Design, synthesis and phenotypic evaluation of *N*-biaryl amides for IL-17A suppression

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Experimental

Chemistry

All reactions were carried out on solid phase. All commercially available reagents were used without further purification unless otherwise stated. Compounds were purified in last step using preparation thin layer chromatography (pTLC), SilicaGel GF254 plates (Rushan Taiyang Desiccant co, .ltd, 0.4 mm thick). ^{1}H-NMR data was recorded on Varian 400 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of $CDCl_3$ (7.26 ppm) or CD_3OD (3.31 ppm). Data are reported as follows: chemical shift(δ ppm), multiplicity (s=singlet, d= doublet, t= triplet, m= multiplet, br = Broad),coupling constant in hertz (Hz), and integration.LC-MS data was recorded on Agilent Technologies 6120 quadrupole mass spectrometer.

Procedure for optimization of Suzuki reaction conditions

To mixture of amine loaded DMHB resin (100mg, 0.13mmol) in 1mL solvent were added amine loaded DMHB resin (100mg, 0.13mmol),base (0.39mmol). After bubbled with nitrogen for 5 min, the mixture was added $Pd(dppf)Cl_2$ (14.3mg, 0.15mmol) and set up in microwave reactor at appointed temperature, 1h, pre-stirring for 30 seconds. The resulting resin was washed with THF, THF:H_2O (1:1), H_2O, THF:H_2O (1:1), THF, DCM successively and dried in vacuum for 6 hours. An analytical amount of the resin was cleaved with 15% TFA in DCM for 10 min. The resulting solution was evaporated and basified by saturated sodium carbonate solution and extracted with 0.5mL DCM detected by LC-MS.

General procedure for synthesis of compounds 2, 4a-4t, 5a-5d and 6a-6i

To a 250mL flask were added 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) (10g, 15mmol) and 100mL 1-methyl-2-pyrrolidinone (NMP) and swelled for 5 min. Aniline (75mmol), DIPEA (13mL, 75mmol) and acetic acid (15mL) were then added. After

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shaking at room temperature for 2 hours, sodium triacetoxyborohydride (19g, 90mmol) was added gradually and then the mixture continued to shake for 24 hours at room temperature. The loaded resin was washed with MeOH, DMF, H_2O, MeOH and DCM successively and dried in vacuum overnight to yield DMHB resin-bound 4-bromo-benzylamine.

To mixture of the above DMHB resin-bound 4-bromo-benzylamine (100mg, 0.13mmol) in 1mL NMP were added boronic acid (125mg, 0.52mmol), K_3PO_4•$3H_2O$ (104mg, 0.39mmol). After bubbled with nitrogen for 5 min, the mixture was added $Pd(dppf)Cl_2$ (14.3mg, 0.15mmol) and set up in microwave reactor at 90 ^oC, 1h, pre-stirring for 30 seconds. The resulting resin was washed with THF, THF:H_2O (1:1), H_2O, THF:H_2O (1:1), THF, DCM successively and dried in vacuum for 6 hours. An analytical amount of the resin was cleaved with 15% TFA in DCM for 10 min. The resulting solution was evaporated and basified by saturated sodium carbonate solution and extracted with 0.5mL DCM detected by LC-MS.

To mixture of the above DMHB resin-bound in 2mL DMF:DCE (1:1) were added carboxylic acid (2.5mmol), *N*,*N'*-methanediylidenebis (propan-2-amine) (DIC) (381μL, 2.5mmol). The mixture was sealed in a tube and set up in microwave reactor at 60^oC, 1h, pre-stirring for 30 seconds. The resulting resin was washed with MeOH, DMF, H2O, MeOH and DCM successively and dried in vacuum overnight, and then treated with 50% TFA in DCE for 30 min. The cleaved solution was concentrated and basified by saturated sodium carbonate solution and extracted with DCM. The combined organic phase was evaporated and isolated by PTLC to get the desired compound.

2-chloro-*N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)benzamide (2) white solid (7mg，7.52% yield) ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.77 (dd, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.53 – 7.45 (m, 3H), 7.45 – 7.38 (m, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 3.0 Hz, 1H), 6.84 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 371.05, found 371.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)benzamide (4a)** white solid (20mg，23.68% yield) ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.41 (m, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.91 – 6.86 (m, 1H), 6.86 – 6.80 (m, 1H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 337.09, found 337.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-fluorobenzamide(4b)** white solid (13.3mg，14.95% yield) ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 15.6 Hz, 1H), 8.19 (td, *J* = 8.0, 1.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.54 (td, *J* = 7.3, 1.7 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.34 (dd, *J* = 15.7, 8.1 Hz, 2H), 7.20 (dd, *J* = 12.3, 8.3 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.84 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 355.08, found 355.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-(trifluoromethyl)benzamide (4c)** white solid (7.4mg，7.29% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.72 – 7.65 (m, 4H), 7.65 – 7.56 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 3.0 Hz, 1H), 6.84 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 405.07, found 405.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-3-fluoropicolinamide (4d)** white solid (9mg，10.09% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.46 (d, *J* = 4.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.67 – 7.59 (m, 1H), 7.59 – 7.52 (m, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 356.07, found 356.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2,6-difluorobenzamide (4e)** white solid (18.5mg，19.80% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 3H), 7.50 – 7.38 (m, 3H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 2H), 6.85 (dd, *J* = 9.9, 7.1 Hz, 2H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 373.07, found 373.1.

2-chloro-*N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-6-fluorobenzamide (4f) white solid (7.3mg，7.48% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.61 (s, 1H), 7.51 – 7.45 (m, 2H), 7.41 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.11 (td, *J* = 8.5, 0.9 Hz, 1H), 6.90 – 6.79 (m, 2H), 3.82 (s, 3H). LC-MS (ESI) $[M+H]^+$ 389.04, found 389.0.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-phenylacetamide (4g)** white solid (7.9mg，8.98% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.30 (m, 7H), 7.12 (s, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 2H). LC-MS (ESI) $[M+H]^+$ 351.10, found 351.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-(2-fluorophenyl)acetamide (4h)** white solid (9.2mg,9.95% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.36 (m, 3H), 7.36 – 7.28 (m, 3H), 7.23 – 7.06 (m, 2H), 6.82 (d, *J* = 9.5 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 2H). LC-MS (ESI) $[M+H]^+$ 369.09, found 369.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-3-phenylpropanamide (4i)** white solid (11.6mg，12.68% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 15.3, 7.9 Hz, 3H), 7.26 – 7.20 (m, 3H), 7.18 (s, 1H), 6.82 (dd, *J* = 11.7, 3.0 Hz, 2H), 3.80 (s, 3H), 3.07 (t, *J* = 7.4 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H). LC-MS (ESI) $[M+H]^+$ 365.12, found 365.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)cyclohexanecarboxamide (4j)** white solid (18.8mg，21.87% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.73 (m, 2H), 3.80 (s, 3H), 2.25 (t, *J* = 11.8 Hz, 1H), 1.97 (d, *J* = 12.8 Hz, 2H), 1.85 (d, *J* = 11.5 Hz, 2H), 1.61 (dd, *J* = 43.4, 28.9 Hz, 4H), 1.41 – 1.31 (m, 2H). LC-MS (ESI) $[M+H]^+$ 343.13, found 343.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)tetrahydro-2H-pyran-4-carboxamide (4k)** white solid (16.4mg，18.97% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.89 – 6.76 (m, 2H), 4.08 (d, *J* = 10.4 Hz, 2H), 3.81 (s, 3H), 3.47 (t, *J* = 10.7 Hz, 2H), 2.59 – 2.46 (m, 1H), 1.96 – 1.81 (m, 4H). LC-MS (ESI) $[M+H]^+$ 345.11, found 345.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-(tetrahydro-2H-pyran-4-yl)acetamide (4l)** white solid (35.1mg，30.02% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.37 (m, 3H), 7.34 (d, *J* = 8.6 Hz, 1H), 6.88 – 6.77 (m, 2H), 3.97 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 11.3 Hz, 2H), 2.31 (d, *J* = 7.0 Hz, 2H), 1.72 (d, *J* = 12.0 Hz, 3H), 1.45 – 1.35 (m, 2H). LC-MS (ESI) $[M+H]^+$ 359.13, found 359.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-1-methylpiperidine-4-carboxamide (4m)** white solid (14.7mg，16.39% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 1H), 6.89 – 6.76 (m, 2H), 3.80 (s, 3H), 2.70 (s, 3H), 2.49 – 1.54 (m, 9H). LC-MS (ESI) $[M+H]^+$ 358.14, found 358.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)cyclopentanecarboxamide (4n)**white solid (22.7mg，27.53% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.28 (m, 4H), 6.90 – 6.72 (m, 2H), 3.80 (s, 3H), 2.77 – 2.63 (m, 1H), 2.04 – 1.86 (m, 4H), 1.85 – 1.71 (m, 2H), 1.71 – 1.54 (m, 2H). LC-MS (ESI) $[M+H]^+$ 329.12, found 329.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)tetrahydrofuran-2-carboxamide (4o)** white solid (22.7mg，27.53% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 12.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 6.93 – 6.75 (m, 2H), 4.49 (dd, *J* = 8.2, 5.9 Hz, 1H), 4.06 (dd, *J* = 14.2, 7.0 Hz, 1H), 3.97 (dd, *J* = 14.5, 7.4 Hz, 1H), 3.81 (s, 3H), 2.38 (td, *J* = 15.5, 7.6 Hz, 1H), 2.20 (td, *J* = 13.3, 6.1 Hz, 1H), 2.05 – 1.86 (m, 2H). LC-MS (ESI) $[M+H]^+$ 331.10, found 331.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)cyclopropanecarboxamide (4p)** white solid (9.5mg，12.59% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.47 (m, 3H), 7.40 (d, *J* = 8.3

Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 6.88 – 6.77 (m, 2H), 3.80 (s, 3H), 1.36 – 1.18 (m, 1H), 1.16 – 0.97 (m, 2H), 0.92 – 0.80 (m, 2H). LC-MS (ESI) $[M+H]^+$ 301.09, found 301.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-cyclopropylacetamide (4q)** white solid (8.7mg，11.02% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.75 (m, 2H), 3.81 (s, 3H), 2.36 (d, *J* = 7.2 Hz, 2H), 1.19 – 1.02 (m, 1H), 0.72 (d, *J* = 7.0 Hz, 2H), 0.32 (d, *J* = 4.3 Hz, 2H). LC-MS (ESI) $[M+H]^+$ 315.10, found 315.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)isobutyramide (4r)** white solid (8.1mg，10.67% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 6.93 – 6.72 (m, 2H), 3.81 (s, 3H), 2.53 (h, *J* = 13.5, 6.8 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 6H). LC-MS (ESI) $[M+H]^+$ 303.10, found 303.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2-methoxyacetamide (4s)** white solid (4.7mg，6.15% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 6.89 – 6.77 (m, 2H), 4.04 (s, 2H), 3.81 (s, 3H), 3.53 (s, 3H). LC-MS (ESI) $[M+H]^+$ 305.08, found 305.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-4-yl)acetamide (4t)** white solid (5.0mg，9.72% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 1H), 6.88 – 6.74 (m, 2H), 3.81 (s, 3H), 2.21 (s, 3H). LC-MS (ESI) $[M+H]^+$ 275.07, found 275.1.

***N*-(2'-chloro-5'-methoxy-[1,1'-biphenyl]-3-yl)-2,6-difluorobenzamide (5a)** white solid (19.0mg，20.33% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 13.9 Hz, 1H), 7.47 – 7.31 (m, 3H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.07 – 6.73 (m, 4H), 3.80 (s, 3H). LC-MS (ESI) $[M+H]^+$ 373.07, found 373.1.

***N*-(6-(2-chloro-5-methoxyphenyl)pyridin-3-yl)-2,6-difluorobenzamide (5b)** white solid (7.0mg，7.47% yield) ^{1}H NMR (400 MHz, CD_3OD) δ 8.91 (s, 1H), 8.32 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 15.0, 8.4 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.22 – 7.08 (m, 3H), 7.00 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.84 (s, 3H). LC-MS (ESI) $[M+H]^+$ 374.06, found 374.1.

***N*-(2'-chloro-2-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2,6-difluorobenzamide (5c)** white solid (20.1mg，20.52% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.70 (d, *J* = 11.1

Hz, 1H), 7.45 (dd, *J* = 13.9, 7.4 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.01 (t, *J* = 8.2 Hz, 2H), 6.94 – 6.79 (m, 2H), 3.81 (s, 3H).. LC-MS (ESI) $[M+H]^+$ 391.06, found 391.1.

***N*-(2,2'-dichloro-5'-methoxy-[1,1'-biphenyl]-4-yl)-2,6-difluorobenzamide (5d)** white solid (12.7mg，12.44% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 4.0 Hz, 1H), 7.05 – 6.92 (m, 2H), 6.92 – 6.85 (m, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 3.81 (s, 3H). LC-MS (ESI) $[M+H]^+$ 407.03, found 407.0.

***N*-([1,1'-biphenyl]-4-yl)-2,6-difluorobenzamide (6a)** white solid (4.9mg，6.34% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.65 (m, 3H), 7.61 (t, 3H), 7.46 (p, 3H), 7.40 – 7.30 (m, 1H), 7.02 (t, *J* = 8.2 Hz, 2H). LC-MS (ESI) $[M+H]^+$ 309.10, found 309.1

2,6-difluoro-*N*-(4-(pyridin-3-yl)phenyl)benzamide (6b) white solid (11.9mg，15.34% yield) ^{1}H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.51 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.63 – 7.46 (m, 2H), 7.12 (t, *J* = 8.1 Hz, 2H).LC-MS(ESI) $[M+H]^+$ 310.09, found 310.1.

2,6-difluoro-*N*-(4-(6-methylpyridin-3-yl)phenyl)benzamide (6c)white solid (4.6mg，5.45% yield) ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.54 (p, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 8.1 Hz, 2H), 2.58 (s, 3H). LC-MS (ESI) $[M+H]^+$ 324.11, found 324.1.

2,6-difluoro-*N*-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)benzamide (6d)white solid (8.8mg，9.89% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.69 (s, 1H), 7.66 – 7.57 (m, 3H), 7.52 – 7.35 (m, 3H), 7.01 (t, *J* = 8.2 Hz, 2H), 3.94 (s, 3H). LC-MS (ESI) $[M+H]^+$ 313.10, found 313.1.

2,6-difluoro-*N*-(2'-methyl-[1,1'-biphenyl]-4-yl)benzamide (6e) white solid (9.4mg，12.44% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.63 (m, 3H), 7.57 – 7.37 (m, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 4.3 Hz, 2H), 7.01 (t, *J* = 8.1 Hz, 2H), 2.29 (s, 3H). LC-MS (ESI) $[M+H]^+$ 323.11, found 323.1.

***N*-(2'-chloro-[1,1'-biphenyl]-4-yl)-2,6-difluorobenzamide (6f)** white solid (5.5mg，6.40% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 3H), 7.47 (d, *J* = 8.3 Hz, 3H), 7.45 – 7.38 (m, 1H), 7.36 – 7.29 (m, 2H), 7.02 (t, *J* = 8.2 Hz, 2H). LC-MS (ESI) $[M+H]^+$ 343.06, found 343.1.

2,6-difluoro-*N*-(5'-methoxy-2'-methyl-[1,1'-biphenyl]-4-yl)benzamide (6g) white solid(3.3mg，3.74% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.44 (p, *J* = 6.5 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.03 (t, *J* = 8.2 Hz, 2H), 6.88 – 6.75 (m, 2H), 3.81 (s, 3H), 2.21 (s, 3H). LC-MS (ESI) $[M+H]^+$ 353.12, found 353.1.

***N*-(2'-chloro-5'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-2,6-difluorobenzamide(6h)**white solid(15.8mg，14.77% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.35 (m, 4H), 7.22 (s, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.01 (t, *J* = 8.2 Hz, 2H). LC-MS (ESI) $[M+H]^+$ 427.04, found 427.0.

6-chloro-4'-(2,6-difluorobenzamido)-[1,1'-biphenyl]-3-carboxylic acid (6i) white solid(17.2mg, 17.74% yield) ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.17 – 7.07 (m, 2H).LC-MS (ESI) $[M+H]^+$387.05, found 388.1.

Biology

Flow cytometry

For analysis of IL-17A production, cells were stimulated with PMA (50 ng/ml, Sigma-Aldrich) and ionomycin (500 ng/ml, Sigma-Aldrich) for 4 h. Cells were stained with LIVE/DEAD® Fixable Dead Cell Stains (ThermoFisher) at room temperature for 30min.Cells were stained withanti-mouse CD4-FITC (Ebioscience) in at 4℃ for 30 min. Cells were then fixed and permeabilized using Cytofix/Cytoperm and Perm/Wash buffer (BD Biosciences) according to the manufacturer's instructions. Cells were then stained with anti-mouse IL-17A-PE (Ebioscience) in wash buffer at 4℃ for 45 min. All data were analyzed using Gallios™ Flow Cytometer (Beckman Coulter) and FlowJo software (Tree Star Inc).