Supporting information for:

N-H Insertion Reactions of Boc-Amino Acid Amides:
Solution- and Solid-Phase Synthesis of Pyrazinones and
Pyrazines

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Representative Procedures

General procedure for the Rhodium-catalyzed N-H insertion reaction.

2-(*tert*-Butoxycarbonylamino-3-methyl-butylalamino)-3-oxo-butyric acid ethyl ester **3a**.

A round bottomed flask was charged with α -diazo- β -ketoester **1a** (500 mg, 3.20 mmol) and Boc-Val-NH₂ **2** (1.04 g, 4.80 mmol), purged with argon and toluene (15 mL) was added. This mixture was heated to 80 °C for 10 min and a solution of rhodium octanoate (49.8 mg, 0.064 mmol) in toluene (5 mL) was slowly added. Nitrogen effervescence was observed and subsided after approximately 10 min. After heating additional 20 min, the mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was purified by chromatography (20% EtOAc in toluene) to give insertion product **3a** (813.2 mg, 2.36 mmol, 74 %) as a light yellow powder; mp 94 – 95.5 °C; IR 3318, 2969, 1744, 1722, 1689, 1651, 1518, 1159 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.88 (0.89) (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 7.0 Hz), 1.26 (3H, t, J = 7.5 Hz), 1.40 (1.40) (9H, s), 2.10 – 2.18 (1H, m), 2.34 (2.34) (3H, s), 4.06 (1H, br s), 4.19 – 4.26 (2H, m), 5.10 – 5.14 (1H, m), 5.20 (1H, d, J = 6.0 Hz), 7.15 (7.19) (1H, d, J = 5.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 13.9, 17.3 (17.5), 19.1 (19.1), 27.9 (28.0), 28.2, 30.7 (30.9), 59.3 (59.3), 62.5, 63.0 (63.0), 79.8, 155.7, 165.7 (165.8), 171.5, 198.1 (198.2); HRMS m/z = 367.1832 [M+H], calcd for C₁₆H₂₈N₂O₆Na = 367.1839.

General procedure for cyclization and oxidation (**3**→**5**)

5-Isopropyl-6-oxo-3-phenyl-1,6-dihydro-pyrazine-2-carboxylic acid ethyl ester **5b**

To a solution of insertion product **3b** (0.34 g, 0.84 mmol) in ClCH₂CH₂Cl (15 mL) was added TFA (0.70 mL, 9.38 mmol). The resultant mixture was heated to 100 °C for 2 h, cooled to room temperature and concentrated under reduced pressure. Purification of this residue by chromatography (20 % EtOAc in toluene) gave pyrazine-6-one **5b** (201.1 mg, 0.70 mmol, 83 %) as a white solid; mp 113 – 114.5 °C; IR 1731, 1643, 1594, 1223 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.10 (3H, t, J = 7.0 Hz), 1.29 (6H, d, J = 7.0 Hz), 3.57 (1H, sep. J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.39 – 7.49 (5H, m), 10.24 (1H, br s); ¹³C NMR (125 MHz, CDCl₃) δ 13.5 (q), 19.9 (q), 31.1 (d), 62.6 (t), 121.1 (s), 127.7 (d), 128.6 (d), 129.5 (d), 137.1 (s), 137.5 (s), 153.8 (s), 162.1 (s), 169.0 (s); HRMS m/z = 287.1394 [M+H], calcd for C₁₆H₁₉N₂O₃ = 287.1390.

General procedure for bromination (**5**→**6**)

6-Bromo-5-isopropyl-3-methyl-pyrazine-2-carboxylic acid ethyl ester **6a**

To a solution of pyrazine-6-one **5a** (49.5 mg, 0.22 mmol) in toluene (4 mL) was added POBr₃ (252.6 mg, 0.88 mmol). The resultant mixture was heated to 100 °C for 2 h, cooled to room temperature and separated over saturated NaHCO₃, which was extracted with CHCl₃. The extracts were combined, dried over Na₂SO₄ and concentrated under reduced pressure to give the crude product. Chromatography (20% EtOAc in hexanes) gave bromopyrazine **6a** (46.2 mg, 74 %) as a yellow oil; IR 1722, 1386, 1269 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.28 (6H, d, J = 6.5 Hz), 1.42 (3H, t, J = 7.0 Hz), 2.75 (3H, s), 3.53 (1H, sep, J = 6.5 Hz), 4.44 (2H, q, J = 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (q), 20.9 (q), 22.4 (q), 33.4 (d), 62.1 (t), 136.9 (s), 140.0 (s), 152.9 (s), 163.7 (s), 164.4 (s); HRMS m/z = 287.0395 [M+H], calcd for C₁₁H₁₆BrN₂O₂ = 287.0390.

General procedure for Suzuki coupling reaction (**6**→**7**)

6-Biphenyl-4-yl-5-isopropyl-3-methyl-pyrazine-2-carboxylic acid ethyl ester **7a**

A 25 mL round bottomed flask was charged with bromopyrazine **6a** (34.6 mg, 0.10 mmol), 4-biphenylboronic acid (59.4 mg, 0.30 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (2.4 mg, 0.0030 mmol), and Cs₂CO₃

(97.7 mg, 0.30 mmol). The flask was evacuated and filled with argon, and toluene (6 mL) was added. The resulting suspension was heated to 90 °C for 1.5 h. After cooling to room temperature, the reaction was separated over NaHCO₃ (2mL) and brine (2 mL) and then extracted with EtOAc. The combined extracts were dried over Na₂SO₄ and concentrated under reduced pressure to give the crude product. Chromatography (prep.TLC, 20 % EtOAc in hexanes) gave arylpyrazine **7a** (43.9 mg, 0.10 mmol, 100 %) as a white solid; mp 95 – 96 °C; IR 1718, 1410, 1236 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.28 (6H, d, *J* = 7.0 Hz), 1.43 (3H, t, *J* = 7.0 Hz), 2.84 (3H, s), 3.43 (1H, sep, *J* = 7.0 Hz), 4.47 (2H, q, *J* = 7.0 Hz), 7.37 – 7.40 (1H, m), 7.46 – 7.49 (2H, m), 7.61 – 7.65 (4H, m), 7.69 – 7.71 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (q), 22.3 (q), 22.8 (q), 31.3 (d), 61.8 (t), 127.1 (d), 127.2 (d), 127.5 (d), 128.8 (d), 129.6 (d), 136.9 (s), 139.8 (s), 140.5 (s), 141.5 (s), 149.3 (s), 152.1 (s), 161.3 (s), 166.0 (s); HRMS *m/z* = 361.1905 [M+H], calcd for C₂₃H₂₅N₂O₂ = 361.1910.

Representative solid-phase procedures:

General procedure for the solid-phase rhodium-catalyzed Boc-Val-NH₂ insertion reaction (8→)

A round bottomed flask was charged with resin **8** (R¹ = Me, 605.5 mg, 0.60 mmol), NBoc-Val-NH₂ **2** (388.8 mg, 1.80 mmol), purged with argon and ClCH₂CH₂Cl (10 mL) and toluene (4 mL) were added. This mixture was heated to 80 °C for 10 min and a solution of rhodium octanoate (49.8 mg, 0.064 mmol) in toluene (1 mL) was slowly added. Nitrogen effervescence was observed and subsided after approximately 10 min. After heating additional 1 h, the resin was collected in a plastic syringe equipped with a polyethylene frit and washed several times with DMF, THF, ether CHCl₃, hexanes, then dried in vacuo to give resin bound insertion product (687.3 mg, 96 %) as a light yellow powder; IR 1720, 1674 cm⁻¹.

General procedure for solid-phase cyclization/pyrazine formation (→10)

The polymer bound insertion product (R¹ = Ph, R² = Ph, 1.72 g, 1.40 mmol) prepared as above was suspended in ClCH₂CH₂Cl (18 mL) and TFA (1.00 mL) was added. After stirring for 3 h, the resin was isolated by filtration, washed (CHCl₃) and then resuspended in ClCH₂CH₂Cl (15 mL). Acetic acid (1.64 mL, 14.0 mmol) was added, the mixture was heated to 100 °C for 3 h and the polymer-bound pyrazine-6-one **10** (1.60 g, 100%) was isolated by filtration and washing (DMF, THF, ether, hexanes); IR 3381, 1668 cm⁻¹.

General procedure for solid-phase N-alkylation

Polymer bound pyrazine-2-one **10** (R¹ = Ph, R² = Ph, 0.30 g, 0.27 mmol) was suspended in THF (1 mL) and DMF (2 mL) and then cooled to 0 °C. A solution of LiOtBu (1.0 M in THF, 1.35 mL, 1.35 mmol) was added and the mixture was stirred for 1 h before iodomethane (168 μL, 2.70 mmol) was added. The resulting mixture was stirred for 24 h, quenched by the addition of AcOH (1.0 mL), collected by filtration and washed sequentially with DMF, DMF-H₂O, THF, MeOH, CHCl₃ and hexanes to give N-methyl pyrazine-6-one **11** (277 mg, 91%); IR 1728, 1660 cm⁻¹.

General procedure for solid-phase bromination

Polymer bound pyrazine-6-one **10** (R¹ = Ph, R² = ⁱPr, 1.92 g, 1.81 mmol) was suspended in ClCH₂CH₂Cl (20 mL) and a solution of POBr₃ (3.64 g, 12.7 mmol) in ClCH₂CH₂Cl (7 mL) was slowly added. The resulting mixture was heated to 100 °C for 4 h, isolated by filtration and then washed with DMF, THF, ether, CHCl₃, hexanes, to give polymer-bound bromopyrazine (2.01 g, 98 %) as a yellow powder; IR 1733 cm⁻¹.

General procedure for solid-phase Suzuki coupling reaction

A small vial was charged with polymer-bound bromopyrazine ($R^1 = \text{Me}$, $R^2 = \text{iPr}$, 246.8 mg, 0.22 mmol), 4-biphenylboronic acid (305.0 mg, 1.54 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (5.4 mg, 6.6 μmol), and Cs_2CO_3 (501.8 mg, 1.54 mmol). The vial was evacuated and filled with argon. Toluene (6 mL) was added, the vial was closed tightly with a Teflon lined lid and the resulting suspension was vigorously shaken for 24 h. The resin was collected in a plastic syringe equipped with a polyethylene frit and washed several times with H_2O , DMF, THF, ether, CHCl_3 and hexanes to give the polymer-bound arylpyrazine **12** (259.4 mg, 99 %); IR 1721, 1239 cm^{-1} .

2-(tert-Butoxycarbonylamino-3-methyl-butyrylamino)-3-oxo-3-phenyl-propionic acid ethyl ester 3b; yellow solid; mp 115 – 117 °C; IR 3305, 2969, 1747, 1708, 1656, 1496, 1156 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.91 (3H, d, $J = 7.0$ Hz), 0.96 (3H, d, $J = 7.0$ Hz), 1.33 (3H, t, $J = 7.0$ Hz), 1.44 (9H, s), 2.19 – 2.26 (1H, m), 4.11 – 4.19 (3H, m), 5.07 (1H, br d, $J = 8.0$ Hz), 6.14 (1H, d, $J = 6.5$ Hz), 7.33 (1H, d, $J = 8.0$ Hz), 7.50 (2H, dd, $J = 8.0$, 8.0 Hz), 7.63 (1H, dd, $J = 7.0$ Hz), 8.10 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 13.7, 17.3 (17.3), 19.0 (19.1), 28.2, 30.8 (31.0), 58.1, 59.4 (59.4), 62.3, 79.7 (79.8), 128.1 (128.2), 128.5 (128.6), 129.4 (129.5), 134.2, 155.6, 166.2 (166.3), 171.5, 191.1 (191.2); HRMS $m/z = 429.1987$ [$\text{M}+\text{H}$], calcd for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_6\text{Na} = 429.1996$.

5-Isopropyl-3-methyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid ethyl ester 5a; yellow solid; mp 114 – 116 °C; IR 1725, 1636, 1597, 1445 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.24 (6H, d, $J = 7.0$ Hz), 1.41 (3H, t, $J = 7.0$ Hz), 2.63 (3H, s), 3.51 (1H, sep. $J = 7.0$ Hz), 4.42 (2H, q, $J = 7.0$ Hz), 9.81 (1H, br s); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (q), 19.9 (q), 21.1 (q), 30.8 (d), 62.7 (t), 120.1 (s), 136.4 (s), 153.7 (s), 161.7 (s), 170.2 (s); HRMS $m/z = 225.1230$ [$\text{M}+\text{H}$], calcd for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_3 = 225.1234$.

6-Bromo-5-isopropyl-3-phenyl-pyrazine-2-carboxylic acid ethyl ester 6b; colorless solid; mp 91 °C; IR 1733, 1461, 1268 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.18 (3H, t, $J = 7.0$ Hz), 1.35 (6H, d, $J = 7.0$ Hz), 3.61 (1H, sep. $J = 6.5$ Hz), 4.28 (2H, q, $J = 7.0$ Hz), 7.45 – 7.48 (3H, m), 7.64 – 7.66 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 13.7 (q), 21.0 (q), 33.6 (d), 62.3 (t), 128.5 (d), 128.7 (d), 129.7 (d), 136.3 (s), 137.7 (s), 141.3 (s), 150.8 (s), 162.7 (s), 165.4 (s); HRMS $m/z = 349.0541$ [$\text{M}+\text{H}$], calcd for $\text{C}_{16}\text{H}_{18}\text{BrN}_2\text{O}_2 = 349.0546$.

6-Biphenyl-4-yl-5-isopropyl-3-phenyl-pyrazine-2-carboxylic acid ethyl ester 7b; colorless solid; mp 96.5 °C; IR 1731, 1409, 1246, 1142 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.20 (3H, t, $J = 7.0$ Hz), 1.36 (6H, d, $J = 7.0$ Hz), 3.54 (1H, sep. $J = 7.0$ Hz), 4.32 (2H, q, $J = 7.0$ Hz), 7.38 – 7.41 (1H, m), 7.48 – 7.53 (5H, m), 7.67 – 7.75 (6H, m), 7.78 – 7.80 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 13.7 (q), 22.4 (q), 31.5 (d), 62.0 (t), 127.1 (d), 127.2 (d), 127.6 (d), 128.4 (d), 128.7 (d), 128.8 (d), 129.4 (d), 129.7 (d), 136.6 (s), 137.4 (s), 140.5 (s), 141.1 (s), 141.7 (s), 149.6 (s), 150.1 (s), 160.3 (s), 167.0 (s); HRMS $m/z = 423.2069$ [$\text{M}+\text{H}$], calcd for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_2 = 423.2067$.

5-Isopropyl-3-methyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid methyl ester 13; Entry 1; colorless solid; mp 155 – 156 °C; IR 1734, 1637, 1598 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.24 (6H, d, $J = 7.0$ Hz), 2.63 (3H, s), 3.52 (1H, sep, $J = 7.0$ Hz), 3.97 (3H, s), 9.63 (1H, br s); ^{13}C NMR (125 MHz, CDCl_3) δ 19.9 (q), 21.1 (q), 31.1 (d), 53.2 (q), 119.8 (s), 136.5 (s), 162.3 (s); HRMS $m/z = 211.1077$ [M+H], calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3 = 211.1077$

5-Isopropyl-3-methyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid butylamide 14; entry 2; colorless sticky oil; IR 3315, 2929, 1694, 1645, 1255 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.96 (3H, t), 1.26 (6H, d, $J = 7.0$ Hz), 1.37 – 1.45 (2H, m), 1.58 – 1.64 (2H, m), 2.70 (3H, s), 3.41 – 3.47 (3H, m), 6.79 (1H, br s), 8.88 (1H, br s); HRMS $m/z = 252.1700$ [M+H], calcd. for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}_2 = 252.1706$.

5-Isopropyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid butylamide 14; entry 3; colorless solid; mp 166 – 168 °C; IR 3334, 1635, 1588, 1542, 1225 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.88 (3H, t, $J = 7.5$ Hz), 1.01 – 1.09 (2H, m), 1.17 – 1.23 (2H, m), 1.26 (6H, d, $J = 7.0$ Hz), 3.18 (2H, q, $J = 7.5$ Hz), 3.54 (1H, sep, $J = 7.0$ Hz), 5.68 (1H, br s), 7.50 – 7.54 (5H, m), 9.85 (1H, br s); ^{13}C NMR (125 MHz, CDCl_3) δ 13.5 (q), 19.7 (t), 20.4 (q), 31.0 (t), 31.3 (d), 40.3 (t), 123.8 (s), 129.2 (d), 129.6 (d), 129.8 (d), 132.7 (s), 136.3 (s), 153.7 (s), 160.5 (s), 168.0 (s); HRMS $m/z = 314.1860$ [M+H], calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_2 = 314.1863$.

5-Benzyl-3-methyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid butylamide 14; entry 4; light brown sticky oil; IR 3381, 1645, 1536, 1253 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.95 (3H, t, $J = 7.5$ Hz), 1.35 – 1.43 (2H, m), 1.55 – 1.61 (2H, m), 2.73 (3H, s), 3.41 – 3.44 (2H, m), 4.71 (2H, s), 6.82 (1H, br s), 7.19 – 7.22 (1H, m), 7.26 – 7.29 (2H, m), 7.35 – 7.36 (2H, m); HRMS $m/z = 300.1706$ [M+H], calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_3\text{O}_2 = 300.1706$.

5-Benzyl-3-methyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid benzylamide 14; entry 5 white solid; mp 167 – 168 °C; IR 3250, 1661, 1635 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.76 (3H, s), 4.15 (2H, s), 4.58 (2H, d, $J = 5.5$ Hz), 7.18 – 7.34 (10H, m). HRMS $m/z = 334.1552$ [M+H], calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2 = 334.1550$.

5-Benzyl-6-oxo-3-phenyl-1,6-dihydro-pyrazine-2-carboxylic acid methyl ester 13; entry 6; colorless oil; IR 1732, 1652, 1593, 1265, 1209 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.22 (6H, d, $J = 6.5$ Hz), 2.29 (3H, s), 3.45 (3H, s), 3.49 (1H, sep, $J = 6.5$ Hz), 3.97 (3H, s); HRMS $m/z = 225.1234$ [M+H], calcd. for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_3 = 225.1234$.

1-Benzyl-5-isopropyl-3-methyl-6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid methyl ester 13; entry 7; colorless oil; IR 1731, 1652 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.24 (6H, d, $J = 7.0$ Hz), 2.24 (3H, s), 3.55 (1H, sep, $J = 7.0$ Hz), 3.68 (3H, s), 5.31 (2H, s), 7.15 – 7.17 (2H, m), 7.26 – 7.31 (3H, m); HRMS $m/z = 301.1543$ [M+H], calcd. for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_3 = 301.1547$.

5-Isopropyl-6-oxo-3-phenyl-1,6-dihydro-pyrazine-2-carboxylic acid methyl ester 13; entry 8; colorless oil; IR 1730, 1651, 1588, 1212, 1092 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.28 (6H, d, $J = 7.0$ Hz), 3.53 -3.58 (1H, m), 3.54 (3H, s), 3.72 (3H, s), 7.35 – 7.42 (3H, m), 7.50 – 7.52 (2H, m); HRMS $m/z = 287.1389$ [M+H], calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3 = 287.1390$.

1-Methyl-6-oxo-3,5-diphenyl-1,6-dihydro-pyrazine-2-carboxylic acid butylamide 14; entry 9; white solid; mp 108 – 109 $^{\circ}\text{C}$; IR 3272, 1648, 1453, 1265 cm^{-1} ; ^1H NMR: complex mixture of rotamers; HRMS $m/z = 362.1862$ [M+H], calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_3\text{O}_2 = 362.1863$.

1-Benzyl-6-oxo-3,5-diphenyl-1,6-dihydro-pyrazine-2-carboxylic acid phenylamide 14; entry 10; brown oil; IR 3378, 1663, 1595, 1517, 1495, 1437 cm^{-1} ; ^1H NMR: complex mixture of rotamers; HRMS $m/z = 458.1863$ [M+H], calcd. for $\text{C}_{30}\text{H}_{24}\text{N}_3\text{O}_2 = 458.1863$.

1-(4-Chloro-benzyl)-6-oxo-diphenyl-1,6-dihydro-pyrazine-2-carboxylic acid butylamide 14; entry 11; colorless oil; IR 3408, 1663, 1491 cm^{-1} ; ^1H NMR: complex mixture of rotamers; HRMS $m/z = 472.1789$ [M+H], calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_2 = 472.1786$.

1-(3-Methoxy-benzyl)-6-oxo-3,5-diphenyl-1,6-dihydro-pyrazine-2-carboxylic acid benzylamide 14; entry 12; light yellow oil; IR 3399, 1660, 1597, 1489, 1260 cm^{-1} ; ^1H NMR: complex mixture of rotamers; HRMS m/z = 502.2130 $[\text{M}+\text{H}]$, calcd. for $\text{C}_{32}\text{H}_{28}\text{N}_3\text{O}_3$ = 502.2125.

6-Biphenyl-4-yl-5-isopropyl-3-methyl-pyrazine-2-carboxylic acid ethyl ester 15; entry 13; colorless oil; IR 1726, 1413 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.27 (6H, s, J = 6.5 Hz), 2.86 (3H, s), 3.42 (1H, sep, J = 6.5 Hz), 3.98 (3H, s), 7.37 – 7.40 (1H, m), 7.46 – 7.49 (2H, m), 7.59 – 7.60 (2H, m), 7.63 – 7.65 (2H, m), 7.69 – 7.70 (2H, m); HRMS m/z = 347.1755 $[\text{M}+\text{H}]$, calcd. for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2$ = 347.1754.

(6-Biphenyl-4-yl-5-isopropyl-3-methyl-pyrazin-2-yl)-piperidin-1-yl-methanone 16; entry 14; colorless solid; mp 100 – 103 $^{\circ}\text{C}$; IR 2926, 1629, 1446, 1255 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.27 (6H, d, J = 6.5 Hz), 1.56 – 1.59 (2H, m), 1.68 – 1.71 (4H, m), 2.62 (3H, s), 3.27 – 3.29 (2H, m), 3.39 (1H, sep, J = 6.5 Hz), 3.75 – 3.78 (2H, m), 7.36 – 7.40 (1H, m), 7.45 – 7.49 (2H, m), 7.55 – 7.57 (2H, m), 7.62 – 7.65 (2H, m), 7.67 – 7.70 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 20.9 (q), 22.5 (q), 24.5 (t), 25.5 (t), 26.6 (t), 31.1 (d), 42.7 (t), 47.9 (t), 127.1 (d), 127.1 (d), 127.5 (d), 128.8 (d), 129.5 (d), 137.2 (s), 140.6 (s), 141.3 (s), 145.6 (s), 148.7 (s), 148.9 (s), 159.0 (s), 166.4 (s); HRMS m/z = 400.2388 $[\text{M}+\text{H}]$, calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_3$ = 400.2383.

5-Isopropyl-6-(4-methoxy-phenyl)-3-methyl-pyrazine-2-carboxylic acid benzylamide 16; entry 15; colorless solid; mp 112.5 – 114 $^{\circ}\text{C}$; IR 3321, 1641, 1608, 1512, 1408, 1248 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.24 (6H, d, J = 6.5 Hz), 3.02 (3H, s), 3.36 (1H, sep, J = 6.5 Hz), 3.87 (3H, s), 4.63 (2H, d, J = 6.0 Hz), 6.98 – 7.02 (2H, m), 7.24 – 7.36 (5H, m), 7.41 – 7.44 (2H, m), 8.34 (1H, br t, J = 6.0 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 22.3 (q), 23.4 (q), 31.2 (d), 43.2 (t), 55.4 (q), 113.9 (d), 127.3 (d), 127.7 (d), 128.6 (d), 130.3 (d), 130.4 (s), 138.5 (s), 138.5 (s), 147.9 (s), 152.5 (s), 160.0 (s), 161.3 (s), 165.2 (s); HRMS m/z = 376.2019 $[\text{M}+\text{H}]$, calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_2$ =

376.2019.

5-Isopropyl-3,6-diphenyl-pyrazine-2-carboxylic acid butylamide 16; entry 16; colorless solid; mp 155 – 158 °C IR 3353, 1650, 1529, 1403, 1165 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.93 (3H, t, $J = 7.0$ Hz), 1.29 (6H, d, $J = 7.0$ Hz), 1.34 – 1.41 (2H, m), 1.54 – 1.60 (2H, m), 3.38 – 3.43 (3H, m), 7.44 – 7.55 (7H, m), 7.59 – 7.61 (2H, m), 7.74 – 7.76 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 13.8 (q), 20.1 (t), 22.4 (q), 31.4 (d), 31.6 (t), 39.3 (t), 127.8 (d), 128.5 (d), 128.9 (d), 129.0 (d), 129.1 (d), 129.3 (d), 137.9 (s), 138.2 (s), 140.0 (s), 148.3 (s), 151.4 (s), 160.0 (s), 165.0 (s); HRMS $m/z = 374.2230$ $[\text{M}+\text{H}]$, calcd. for $\text{C}_{24}\text{H}_{28}\text{N}_3\text{O} = 374.2227$.

2-(5-Isopropyl-3,6-diphenyl-pyrazin-2-yl)-benzothiazole 16a; entry 17; light yellow solid; mp 187.5 – 189 °C; IR 2968, 2928, 1409 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.35 (6H, d, $J = 6.5$ Hz), 3.50 (1H, sep, $J = 6.5$ Hz), 7.37 – 7.46 (5H, m), 7.49 – 7.56 (3H, m), 7.73 – 7.74 (2H, m), 7.79 – 7.81 (2H, m), 7.85 (1H, d, $J = 7.5$ Hz), 7.90 (1H, d, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 22.5 (q), 31.3 (d), 121.5 (d), 124.0 (d), 125.5 (d), 125.9 (d), 127.9 (d), 128.5 (d), 128.9 (d), 129.1 (d), 129.3 (d), 130.0 (d), 136.3 (s), 137.6 (s), 137.8 (s), 140.4 (s), 149.3 (s), 149.8 (s), 154.0 (s), 158.9 (s), 167.7 (s); HRMS $m/z = 408.1527$ $[\text{M}+\text{H}]$, calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O} = 408.1529$.

6-Biphenyl-4-yl-5-isopropyl-3-phenyl-pyrazine-2-carboxylic acid methyl ester 15; entry 18; colorless solid; mp 123 – 124 °C; IR 1737, 1411, 1145 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.34 (6H, d, $J = 7.0$ Hz), 3.52 (1H, sep, $J = 7.0$ Hz), 3.85 (3H, s), 7.38 – 7.41 (1H, m), 7.47 – 7.53 (5H, m), 7.65 – 7.77 (8H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 22.5 (q), 31.5 (d), 52.8 (q), 127.2 (d), 127.3 (d), 127.6 (d), 128.5 (d), 128.7 (d), 128.9 (d), 129.5 (d), 129.6 (d), 136.5 (s), 137.3 (s), 140.5 (s), 140.5 (s), 141.7 (s), 149.6 (s), 150.3 (s), 160.5 (s), 167.4 (s); HRMS $m/z = 409.1915$ $[\text{M}+\text{H}]$, calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_2 = 409.1910$.

6-Biphenyl-4-yl-5-isopropyl-3-phenyl-pyrazine-2-carboxylic acid diethylamide 16; entry 19; white solid; mp 176 – 179 °C; IR 1635, 1406 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.93 (3H, t, $J = 7.0$ Hz), 1.17 (3H, t, $J = 7.0$ Hz), 1.35 (6H, d, $J = 6.5$ Hz), 3.06 (2H, q, $J = 7.0$ Hz), 3.49 – 3.55 (3H, m), 7.37 – 7.40 (1H, m), 7.45 – 7.49 (5H, m), 7.65 – 7.72 (6H, m), 7.91 – 7.93 (2H, m); HRMS $m/z = 450.2540$ $[\text{M}+\text{H}]$, calcd. for $\text{C}_{30}\text{H}_{32}\text{N}_3\text{O} = 450.2540$.

6-Biphenyl-4-yl-5-isopropyl-3-phenyl-pyrazine-2-carboxylic acid benzylamide 16; entry 20; white solid; mp 206 – 207 °C; IR 3341, 1653, 1536, 1406 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.33 (6H, d, $J = 6.5$ Hz), 3.48 (1H, sep, $J = 6.5$ Hz), 4.62 (2H, d, $J = 6.0$ Hz), 7.28 – 7.34 (5H, m), 7.38 – 7.42 (1H, m), 7.47 – 7.50 (5H, m), 7.65 – 7.67 (4H, m), 7.73 – 7.78 (4H, m), 7.91 (1H, br t, $J = 6.0$ Hz); HRMS $m/z = 484.2388$ $[\text{M}+\text{H}]$, calcd. for $\text{C}_{33}\text{H}_{30}\text{N}_3\text{O} = 484.2383$.

[5-Isopropyl-6-(4-methoxy-phenyl)-3-phenyl-pyrazin-2-yl]-morpholin-4-yl-mehtanone 16; entry 21; light yellow solid; mp 239 – 240 °C; IR 1644, 1406, 1251 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.31 (6H, d, $J = 7.0$ Hz), 3.04 – 3.10 (4H, m), 3.49 (1H, sep, $J = 7.0$ Hz), 3.58 – 3.60 (2H, m), 3.71 – 3.73 (2H, m), 3.88 (3H, s), 7.04 (2H, d, $J = 8.5$ Hz), 7.47 – 7.56 (5H, m), 7.86 – 7.87 (2H, m); HRMS $m/z = 418.2128$ $[\text{M}+\text{H}]$, calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_3 = 418.2125$.

HM-3-10 (file name: 3-10-1) , CDCl₃, 500MHz

bc4-199 (file name: bc4-1992) , CDCl₃, 500MHz

7.260

4.441
4.427
4.413
4.398

3.555
3.541
3.528
3.514
3.500
3.487
3.473
2.626

1.424
1.410
1.396
1.245
1.231

HM-3-24 (file name:3-24h) , 1H, CDCl3,500MHz

7.660
7.657
7.650
7.647
7.641
7.484
7.474
7.471
7.465
7.460
7.454
7.260

4.306
4.291
4.277
4.263
3.647
3.634
3.620
3.607
3.594
3.580
3.567

1.593
1.359
1.345
1.191
1.176
1.162

HM-3-36-1 (file name: 3-36-1h) , 1H, CDCl3, 500MHz

1.648
1.446
1.431
1.417
1.286
1.272

3.475
3.461
3.448
3.434
3.421
3.408
3.394
2.840

4.488
4.474
4.460
4.445

7.708
7.692
7.652
7.638
7.624
7.607
7.490
7.475
7.460
7.398
7.383
7.369
7.260

HM-3-38 (file name: 3-38), 1H, CDCl3, 500MHz

1.366
1.353
1.211
1.197
1.183

3.579
3.565
3.552
3.538
3.525
3.512
3.498

4.344
4.329
4.315
4.301

7.795
7.791
7.780
7.776
7.750
7.733
7.713
7.696
7.681
7.665
7.528
7.519
7.516
7.507
7.495
7.476
7.414
7.399
7.384
7.260

ppm (τ)

HN-3-200 H (file name: 3-200c), CDCl₃, 500MHz

9.629
9.624

7.260

3.969

3.556

3.542

3.529

3.515

3.501

3.488

3.474

2.628

1.251

1.237

0.95

3.00

0.98

2.93

9.37

0.0

5.0

ppm (t1)

HM-3-124 (file name: 3-124h), CDCl₃, 500MHz

HM-3-114 (file name 3-114h), CDCl₃, 500MHz

7.341
7.338
7.324
7.313
7.299
7.294
7.285
7.278
7.260
7.247
7.212
7.198

4.588
4.577
4.150

2.759

HM-3-202 (file name: 3-202h) , CDCl3, 500MHz

HM-3-204 (file name: 3-204h) . CDCl₃, 500MHz

HM-3-222 (file name: 3-222h) , CDCl₃, 500MHz

7.521
7.518
7.514
7.504
7.422
7.419
7.408
7.393
7.375
7.365
7.360
7.346
7.260

3.721
3.582
3.568
3.555
3.541
3.536
3.527

1.284
1.270

HM-3-284 (file name: 3-284h1) , CDCl₃, 500MHz

HM-3-288 (file name: 3-288h) , CDCl₃, 500MHz

HN-3-250 (file name: 3-250h) , CDCl₃, 500MHz

HM-4-34 (file name: 4.34h), CDCl₃, 500MHz

HM-3-62 (file name: 3-62h) . CDCl₃, 500MHz

HM-4-36-2 main spot (file name: 4-36-2h) : CDCl₃, 500MHz

8.327
8.339
8.351

7.432
7.419
7.415
7.335
7.330
7.322
7.272
7.260
7.008
6.994
6.990

4.632
4.620

3.867

3.400
3.386
3.373
3.359
3.346
3.332
3.319
3.017

1.251
1.238

ppm (t1)

HM-4-22-1 (file name: 4-22-1h), CDCl₃, 500MHz

7.755
7.750
7.739
7.736
7.612
7.609
7.596
7.549
7.544
7.540
7.531
7.517
7.507
7.501
7.474
7.470
7.463
7.451
7.449
7.442
7.260

3.431
3.421
3.407
3.395
3.380

1.598
1.583
1.566
1.554
1.539
1.413
1.398
1.383
1.368
1.353
1.339
1.295
1.281
1.256

0.0

5.0

ppm (t1)

HM-4-46 (file name: 4-46h), CDCl₃, 500MHz

7.912
7.897
7.859
7.844
7.802
7.789
7.786
7.736
7.723
7.556
7.543
7.528
7.516
7.503
7.488
7.461
7.446
7.433
7.429
7.414
7.403
7.400
7.396
7.380
7.365

3.540
3.527
3.514
3.500
3.487
3.473
3.460

1.360
1.347

HM-3-84 (file name: 3-84n) , CDCl₃, 500MHz

7.773
7.769
7.757
7.754
7.736
7.719
7.690
7.673
7.666
7.652
7.625
7.517
7.514
7.507
7.500
7.495
7.492
7.486
7.470
7.409
7.394
7.379
7.260

3.854
3.559
3.546
3.533
3.519
3.506
3.493
3.479

1.351
1.337

8.18
5.23
1.04

3.05

1.00

6.08

0.0

5.0

ppm (t1)

HM-4-48 (file name: 4-48h), CDCl₃, 500MHz

1.588
1.359
1.346
1.184
1.169
1.155
0.941
0.926
0.912

3.550
3.544
3.535
3.531
3.521
3.504
3.491
3.082
3.068
3.054
3.040

7.931
7.926
7.915
7.912
7.721
7.704
7.678
7.665
7.661
7.650
7.494
7.478
7.463
7.456
7.453
7.447
7.400
7.385
7.371
7.260

HM-4 50 (file name: 4-50n), CDCl₃, 500MHz

HM-4-52 (file name: 4-52h) , CDCl₃, 500MHz