SAR Studies of*N*-[2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide Derivatives as Potent GPR35 Agonists

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Supporting information

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1. Chemistry

General information

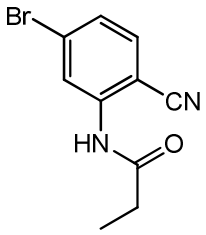
All experimental reagents and solvents were obtained from various providers and used without any additional purification or drying except for tetrahydrofuran, which was distilled over calcium. The purity of all compounds was ≥ 95%. The reactions were monitored by thin layer chromatography (TLC). NMR data were collected on a Bruker Ascend 600 MHz NMR spectrometer at 600 MHz (^{1}H) or 151 MHz (^{13}C). The chemical shifts were reported in parts per million (ppm) relative to the deuterated solvent DMSO-*d6*; that is: δ^{1}H, 2.49 ppm; ^{13}C, 39.7 ppm.High-resolution mass spectra (HRMS) were performed on an Agilent 1290 Infinity LC instrument (Agilent, USA) coupled to an Agilent 6540 series QTOF-MS (Agilent, USA) equipped with an ESI source, a diode-array detector (DAD), an automatic sample injector, a degasser and a column thermostat.

The purity of all synthetic compounds was analyzed by HPLC. The determination of purity was conducted on a Waters ACQUITY UPLC^{TM} system (Waters Corp., Milford, MA, USA) with ACQUITY UPLC$^{®}$ HSS T3 column (2.1×100 mm,1.8 μm). Elution was performed with a gradient of water/acetonitrile (containing 0.1% formic acid) from 95/5 to 5/95 for 10 min and maintained 5/95 for another 10 min. The flow rate was 200 μL/min. Peaks were detected at 254 nm or 290 nm.

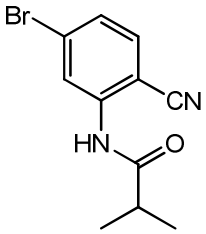
General procedures of method A for the synthesis of compounds 9-13 and 19-41

The appropriate 2-aminobenzonitrile derivatives and 4-aminobenzonitrile (1.0 equiv) were dissolved in pyridine (10 mL). Then a solution of the appropriate acid chloride (1.5 equiv) in DCM (2 mL) was added and the reaction mixture was stirred at room temperature (rt) overnight under an argon atmosphere. The resulting mixture was poured into a large amount of iced water. The precipitated products were filtered, washed with water, and dried under vacuum. The crude solids were recrystallized from methanol. The products were filtered off, and dried under vacuum at 50 ^{o}C. The ^{1}H NMR data of all these compounds was shown in support information.

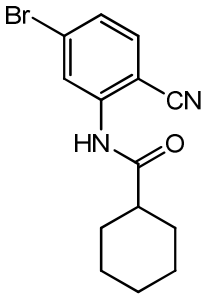
^{1}H NMR data ofcompounds **9-13** and **19-41**



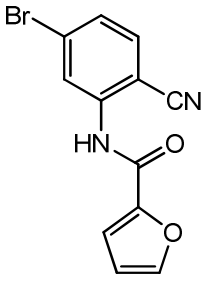
***N*-(5-bromo-2-cyanophenyl)propionamide** (**9**).**9** was obtained as described from method A. 72% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 10.22 (s, 1H), 7.91 (d, *J* = 1.9 Hz, 1H), 7.83 – 7.71 (m, 1H), 7.55 (dd, *J* = 8.4, 1.9 Hz, 1H), 2.41 (q, *J* = 7.5 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H).



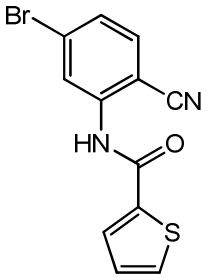
***N*-(5-bromo-2-cyanophenyl)isobutyramide** (**10**).**10** was obtained as described from method A. 77% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.19 (s, 1H), 7.84 (d, *J* = 1.9 Hz, 1H), 7.79 – 7.77 (m, 1H), 7.57 (dd, *J* = 8.4, 1.9 Hz, 1H), 2.68 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 6H).



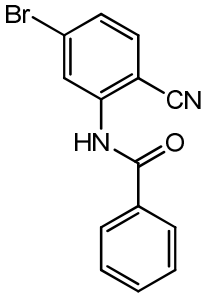
***N*-(5-bromo-2-cyanophenyl)cyclohexanecarboxamide** (**11**).**11** was obtained as described from method A. 81% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 10.15 (s, 1H), 7.84 (d, *J* = 1.9 Hz, 1H), 7.77 (dd, *J* = 9.2, 5.0 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.9 Hz, 1H), 2.47 – 2.38 (m, 1H), 1.84 (dd, *J* = 13.3, 2.1 Hz, 2H), 1.79 – 1.73 (m, 2H), 1.65 (dd, *J* = 9.2, 3.3 Hz, 1H), 1.41 (qd, *J* = 12.5, 3.1 Hz, 2H), 1.33 – 1.24 (m, 2H), 1.24 – 1.14 (m, 1H).



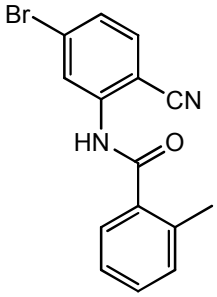
***N*-(5-bromo-2-cyanophenyl)furan-2-carboxamide** (**12**).**12** was obtained as described from method A. 71% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.62 (s, 1H), 8.02 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.39 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.76 (dd, *J* = 3.5, 1.7 Hz, 1H)



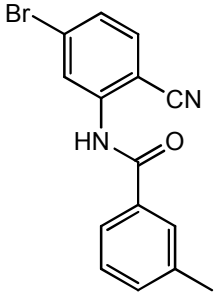
***N*-(5-bromo-2-cyanophenyl)thiophene-2-carboxamide(13).** **13** was obtained as described from method A. 68% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.74 (s, 1H), 8.00 (t, *J* = 6.4 Hz, 1H), 7.95 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.67 (dt, *J* = 6.1, 3.1 Hz, 1H), 7.28 (dd, *J* = 5.0, 3.8 Hz, 1H).



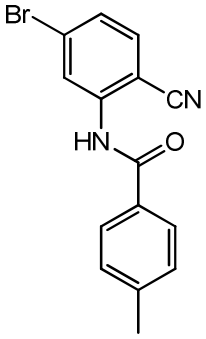
***N*-(5-bromo-2-cyanophenyl)benzamide(19).19** was obtained as described from method A. 85% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.73 (s, 1H), 8.06 – 7.96 (m, 2H), 7.89 (d, *J* = 1.9 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 2H).



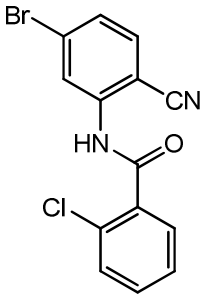
***N*-(5-bromo-2-cyanophenyl)-2-methylbenzamide (20).20** was obtained as described from method A. 82% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.70 (s, 1H), 7.89 (d, *J* = 1.7 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.46 – 7.41 (m, 1H), 7.34 (t, *J* = 6.8 Hz, 2H), 2.45 (s, 3H).



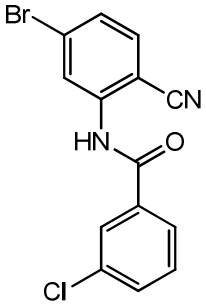
***N*-(5-bromo-2-cyanophenyl)-3-methylbenzamide(21).21** was obtained as described from method A. 79% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.63 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 1.9 Hz, 1H), 7.87 – 7.82 (m, 1H), 7.68 – 7.63 (m, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H).



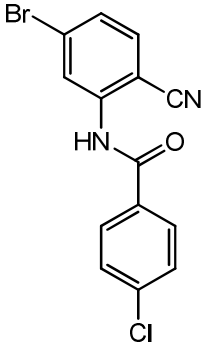
***N*-(5-bromo-2-cyanophenyl)-4-methylbenzamide(22).22** was obtained as described from method A. 84% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.67 (s, 1H), 7.86 (dd, *J* = 6.9, 5.1 Hz, 2H), 7.81 (s, 1H), 7.80 – 7.76 (m, 1H), 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.49 – 7.45 (m, 2H), 2.41 (s, 3H).



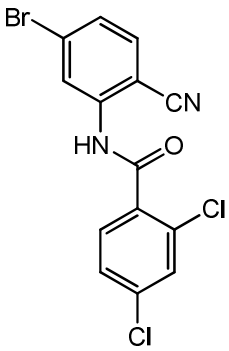
***N*-(5-bromo-2-cyanophenyl)-2-chlorobenzamide(23).23** was obtained as described from method A. 69% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.99 (s, 1H), 7.94 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.67 (ddd, *J* = 7.3, 4.8, 1.7 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.56 (td, *J* = 7.7, 1.6 Hz, 1H), 7.51 (td, *J* = 7.4, 1.0 Hz, 1H).



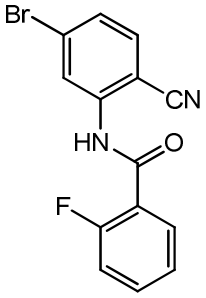
***N*-(5-bromo-2-cyanophenyl)-3-chlorobenzamide(24).24** was obtained as described from method A. 71% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.86 (s, 1H), 8.04 (t, *J* = 1.8 Hz, 1H), 7.96 – 7.94 (m, 1H), 7.89 (d, *J* = 1.9 Hz, 2H), 7.86 (t, *J* = 6.0 Hz, 1H), 7.74 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 7.63 (t, *J* = 4.9 Hz, 1H).



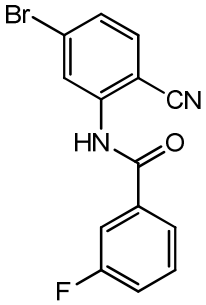
***N*-(5-bromo-2-cyanophenyl)-4-chlorobenzamide (25).25** was obtained as described from method A. 73% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.82 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 1.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.68 (dd, *J* = 8.4, 1.7 Hz, 3H).



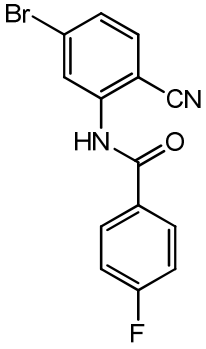
***N*-(5-bromo-2-cyanophenyl)-2,4-dichlorobenzamide** (**26**).**26** was obtained as described from method A. 70% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 11.03 (s, 1H), 7.96 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.62 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.0 Hz, 1H).



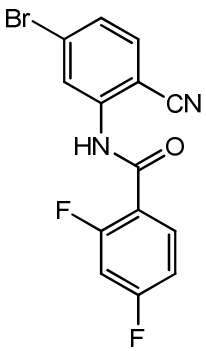
***N*-(5-bromo-2-cyanophenyl)-2-fluorobenzamide** (**27**).**27** was obtained as described from method A. 81% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.70 (s, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.87 – 7.84 (m, 1H), 7.79 (td, *J* = 7.5, 1.7 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.43 – 7.37 (m, 2H).



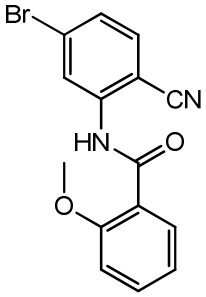
***N*-(5-bromo-2-cyanophenyl)-3-fluorobenzamide**(**28**).**28** was obtained as described from method A. 83% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.83 (s, 1H), 7.90 (d, *J* = 1.8 Hz, 1H), 7.86 (s, 1H), 7.80 (dd, *J* = 9.8, 1.5 Hz, 1H), 7.69 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.65 (dd, *J* = 7.9, 2.1 Hz, 1H), 7.54 (dd, *J* = 8.9, 2.8 Hz, 1H).



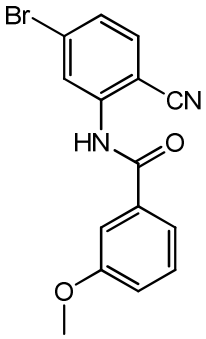
***N*-(5-bromo-2-cyanophenyl)-4-fluorobenzamide** (**29**).**29** was obtained as described from method A. 74% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.76 (s, 1H), 8.08 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.67 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.43 (t, *J* = 8.7 Hz, 2H).



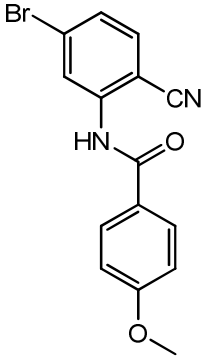
***N*-(5-bromo-2-cyanophenyl)-2,4-difluorobenzamide(30).30** was obtained as described from method A. 79% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 10.70 (s, 1H), 8.00 (q, *J* = 3.3 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.86 (d, *J* = 2.2 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.30 (td, *J* = 8.4, 2.3 Hz, 1H).



***N*-(5-bromo-2-cyanophenyl)-2-methoxybenzamide(31).31** was obtained as described from method A. 78% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.76 (s, 1H), 8.67 (s, 1H), 8.03 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.53 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 4.06 (s, 3H).

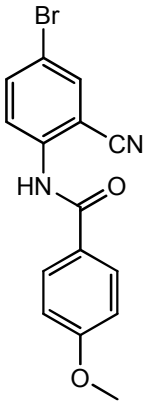


***N*-(5-bromo-2-cyanophenyl)-3-methoxybenzamide(32).32** was obtained as described from method A. 81% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.69 (s, 1H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.58 (dd, *J* = 6.7, 1.3 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 3.85 (s, 3H).

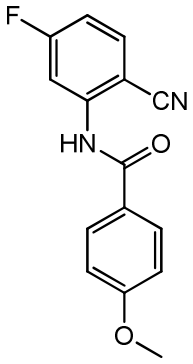


***N*-(5-bromo-2-cyanophenyl)-4-methoxybenzamide (33).33** was obtained as described from method A. 78% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.55 (s, 1H), 8.01 – 7.97 (m, 2H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.64 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.14 – 7.08 (m, 2H), 3.86 (s, 3H).

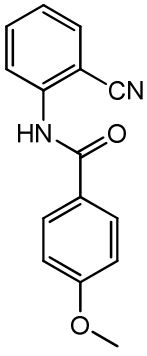
was obtained as described from method A. 69% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.54 (s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.65 (td, *J* = 8.4, 2.0 Hz, 2H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.16 – 7.13 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H).



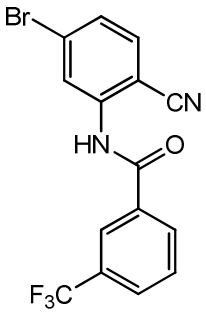
***N*-(4-bromo-2-cyanophenyl)-4-methoxybenzamide(35).35** was obtained as described from method A. 72% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.52 (s, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.02 – 8.00 (m, 1H), 8.00 – 7.99 (m, 1H), 7.93 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.13 – 7.11 (m, 1H), 7.11 – 7.10 (m, 1H).



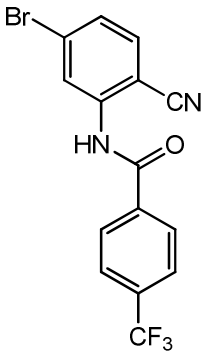
***N*-(2-cyano-5-fluorophenyl)-4-methoxybenzamide(36).36** was obtained as described from method A. 78% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.55 (s, 1H), 8.01 – 7.95 (m, 3H), 7.53 (dd, *J* = 10.2, 2.6 Hz, 1H), 7.31 (td, *J* = 8.5, 2.6 Hz, 1H), 7.13 – 7.09 (m, 2H), 3.86 (s, 3H).



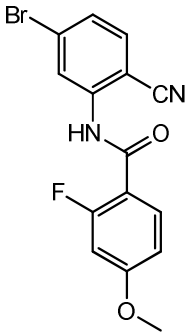
***N*-(2-cyanophenyl)-4-methoxybenzamide(37).37** was obtained as described from method A. 71% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.46 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.88 (t, *J* = 13.1 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H).



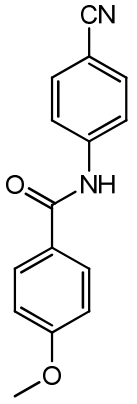
***N*-(5-bromo-2-cyanophenyl)-3-(trifluoromethyl)benzamide**(**38**). **38** was obtained as described from method A. 78% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 10.98 (s, 1H), 8.50 (d, *J* = 1.8 Hz, 1H), 8.33 (s, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 8.03 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.9 Hz, 1H).



***N*-(5-bromo-2-cyanophenyl)-4-(trifluoromethyl)benzamide** (**39**).**39** was obtained as described from method A. 69% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 10.98 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 2H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 1.9 Hz, 1H), 7.89 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.9 Hz, 1H).



***N*-(5-bromo-2-cyanophenyl)-2-fluoro-4-methoxybenzamide**(**40**). **40** was obtained as described from method A. 77% yield as white solid; [1]H NMR (600 MHz, DMSO-*d6*) δ 10.35 (s, 1H), 8.02 (d, *J* = 1.9 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 8.7 Hz, 1H), 7.63 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.03 (dd, *J* = 13.1, 2.4 Hz, 1H), 6.96 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.86 (s, 3H).



***N*-(4-cyanophenyl)-4-methoxybenzamide**(**41**).**41** was obtained as described from method A. 71% yield as white solid;[1]H NMR (600 MHz, DMSO-*d6*) δ 10.49 (s, 1H), 8.01 – 7.97 (m, 4H), 7.83 – 7.79 (m, 2H), 7.11 – 7.07 (m, 2H), 3.85 (s, 3H).

General procedures of method B for the synthesis of compounds 7a, 7b, 14-18 and 42-64.

Aluminum chloride (3.0 equiv) was added to 20 mL of anhydrous tetrahydrofuran. Subsequently, sodium azide (6.0 equiv) and *N*-(2-cyanophenyl)amdio derivatives (1.0 equiv) were added in order. The mixture was refluxed for 5 h with agitation under an argon atmosphere. After the completion of the reaction, the reaction mixture was extracted three times with excessive diluted hydrochloric acid to remove Al^{3+}. The organic phase was dried with anhydrous Na_2SO_4 and was concentrated under reduced pressure until the product started to crystallize and cooled in ice-bath to complete the crystallization. The product was filtered off, washed with methanol, and dried under vacuum at 50^{o}C.

5-bromo-2-(1*H*-tetrazol-5-yl)aniline (7a). 7a was obtained from 2-amino-5-bromobenzonitrile as described from method B. 84% yield as pale yellow soild; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 7.96 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 154.57, 147.09, 134.59, 130.39, 118.90, 106.96, 106.19. Purity: 95.57%. HRMS for $C_7H_5BrN_5$: calcd, 238.9807; found, 237.9764 $[M-H]^-$, 239.9743 $[M-H+2]^-$.

4-bromo-2-(1*H*-tetrazol-5-yl)aniline (7b). 7b was obtained from 2-amino-4-bromobenzonitrile as described from method B. 91% yield as pale yellow soild; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 6.87 (dd, *J* = 8.4, 1.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 153.77, 147.72, 129.58, 124.53, 117.81, 117.74, 103.79. Purity: 98.91%.HRMS for $C_7H_5BrN_5$: calcd, 238.9807; found, 237.9759 $[M-H]^-$, 239.9739 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)propionamide (14). 14** was obtained from **9** as described from method B. 78% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 10.72 (s, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.45 (dt, *J* = 7.5, 5.5 Hz, 2H), 1.14 (dd, *J* = 9.8, 5.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 172.95, 154.62, 138.72, 130.84, 126.99, 125.25, 124.42, 112.83, 30.77, 9.71. Purity: 96.75%.HRMS for $C_{10}H_{10}BrN_5O$: calcd, 295.0069; found, 294.0002 $[M-H]^-$, 295.9982 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)isobutyramide (15). 15** was obtained from **10** as described from method B. 88% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.15 (s, 1H), 8.69 (d, *J* = 1.7 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.8 Hz, 1H), 2.65 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 176.03, 155.62, 138.68, 130.57, 126.78, 124.45, 123.90, 113.88, 36.68, 19.69. Purity: 95.68%.HRMS for $C_{11}H_{12}BrN_5O$: calcd, 309.0225; found, 308.0180 $[M-H]^-$, 310.0160 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)cyclohexanecarboxamide (16). 16** was obtained from **11** as described from method B. 89% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 10.79 (s, 1H), 8.67 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.38 (tt, *J* = 11.4, 3.5 Hz, 1H), 1.93 (dd, *J* = 13.5, 2.0 Hz, 2H), 1.80 – 1.72 (m, 2H), 1.68 – 1.63 (m, 1H), 1.49 – 1.39 (m, 2H), 1.38 – 1.27 (m, 2H), 1.25 – 1.15 (m, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 175.05, 154.77, 138.83, 130.77, 126.94, 125.25, 124.30, 112.80, 46.03, 29.38, 25.85, 25.54.Purity: 99.29%.HRMS for $C_{14}H_{16}BrN_5O$: calcd, 349.0538; found, 348.0490 $[M-H]^-$, 350.0471 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)furan-2-carboxamide (17). 17** was obtained from **12** as described from method B. 85% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.83 (s, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.09 (t, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.36 (d, *J* = 3.2 Hz, 1H), 6.80 (dt, *J* = 8.0, 4.0 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 156.53, 154.91, 147.43, 147.10, 138.27, 130.49, 127.21, 125.40, 123.85, 116.46, 113.23, 112.22.Purity: 97.85%.HRMS for $C_{12}H_8BrN_5O_2$: calcd, 332.9861; found, 331.9808 $[M-H]^-$, 333.9788 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)thiophene-2-carboxamide (18). 18** was obtained from **13** as described from method B. 74% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.72 (s, 1H), 8.76 (d, *J* = 2.0 Hz, 1H), 7.99 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.96 – 7.94 (m, 2H), 7.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.33 (dd, *J* = 4.9, 3.8 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 160.33, 155.00, 139.58, 138.44, 133.54, 130.59, 129.74, 128.99, 127.32, 125.42, 124.11, 112.68.Purity: 95.83%.HRMS

for$C_{12}H_8BrN_5OS$: calcd, 348.9633; found, 347.9579 $[M-H]^-$, 349.9558 $[M-H+2]^-$.

***N*-(2-cyanophenyl)-4-methoxybenzamide (37).37**was obtained as described from method A. 71% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 10.46 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 165.46, 162.81, 141.11, 134.18, 133.54, 130.29, 127.23, 126.59, 126.06, 117.52, 114.28, 109.72, 55.97.Purity:96.97%.HRMS for $C_{15}H_{12}N_2O_2$: calcd, 252.0899; found, 251.0825 $[M-H]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)benzamide (42).42**was obtained from **19** as described from method B. 86% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.71 (s, 1H), 8.88 (d, *J* = 1.4 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 8.4, 1.5 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 165.70, 155.04, 138.77, 134.44, 132.93, 130.63, 129.43, 127.83, 127.37, 125.42, 124.33, 112.96.Purity: 98.83%.HRMS for $C_{14}H_{10}BrN_5O$: calcd, 343.0069; found, 342.0002 $[M-H]^-$, 343.9982 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2-methylbenzamide (43).43**was obtained from **20** as described from method B. 79% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.24 (s, 1H), 8.78 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.68 (dd, *J* = 6.7, 5.7 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.46 (td, *J* = 7.5, 1.3 Hz, 1H), 7.41 – 7.33 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 167.12, 153.84, 137.64, 135.76, 135.13, 130.58, 130.01, 129.82, 126.57, 126.52, 125.45, 124.18, 123.62, 112.66, 19.02.Purity: 97.01%.HRMS for $C_{15}H_{12}BrN_5O$: calcd, 357.0225; found, 356.0184 $[M-H]^-$, 358.0165 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-3-methylbenzamide (44).44**was obtained from **21** as described from method B. 81% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.67 (s, 1H), 8.87 (d, *J* = 2.0 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.53 – 7.46 (m, 2H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 165.76, 155.02, 138.82, 138.79, 134.41, 133.49, 130.60, 129.28, 128.48, 127.28, 125.45, 124.85, 124.22, 112.80, 21.50.Purity: 98.14%.HRMS for$C_{15}H_{12}BrN_5O$: calcd, 357.0225; found, 356.0169 $[M-H]^-$, 358.0150 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-4-methylbenzamide (45).45**was obtained from **22** as described from method B. 89% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.74 (s, 1H), 8.88 (d, *J* = 1.9 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.53 – 7.46 (m, 2H), 2.43 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.69, 154.13, 137.72, 133.37, 132.41, 129.49, 128.22, 127.43, 126.17, 124.25, 123.79, 123.05, 111.90, 20.44.Purity: 97.53%.HRMS for $C_{15}H_{12}BrN_5O$: calcd, 357.0225; found, 356.0174 $[M-H]^-$, 358.0155 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2-chlorobenzamide (46).46**was obtained from **23** as described from method B. 71% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.40 (s, 1H), 8.71 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.63 (ddd, *J* = 11.1, 5.7, 2.9 Hz, 2H), 7.59 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (td, *J* = 7.4, 1.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 165.44, 155.01, 138.12, 136.13, 132.47, 130.98, 130.69, 130.64, 129.53, 128.04, 125.04, 124.86, 114.46.Purity: 95.58%.HRMS for $C_{14}H_9BrClN_5O$: calcd, 376.9679; found, 375.9668 $[M-H]^-$, 377.9668 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-3-chlorobenzamide (47).47**was obtained from **24** as described from method B. 76% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.03 (t, *J* = 1.8 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.74 (tt, *J* = 5.8, 2.3 Hz, 1H), 7.66 (dd, *J* = 9.9, 5.9 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.35, 154.94, 138.37, 136.50, 134.17, 132.64, 131.36, 130.82, 127.92, 127.85, 126.49, 125.26, 125.13, 114.07.Purity: 96.68%.HRMS for $C_{14}H_9BrClN_5O$: calcd, 376.9679; found, 375.9615 $[M-H]^-$, 377.9598 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-4-chlorobenzamide (48).48**was obtained from **25** as described from method B. 69% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.73 (s, 1H), 8.79 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ: 164.65, 155.19, 138.48, 137.77, 133.23, 130.61, 129.72, 129.49, 127.57,125.12, 124.54, 113.69.Purity: 98.14%.HRMS for $C_{14}H_9BrClN_5O$: calcd, 376.9679; found, 375.9611 $[M-H]^-$, 377.9591 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2,4-dichlorobenzamide (49).49**was obtained from **26** as described from method B. 76% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.73 (s, 1H), 8.79 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.65, 155.19, 138.48, 137.77, 133.23, 130.61, 129.72, 129.49, 127.57, 125.12, 124.54, 113.69.Purity: 97.18%.HRMS for $C_{14}H_8BrCl_2N_5O$: calcd, 410.9289; found, 409.9235 $[M-H]^-$, 411.9226 $[M-H+2]^-$, 413.9182 $[M-H+4]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2-fluorobenzamide (50).50**was obtained from **27** as described from method B. 82% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.48 (d, *J* = 2.4 Hz, 1H), 8.81 (d, *J* = 1.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.91 (td, *J* = 7.6, 1.4 Hz, 1H), 7.69 (td, *J* = 7.3, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.44 (dt, *J* = 15.0, 8.1 Hz, 2H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 162.86 (d, *J* = 1.51 Hz), 159.83 (d, *J* = 250.66 Hz), 154.78, 138.21, 134.54 (d, *J* = 9.06 Hz), 131.01 (d, *J* = 1.51Hz), 130.86, 127.84, 125.50 (d, *J* = 3.02 Hz), 125.29, 124.95, 123.25 (d, *J* = 12.08 Hz), 117.15 (d, *J* = 22.65), 113.46.Purity: 98.22%.HRMS for $C_{14}H_9BrFN_5O$: calcd, 360.9975; found, 359.9917 $[M-H]^-$, 361.9898 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-3-fluorobenzamide (51).51**was obtained from **28** as described from method B. 88% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.62 (s, 1H), 8.76 (d, *J* = 1.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.67 (dd, *J* = 13.8, 7.9 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.52 (td, *J* = 8.4, 2.2 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.22 (d, *J* = 1.51 Hz), 162.59 (d, *J* = 244.62 Hz), 154.89, 138.39, 136.71 (d, *J* = 7.55 Hz), 131.58 (d, *J* = 7.55 Hz),130.53, 127.60, 125.43, 124.48, 123.80 (d, *J* = 3.02 Hz), 119.79 (d, *J* = 21.14 Hz), 114.75 (d, *J* = 22.65 Hz), 113.08.Purity: 96.07%.HRMS for $C_{14}H_9BrFN_5O$: calcd, 360.9975; found, 359.9914 $[M-H]^-$, 361.9894 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-4-fluorobenzamide (52).52**was obtained from **29** as described from method B. 84% yield as white solid;^{1}H NMR (600 MHz,DMSO-*d6*): δ 11.61 (s, 1H), 8.80 (d, *J* = 2.0 Hz, 1H), 8.13 – 8.09 (m, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.49 – 7.44 (m, 2H). ^{13}C NMR

(151 MHz, DMSO-*d6*): δ 165.00 (d, *J* = 250.66 Hz), 164.65, 154.99, 138.65, 130.97 (d, *J* = 3.02 Hz), 130.70, 130.62 (d, *J* = 9.06 Hz), 127.56, 125.36, 124.65, 116.46 (d, *J* = 21.14 Hz), 113.38.Purity: 98.78%.HRMS for $C_{14}H_9BrFN_5O$: calcd, 360.9975; found, 359.9936 $[M-H]^-$, 361.9917 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2,4-difluorobenzamide (53).53**was obtained from **30** as described from method B. 91% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.43 (d, *J* = 2.1 Hz, 1H), 8.75 (s, 1H), 7.99 (dd, *J* = 15.3, 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.63 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.32 (td, *J* = 8.5, 1.9 Hz, 1H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 163.71 (dd, *J* = 252.4, 12.5 Hz), 160.93 (d, *J* = 1.8 Hz), 159.48 (dd, *J* = 253.8, 13.1 Hz), 153.67 (s), 137.06 (s), 131.97 (dd, *J* = 10.6, 3.4 Hz), 129.86 (s), 126.91 (s), 124.16 (d, *J* = 7.1 Hz), 118.92 (dd, *J* = 12.8, 3.6 Hz), 112.68 (s), 111.90 (dd, *J* = 21.7, 3.4 Hz), 104.57 (t, *J* = 26.6 Hz).Purity: 96.78%.HRMS for $C_{14}H_8BrF_2N_5O$: calcd, 378.9880; found, 377.9844 $[M-H]^-$, 379.9825 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2-methoxybenzamide (54).54**was obtained from **31** as described from method B. 81% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.83 (s, 1H), 9.00 (d, *J* = 1.9 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.13 (td, *J* = 7.8, 0.9 Hz, 1H), 4.02 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.55, 157.56, 138.59, 134.40, 131.88, 131.04, 127.16, 125.25, 124.91, 122.09, 121.33, 112.73, 56.49.Purity: 98.20%.HRMS for $C_{15}H_{12}BrN_5O_2$: calcd, 373.0174; found, 372.0125 $[M-H]^-$, 374.0106 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-3-methoxybenzamide (55).55**was obtained from **32** as described from method B. 74% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.69 (s, 1H), 8.80 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.49 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.16 – 7.13 (m, 1H), 3.80 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*) δ 165.40, 159.96, 155.16, 138.70, 135.85, 130.60, 130.58, 127.32, 125.33, 124.08, 120.01, 118.86,112.99, 112.79, 55.81.Purity:96.70%. HRMS for $C_{15}H_{12}BrN_5O_2$: calcd, 373.0174; found, 372.0111 $[M-H]^-$, 374.0091 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-4-methoxybenzamide (56). 56**was obtained from **33** as described from method B. 78% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.65 (s, 1H), 8.91 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 165.09, 162.99, 154.96, 139.04, 130.48, 129.76, 126.92, 126.42, 125.52, 123.92, 114.66, 112.23, 56.01.Purity: 95.24%.HRMS for $C_{15}H_{12}BrN_5O_2$: calcd, 373.0174; found, 372.0115 $[M-H]^-$, 374.0097 $[M-H+2]^-$

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-3,4-dimethoxybenzamide (57). 57** was obtained from **34** as described from method B. 82% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 12.58 (s, 1H), 9.00 (d, *J* = 2.0 Hz, 1H), 8.11 (t, *J* = 10.5 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.75 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.46 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*) δ 165.17, 157.19, 152.54, 149.06, 138.66, 130.01, 126.79, 126.46, 123.47, 122.78, 121.41, 115.11, 111.83, 110.82, 56.20, 56.00. Purity: 97.72%.HRMS for $C_{16}H_{14}BrN_5O_3$: calcd, 403.0280; found, 402.0212 $[M-H]^-$, 404.0193 $[M-H+2]^-$

***N*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-4-methoxybenzamide (58). 58** was obtained from **35** as described from method B. 89% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.58 (s, 1H), 8.59 (d, *J* = 8.9 Hz, 1H), 8.22 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.98, 162.90, 154.65, 137.18, 134.62, 131.15, 129.77, 126.67, 123.75, 115.71, 115.68, 114.63, 56.00.Purity: 99.77%.HRMS for $C_{15}H_{12}BrN_5O_2$: calcd, 373.0174; found, 372.0110 $[M-H]^-$, 374.0091 $[M-H+2]^-$.

***N*-(5-fluoro-2-(1*H*-tetrazol-5-yl)phenyl)-4-methoxybenzamide (59). 59**was obtained from **36** as described from method B. 75% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.81 (s, 1H), 8.56 (dd, *J* = 12.0, 2.7 Hz, 1H), 8.09 (dd, *J* = 8.8, 6.3 Hz, 1H), 8.07 – 8.03 (m, 2H), 7.28 – 7.21 (m, 1H), 7.19 – 7.15 (m, 2H), 3.88 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.18 (s), 162.94 (d, *J* = 247.2 Hz),161.98 (s), 153.74 (s), 138.88 (d, *J* = 12.3 Hz), 130.06 (d, *J* = 10.6 Hz), 128.72 (s), 125.43 (s), 113.68 (s), 110.28 (d, *J* = 22.7 Hz), 108.52 (s), 107.16 (d, *J* = 28.2 Hz),

54.97 (s).Purity: 99.17%.HRMS for $C_{15}H_{12}FN_5O_2$: calcd, 313.0975; found, 312.0975 $[M-H]^-$.

***N*-(2-(1*H*-tetrazol-5-yl)phenyl)-4-methoxybenzamide (60).60**was obtained from **37** as described from method B. 81% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.81 (s, 1H), 8.56 (dd, *J* = 12.0, 2.7 Hz, 1H), 8.09 (dd, *J* = 8.8, 6.3 Hz, 1H), 8.07 – 8.04 (m, 2H), 7.25 (ddd, *J* = 10.7, 8.3, 2.7 Hz, 1H), 7.19 – 7.15 (m, 2H), 3.88 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 164.99, 162.73, 156.39, 137.72, 131.39, 129.76, 128.78, 127.16, 124.10, 121.57, 114.95, 114.60, 55.99.Purity: 100%.HRMS for $C_{15}H_{13}N_5O_2$: calcd, 295.1069; found, 294.1067 $[M-H]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-3-(trifluoromethyl)benzamide (61).61**was obtained from **38** as described from method B. 86% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.67 (s, 1H), 8.70 (d, *J* = 2.0 Hz, 1H), 8.35 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.64 (dd, *J* = 8.4, 2.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 163.30 (s), 153.87 (s), 137.24 (s), 134.42 (s), 130.85 (s), 129.89 (s), 129.68 (s), 129.01 (q, *J* = 32.2 Hz), 128.27 (d, *J* = 3.5 Hz), 127.03 (s), 124.36 (s), 124.12 (d, *J* = 8.2 Hz), 123.54 (d, *J* = 3.9 Hz), 122.35 (s), 113.50 (s).Purity: 97.19%.HRMS for $C_{15}H_9BrF_3N_5O$: calcd, 410.9943; found, 409.9880 $[M-H]^-$, 411.9861 $[M-H+2]^-$

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-4-(trifluoromethyl)benzamide (62).62**was obtained from **39** as described from method B. 87% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 12.37 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.56 (dt, *J* = 8.4, 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ 164.57 (s), 156.56 (s), 138.51 (s), 138.07 (s), 132.42 (q, *J* = 32.0 Hz), 130.33 (s), 128.80 (s), 127.58 (s), 126.42 (q, *J* = 3.5 Hz), 125.20 (s), 124.16 (s), 123.81 (s), 123.39 (s), 115.76 (s). Purity: 97.80%. HRMS for $C_{15}H_9BrF_3N_5O$: calcd, 410.9943; found, 409.9898 $[M-H]^-$, 411.9879 $[M-H+2]^-$.

***N*-(5-bromo-2-(1*H*-tetrazol-5-yl)phenyl)-2-fluoro-4-methoxybenzamide (63).63** was obtained from **40** as described from method B. 81% yield as white solid; ^{1}H NMR (600 MHz, DMSO-*d6*): δ 12.08 (s, 1H), 8.88 (d, *J* = 1.1 Hz, 1H), 8.04 (d, *J* = 8.4 Hz,

1H), 7.86 (dd, *J* = 15.7, 6.9 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.06 (d, *J* = 13.2 Hz, 1H), 6.98 (dd, *J* = 8.9, 1.8 Hz, 1H), 3.88 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 163.97 (d, *J* = 11.6 Hz), 162.61 (s), 161.29 (d, *J* = 251.2 Hz), 156.67 (s), 138.15 (s), 132.20 (d, *J* = 3.8 Hz), 130.24 (s), 127.06 (s), 123.88 (s), 123.46 (s), 115.50 (s), 115.41 (d, *J* = 3.8 Hz), 111.71 (d, *J* = 2.4 Hz), 102.64 (d, *J* = 26.4 Hz), 56.60 (s).Purity:95.69%. HRMS for $C_{15}H_{11}BrFN_5O_2$: calcd, 391.0080; found, 390.0025 $[M-H]^-$, 392.0006 $[M-H+2]^-$.

***N*-(4-(1*H*-tetrazol-5-yl)phenyl)-4-methoxybenzamide (64).64**was obtained from **41** as described from method B. 74% yield as white solid;^{1}H NMR (600 MHz, DMSO-*d6*): δ 10.41 (s, 1H), 8.05 (s, 4H), 8.03 (d, *J* = 1.9 Hz, 1H), 8.02 – 8.01 (m, 1H), 7.12 – 7.11 (m, 1H), 7.10 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H).^{13}C NMR (151 MHz, DMSO-*d6*): δ 165.71, 162.59, 155.43, 142.50, 130.24, 128.02, 127.06, 120.91, 119.23, 114.13, 55.91.Purity: 99.59%.HRMS for $C_{15}H_{13}BrN_5O_2$: calcd, 295.1069; found, 294.1002 $[M-H]^-$.

2. Materials and Cell Culture

Zaprinast was obtained from Sigma-aldrich. ML145 was obtained from Tocris. Epic® 384-well biosensor microplates were obtained from Corning Incorporated (Corning, NY). HT-29 cells were cultured at 37°C, 5% CO_2 in McCoy's 5A Medium modified with 10% FBS, 50 μg/mL penicillin and 100 μg/mL streptomycin.

3. DMR Assays Using Epic BT System

All DMR assays were performed using Epic BT system (Corning Incorporated). Epic is a swept wavelength interrogation reader system tailored for resonant waveguide grating biosensors in microtiter plates.[17] Cells were directly seeded in Epic plates and cultured overnight to form a confluent monolayer in the cell culture medium. After being washed, the cells were maintained with Hank's Balanced Salt Solution and further incubated inside the system for 1 h. For agonist profiling, a 2 min baseline was then established. After the compound addition, the cellular responses were recorded immediately. For desensitization assays, cells were initially treated with compounds for 1 h, followed by stimulation with zaprinast at 1μM. The cellular responses were recorded throughout the assays. All EC_{50} or IC_{50} described in the main text were calculated based on the amplitudes of DMR signals at 8 min post-stimulation. All GPR35 agonists led to a sustained positive-DMRsignal. The data represents mean±sd from two independent measurement, each with four replicates (n=8).

Figure S1. DMR assays at GPR35. Dose-response curves of selected compounds at GPR35. EC50

values:**43**, 2050 nM; **44**, 860 nM; **45**, 1330 nM (**a**); **46**, 870 nM; **47**, 2180 nM; **48**, 520 nM (**b**); **50**, 350 nM; **51**, 610 nM; **52**, 450 nM (**c**); **54**, 860 nM; **55**, 1940 nM; **56**, 59 nM (**d**); **37**, inactive; **60**, 650 nM; **64**, 17.58μM (**e**).