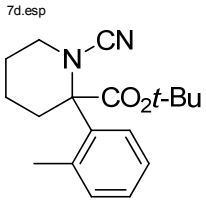

CN
N
CO2i-Pr

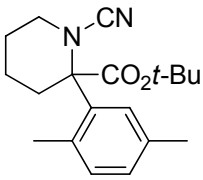
2.608
1.340
1.324
1.317
1.301
7.222
7.170
7.264
7.242
7.229
5.256
5.240
5.224
5.209
5.193
3.501
3.492
3.479
3.470
3.465
3.454
2.448
2.414
2.406
2.207
2.183
2.173
1.860
1.740
1.732
1.727
1.717
1.708
1.466
0.000
4.07
0.95
1.98
3.00
1.04
0.99
3.17
6.09
Chemical Shift (ppm)

7d.esp


CN
N
CO2t-Bu

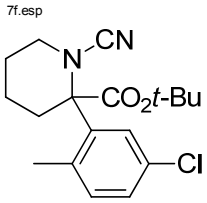
1.554
2.624
7.262
7.223
7.217
7.204
7.180
7.159
3.498
2.418
2.383
2.136
2.126
1.752
1.743
1.730
1.585
0.000
4.34
2.00
3.00
1.04
0.99
2.03
10.75
Chemical Shift (ppm)

7e.esp


CN
N
CO2t-Bu

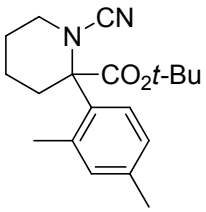
1.575
2.577
2.279
7.262
7.107
7.088
7.048
7.045
7.026
6.995
3.496
2.390
2.355
2.143
2.120
2.110
1.745
1.736
1.732
1.259
0.884
0.000
2.97
1.98
3.00
1.12
1.00
0.00
2.15
1.34
Chemical Shift (ppm)

7f.esp


CN
N
CO2t-Bu
Cl

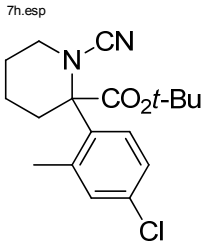
1.554
2.577
7.268
7.220
7.214
7.204
7.160
7.138
3.503
3.496
3.482
2.415
2.406
2.372
2.113
2.089
2.079
1.868
1.747
1.738
1.728
1.509
1.500
1.491
1.483
1.394
0.883
0.000
2.95
2.01
3.00
1.02
1.00
2.18
10.32
Chemical Shift (ppm)

7g.esp


CN
N
CO2t-Bu

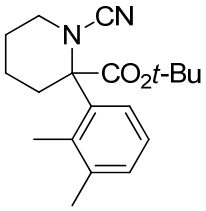
1.550
2.580
2.280
7.261
7.099
7.078
7.025
6.973
6.970
6.952
3.486
2.737
2.624
2.387
2.286
2.125
2.115
1.739
1.730
1.727
1.717
1.707
1.363
1.265
0.901
0.883
0.866
0.000
2.97
1.86
3.00
1.30
0.94
2.47
9.82
Chemical Shift (ppm)

7h.esp


CN
N
CO2t-Bu
Cl

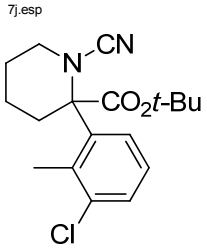
1.534
2.591
7.264
7.155
3.503
3.490
3.482
2.406
2.381
2.372
2.086
2.076
1.743
1.734
1.583
1.490
0.000
3.00
1.93
3.00
1.18
0.99
1.02
2.18
10.32
Chemical Shift (ppm)

7i.esp


CN
N
CO2t-Bu

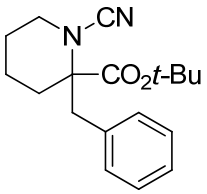
7.262
7.140
7.078
7.073
7.063
3.518
3.511
3.508
2.509
2.381
2.284
2.167
2.157
2.046
1.747
1.739
1.581
1.545
1.501
0.000
2.99
1.98
1.09
1.02
3.14
10.53
Chemical Shift (ppm)

7j.esp


CN
N
CO2t-Bu
Cl

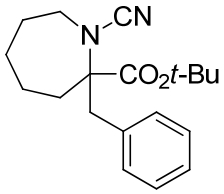
7.397
7.394
7.378
7.374
7.263
7.160
7.157
7.138
7.118
3.531
3.522
3.510
2.647
2.381
2.129
2.120
1.751
1.737
1.540
0.000
0.96
1.98
1.98
3.00
1.00
1.06
2.03
10.83
Chemical Shift (ppm)

7d'.esp


CN
N
CO2t-Bu

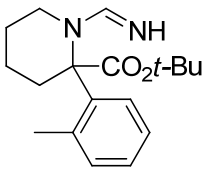
1.517
7.295
7.304
7.286
7.271
3.408
3.403
3.384
3.372
3.235
3.228
3.200
3.173
3.139
2.094
2.084
2.067
2.061
1.673
1.569
1.431
1.399
1.295
1.264
1.233
0.000
4.82
0.97
2.90
0.96
8.54
3.32
Chemical Shift (ppm)

7l.esp


CN
N
CO2t-Bu

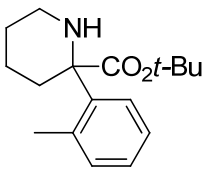
1.534
7.320
7.313
7.302
7.296
7.292
7.280
7.276
7.273
3.196
3.191
1.665
1.488
0.000
5.20
3.11
1.00
0.95
9.82
2.88
Chemical Shift (ppm)

8d.esp


N
NH
CO2t-Bu

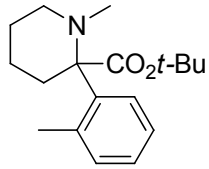
1.536
2.496
7.568
7.210
7.206
7.194
7.187
7.142
7.088
7.085
7.066
4.418
4.388
4.384
2.561
2.554
2.529
2.522
2.317
2.313
2.042
2.004
1.827
1.821
1.797
1.790
1.575
0.000
1.00
4.16
1.00
4.17
1.09
1.11
2.11
11.78
Chemical Shift (ppm)

9d.esp


NH
CO2t-Bu

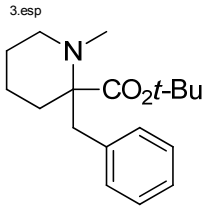
1.435
2.470
7.613
7.606
7.590
7.251
7.157
7.150
7.142
7.132
7.127
7.115
7.109
7.101
2.875
2.852
2.843
2.828
2.819
2.272
2.181
1.808
1.800
1.776
1.768
1.569
1.304
0.000
0.98
2.92
2.01
3.00
2.04
3.04
8.98
Chemical Shift (ppm)

2.esp


N
CO2t-Bu

1.551
2.297
7.113
7.109
7.299
7.240
7.098
2.803
2.774
2.663
2.554
2.174
2.147
1.647
0.000
0.81 3.00
1.05 3.83
1.03
5.10 9.21
Chemical Shift (ppm)

3.esp


N
CO2t-Bu

1.479
2.626
7.262
7.245
7.231
7.212
7.199
7.195
3.301
3.267
2.835
2.802
1.543
1.540
1.514
0.000
5.25
1.00
1.01 5.17
1.28 13.98 1.19
Chemical Shift (ppm)