Trisubstitution of pyridine through sequential and regioselective palladium cross-coupling reactions affording analogs of known GPR54 antagonists.

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General experimental methods:

Chemicals and solvents were purchased from sigma-aldrich and boronic acids were purchased from combi-blocks. 2,6-dichloro-4-iodopyridine was purchased from alfa aesar. Analytical thin-layer chromatography was performed using silica gel plates Merck 60F254 and plates were visualized by exposure to ultraviolet light. Compounds were purified using Armen spot flash chromatography on silica gel Merck 60 (particle size 0.040-0.063mm), or on simply connect C18 from AIT. Yields refer to isolated compounds, estimated to be ≥97% pure as determined by 1H NMR or HPLC/MS. The melting points are uncorrected. 1H and 13C NMR spectra were recorded on Bruker Avance Spectrometer operating at 300 MHz / 400 MHz and 100 MHz, respectively. All chemical shift values and coupling constants J are quoted in ppm and in Hz, respectively. The low-resolution mass spectra were performed on Agilent Technologie 6100 Series by Analytical Service. Elementary analyses were obtained on a Perkin-Elmer 2400 elemental analyser. Microwave irradiation has been performed using Biotage Initiator EXP.

Suzuki reaction:
Method A: 2, 6-dichloro-4-iodopyridine (1 eq.), corresponding boronic acid (1.05 eq.), Na2CO3 (3 eq.) were introduced in a process vial under nitrogen followed by the addition of a mixture of H2O/CH3CN (2/3). The mixture was nitrogen-flushed and Pd(PPh3)Cl2 (0.05 eq.) was introduced. The reaction mixture was then capped properly and heated overnight at 70°C. The reaction mixture was cooled to r.t. and diluted with EtOAc. The organic layer was washed with brine, dried over Na2SO4, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel to give the expected products: 7a, 7b, 7c, 7d.

Method B: Pyridine derivative (1 eq.), appropriate boronic acid (1 eq.), Na2CO3 (3 eq.) were introduced in a process vial under nitrogen followed by the addition of a mixture of DME/H2O (3/1). The mixture was nitrogen-flushed and Pd(PPh3)2 (0.1 eq.) was introduced. The reaction mixture was then capped properly and heated at 120°C under microwave irradiation for 20min. The reaction mixture was concentrated in vacuo and the crude product was purified by chromatography on silica gel to give the expected products: 11a, 11b, 11c, 11d, 15, 17, 19, 20, 24.

Buchwald-Hartwig amination reaction:
Method C: Pyridine derivative (1eq.), appropriate amide (1eq.), Xantphos (0.1eq.), Cs2CO3 (2eq.), were introduced with anhydrous 1,4-dioxane (0.3mmol/mL) in a process vial under nitrogen. The mixture was nitrogen-flushed before the addition of Pd(OAc)2 (0.05eq.). The reaction mixture was then capped properly and heated at 110°C for 4-7 hours. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel to give the expected products: 8, 12a, 12b, 12c, 12d, 13a, 13b, 13c, 13e, 13f.

Method D: Pyridine derivative (1eq.), appropriate amide (1eq.), Xantphos (0.1eq.), Cs2CO3 (2eq.), were introduced with anhydrous 1,4-dioxane (0.3mmol/mL) in a process vial under nitrogen. The mixture was nitrogen-flushed followed by the addition of Pd2(dba)3·CHCl3 (0.05eq.). The reaction mixture was then capped properly and heated at 110°C for 4-7 hours. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel to give the expected product: 12b.

Method E: Pyridine derivative (1eq.), appropriate amine (1eq.), BINAP (0.1eq.), Cs2CO3 (2eq.), were introduced with anhydrous 1,4-dioxane (0.3mmol/mL) in a process vial under nitrogen. The mixture was nitrogen-flushed followed by the addition of Pd(OAc)2 (0.05eq.) The reaction mixture was then capped properly and heated at 110°C for 4-7 hours. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel to give the expected products: 13d, 13g.

Acylation:
Method F:
Aminopyridine derivative (1eq.) was solubilized at r.t. in pyridine (0.15mmol/mL) followed by the addition of acid chloride (1eq.). The solution was stirred at r.t. for 1h. Pyridine was evaporated and the crude product was purified by chromatography on silica gel to give the expected product: 23.

Coupling reaction:
Method G:
Boc-β-Ala-OH (1.1 eq.) was pre-activated with HATU (1.2 eq.) and DIEA (1.3 eq.) in CH2Cl2/DMF: 1/2. Aniline derivative (1 eq.) was added after 10 min. at r.t. The solution was stirred overnight at r.t. The solvent was
evaporated and the crude product was purified by chromatography on silica gel to give the expected products: 7e, 14a, 14c, 18, 21, 26.

Reduction of nitro group:
Method H:
To a solution of nitroaryl (1 eq.) in EtOH/H$_2$O: 1/1 (0.02 mmol/mL) was added NH$_4$Cl (6.4 eq.) and Fe (6 eq.). The resulting reaction mixture was stirred at 80°C for 1h. The reaction mixture was filtered over celite and the filtrate was concentrated under vacuum. The crude product was purified by chromatography on silica gel to give the expected products: 14a, 14c, 21.

2,6-dichloro-4-(2-methoxyphenyl)pyridine 7a:
Following the general method A and starting from 2,6-dichloro-4-iodopyridine (300 mg, 1.1 mmol) and 2-methoxyphenylboronic acid (175 mg, 1.15 mmol), 7a was obtained as a light yellow solid (274 mg, 1.07 mmol). Yield 98%. Eluent for the purification: heptane/EtOAc: 8/2. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.46 (s, 2H), 7.41 - 7.45 (m, 1H), 7.32 (dd, $J$ = 1.88, 7.50 Hz, 1H), 7.07 (dt, $J$ = 1.00, 7.53 Hz, 1H), 7.01 - 7.04 (m, 1H), 3.87 (s, 3H).

2-(2,6-dichloropyridin-4-yl)phenol 7b:
Following the general method A and starting from 2,6-dichloro-4-iodopyridine (300 mg, 1.1 mmol) and 2-hydroxyphenylboronic acid (159 mg, 1.15 mmol), 7b was obtained as a white solid (254 mg, 1.06 mmol). Yield 97%. Eluent for the purification: heptane/EtOAc: 7/3. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.52 (s, 2H), 7.31 - 7.40 (m, 2H), 7.03 - 7.12 (m, 1H), 6.88 - 6.96 (m, 1H), 5.19 (s, 1H).

2,6-dichloro-4-(3-nitrophenyl)pyridine 7c:
Following the general method A and starting from 2,6-dichloro-4-iodopyridine (100 mg, 0.365 mmol) and 3-nitrophenylboronic acid (64 mg, 0.385 mmol), 7c was obtained as a light yellow solid (80 mg, 0.297 mmol). Yield 81%. Eluent for the purification: heptane/EtOAc: 9/1. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.48 (t, $J$ = 1.9 Hz, 1H), 8.40 - 8.36 (m, 1H), 7.96 - 7.92 (m, 1H), 7.74 (t, $J$ = 8.0 Hz, 1H), 7.53 (s, 2H).

3-(2,6-dichloropyridin-4-yl) aniline 7d:
Following the general method A and starting from 2,6-dichloro-4-iodopyridine (1200 mg, 4.38 mmol) and 3-aminophenylboronic acid hydrochloride (836 mg, 4.82 mmol), 7d was obtained as a light yellow solid (1008 mg, 4.22 mmol). Yield 96%. Eluent for the purification: heptane/EtOAc: 8/2. $^1$H-NMR (400MHz, CDCl$_3$): $\delta$ = 7.44 (s, 2H), 7.26 (m, 1H), 7.00 - 6.95 (m, 1H), 6.87 (t, $J$ = 2.1 Hz, 1H), 6.80 (dd, $J$ = 2.4, 8.2 Hz, 1H), 3.85 (br. s., 2H).
tert-butyl (3-[(3-(2,6-dichloropyridin-4-yl)phenyl)amino]-3-oxopropyl)carbamate 7e:
Following the general method G and starting from Boc-β-Ala-OH (297mg, 1.57mmol) and aniline 7d (250mg, 1.05mmol), 7e was obtained as a yellow solid (410mg, 1.0mmol). Yield 73%. Eluent for the purification: heptane/EtOAc: 1/1. 1H NMR (400MHz, CDCl3): δ = 8.13 (br. s., 1 H), 8.01 (s, 1 H), 7.58 - 7.53 (m, 1 H), 7.48 (s, 2 H), 7.47 - 7.43 (m, 1 H), 7.36 - 7.31 (m, 1 H), 5.12 (br.s., 1H), 3.58 - 3.51 (m, 2 H), 2.67 (t, J = 6.0 Hz, 2 H), 1.46 (s, 9 H).

N-(2,6-dichloropyridin-4-yl)thiophene-2-carboxamide 8:
Following the general method C and starting from 2,6-dichloro-4-iodopyridine (100mg, 0.365mmol) and 2-thienylamide (46mg, 0.365mmol), 8 was obtained as a white solid (90mg, 0.329mmol). Yield: 90%. Eluent for the purification: heptane/EtOAc: 8/2. 1H NMR (400 MHz, CDCl3): δ = 8.11 (br. s., 1H), 7.70 (dd, J = 1.25, 3.76 Hz, 1H), 7.63 - 7.67 (m, 3H), 7.16 (dd, J = 3.76, 5.02 Hz, 1H).

**tert-butyl 4-(prop-2-yn-1-yl)piperazine-1-carboxylate:**

**Step 1:** Piperazine (3440mg, 39.94mmol) was solubilized in CH2Cl2 (100mL) at r.t., then a solution of Boc2O (4358mg, 19.97mmol) in CH2Cl2 (50mL) was added dropwise. The solution was stirred overnight at r.t. The precipitate was filtered and the filtrate was extracted with CH2Cl2 and the organic layer was dried over Na2SO4, filtered and concentrated to give a white solid (2289mg, 12.29mmol). Yield 62%. 1H NMR (400 MHz, CDCl3): δ= 1.42 (s, 9 H) 2.70 - 2.78 (m, 4 H) 3.29 - 3.35 (m, 4 H).

**Step 2:** tert-butyl piperazine-1-carboxylate (1g, 5.37mmol), Cs2CO3 (1.75g, 5.37mmol) and propargyl bromide (404µL, 5.37mmol) were solubilized in acetonitrile (15mL) at 0°C. The solution was stirred overnight at r.t. The precipitate was filtered and washed with acetonitrile. The filtrate was concentrated and the residue was extracted with EtOAc. The organic layer was washed with a saturated solution of NaHCO3, dried over Na2SO4. Evaporation under reduce pressure afford the pure piperazine-1-carboxylate (9alkyne) derivative as an orange oil (1.14mg, 5.09mmol). Yield 95%. 1H NMR (300 MHz, CDCl3): δ= ppm 3.44 - 3.53 (m, 4 H) 3.33 (d, J=2.50 Hz, 2 H) 2.50 - 2.56 (m, 4 H) 2.27 (t, J=2.34 Hz, 1 H) 1.47 (s, 9 H).
**tert-butyl 4-[3-(2,6-dichloropyridin-4-yl)prop-2-yn-1-yl]piperazine-1-carboxylate 9:**
2,6-dichloro-4-iodopyridine (400mg, 1.46mmol), tert-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate (360mg, 1.61mmol), anhydrous THF (3mL) and Et$_3$N (1 mL, 7.30mmol) were added in a flamed dried microwave tube nitrogen. The reaction mixture was nitrogen-flushed then Pd(PPh$_3$)$_2$Cl$_2$ (51mg, 0.073mmol) and CuI (28mg, 0.146mmol) were added. The reaction mixture was then capped properly and stirred overnight at r.t. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel using heptane/EtOAc: 6/4 to afford 9 as a yellow oil (513mg, 1.38 mmol). Yield 95%. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ = 7.26 (s, 2 H), 3.57 (s, 2 H), 3.53 - 3.48 (m, 4 H), 2.60 - 2.53 (m, 4 H), 1.48 (s, 9 H).

**tert-butyl 4-[3-(2,6-dichloropyridin-4-yl)-2-oxopropyl]piperazine-1-carboxylate 10:**
2,6-dichloro-4-iodopyridine (100mg, 0.365mmol), tert-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate (90mg, 0.402mmol), anhydrous THF (3mL) and DIEA (189µL, 1.83mmol) were added in a flamed dried microwave tube nitrogen. The reaction mixture was nitrogen-flushed then Pd(PPh$_3$)$_2$Cl$_2$ (13mg, 0.018mmol) and CuI (7mg, 0.037mmol) were added. The reaction mixture was then capped properly and stirred overnight at 70°C. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel using heptane/EtOAc: 6/4 to afford 10 as a yellow oil (105mg, 0.27mmol). Yield 74%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.16 (s, 2 H), 3.80 (s, 2 H), 3.45 - 3.53 (m, 4 H), 3.25 (s, 2 H), 2.45 (t, $J$ = 5.14 Hz, 4H), 1.47 (s, 9 H).

**2-[6-chloro-4-(3-nitrophenyl)pyridin-2-yl]phenol 11a:**
Following the general method B and starting from 7c (100mg, 0.372mmol) and 2-hydroxyphenylboronic acid (51mg, 0.372mmol), 11a was obtained as a light yellow solid (86mg, 0.27mmol). Yield 70%. Eluent for the purification: heptane/EtOAc: 8/2. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ = 12.51 (s, 1H), 8.55 (t, $J$ = 2.0 Hz, 1 H), 8.42 - 8.38 (m, 1 H), 8.00 (d, $J$ = 1.0 Hz, 2 H), 7.87 (dd, $J$ = 1.5, 8.0 Hz, 1 H), 7.76 (t, $J$ = 8.0 Hz, 1 H), 7.51 (d, $J$ = 1.3 Hz, 1 H), 7.39 (ddd, $J$ = 1.5, 7.2, 8.4 Hz, 1 H), 7.08 (dd, $J$ = 1.1, 8.4 Hz, 1 H), 7.01 - 6.96 (m, 1 H).
2-chloro-6-(2-methoxyphenyl)-4-(3-nitrophenyl)pyridine 11b:

Following the general method B and starting from 7c (200mg, 0.743mmol) and 2-methoxyphenylboronic acid (113mg, 0.743mmol), 11b was obtained as a white solid (177mg, 0.52mmol). Yield 71%. Eluent for the purification: heptane/EtOAc: 7/3. 1H NMR (300MHz, CDCl3): 8 = 8.53 (t, J = 2.0 Hz, 1 H), 8.38 - 8.31 (m, 1 H), 8.10 (d, J = 0.9 Hz, 1 H), 7.99 (td, J = 1.2, 7.6 Hz, 1 H), 7.92 (dd, J = 1.7, 7.6 Hz, 1 H), 7.74 - 7.68 (m, 1 H), 7.49 (d, J = 1.6 Hz, 1 H), 7.47 - 7.41 (m, 1 H), 7.16 - 7.10 (m, 1 H), 7.05 (d, J = 8.4 Hz, 1 H), 3.92 (s, 3 H).

tert-butyl (3-((3-2-chloro-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 11c:

Following the general method B and starting from 7e (100mg, 0.24mmol) and 2-hydroxyphenylboronic acid (34mg, 0.24mmol), 11c was obtained as a light yellow solid (58mg, 0.12mmol). Yield 51%. Eluent for the purification: heptane/EtOAc: 8/2. 1H NMR (500 MHz, CDCl3): 8 = 8.02 - 8.05 (m, 1H), 7.97 (s, 1H), 7.84 (dd, J = 1.42, 8.04 Hz, 1H), 7.54 - 7.57 (m, 1H), 7.41 - 7.47 (m, 2H), 7.34 - 7.38 (m, 1H), 7.29 - 7.34 (m, 1H), 7.01 (d, J = 8.51 Hz, 1H), 6.92 (s, 1H), 3.42 (t, J = 6.50 Hz, 2H), 2.57 (t, J = 6.46 Hz, 2H), 1.41 (s, 9H).

tert-butyl (3-((3-2-chloro-6-(2-methoxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 11d:

Following the general method B and starting from 7e (1000mg, 2.44mmol) and 2-methoxyphenylboronic acid (370mg, 2.44mmol), 11d was obtained as a light yellow solid (941mg, 1.95mmol). Yield 80%. Eluent for the purification: heptane/EtOAc: 9/1. 1H NMR (400 MHz, CDCl3): 8 = 8.06 (br. s., 1H), 7.94 (d, J = 1.51 Hz, 1H), 7.87 - 7.91 (m, 1H), 7.78 (dd, J = 1.88, 7.65 Hz, 1H), 7.45 - 7.52 (m, 1H), 7.36 - 7.41 (m, 2H), 7.30 - 7.36 (m, 2H), 7.02 (dt, J = 1.13, 7.47 Hz, 1H), 6.92 - 6.97 (m, 1H), 5.08 (br. s., 1H), 3.82 (s, 3H), 3.45 (q, J = 5.90 Hz, 2H), 2.57 (t, J = 5.90 Hz, 2H), 1.36 - 1.38 (m, 9H).
**thiophene-2-carboxamide**:  
2-thiophenecarboxyl chloride (3g, 20.5mmol) was solubilized in H$_2$O (10mL) followed by the dropwise addition of an aqueous solution of NH$_3$ 30% (5.28 mL, 25.46mmol). After 2h at r.t., a precipitated was formed and it was filtered to obtain a white solid (2.05g, 16.195mmol). Yield 79%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.55 (dd, $J = 3.64$, 1.20 Hz, 1 H), 7.53 (dd, $J = 4.89$, 1.20 Hz, 1 H), 7.11 (dd, $J = 4.89$, 3.64 Hz, 1 H), 5.68 (br. s., 2 H).

**N-[6-chloro-4-(2-methoxyphenyl)pyridin-2-yl]thiophene-2-carboxamide 12a**:  
Following the general method C and starting from 7a (268mg, 1.055mmol) and thiophene-2-carboxamide (134mg, 1.055mmol), 12a was obtained as a white solid (160mg, 0.464mmol). Yield 44%. Eluent for the purification: heptane/EtOAc: 5/5. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.45 (s, 1H), 8.41 (br. s, 1H), 7.68 - 7.64 (m, 1H), 7.37 - 7.46 (m, 2H), 7.34 (s, 1H), 7.14 - 7.20 (m, 1H), 6.99 - 7.10 (m, 2H), 3.88 (s, 3H).

**N-[6-chloro-4-(3-nitrophenyl)pyridin-2-yl]thiophene-2-carboxamide 12b**:  
Following the general method C and starting from 7c (500mg, 1.85mmol) and thiophene-2-carboxamide (236mg, 1.85mmol), 12b was obtained as a light yellow solid (226mg, 0.74mmol). Yield 40%. Eluent for the purification: heptane/EtOAc: 7/3. Using the general method D, yield is 70%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.61 (d, $J = 1.51$ Hz, 1H), 8.53 (t, $J = 2.01$ Hz, 1H), 8.48 (br. s, 1H), 8.35 (ddd, $J = 1.00$, 2.26, 8.28 Hz, 1H), 8.03 (td, $J = 1.51$, 7.78 Hz, 1H), 7.68 - 7.74 (m, 2H), 7.66 (dd, $J = 1.25$, 5.02 Hz, 1H), 7.38 (d, $J = 1.51$ Hz, 1H), 7.20 (dd, $J = 3.76$, 5.02 Hz, 1H).

**tert-butyl (3-((3-(2-chloro-6-(thiophene-2-carboxamido)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 12c**:  
Following the general method C and starting from 7e (103mg, 0.261mmol) and thiophene-2-carboxamide (33mg, 0.261mmol), 12c was obtained as a light yellow solid (46mg, 0.091mmol). Yield 35%. Eluent for the purification: heptane/EtOAc: 6/4. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ = 8.54 (d, $J = 1.3$ Hz, 1 H), 8.44 (s, 1 H), 8.00 (br. s., 1H), 7.89 - 7.86 (m, 2 H), 7.69 (dd, $J = 1.3$, 3.8 Hz, 1 H), 7.67 (br. s., 1H), 7.64 (dd, $J = 1.1$, 4.9 Hz, 1 H), 7.48 (s, 1H), 7.35 (d, $J = 1.3$ Hz, 1 H), 7.18 (dd, $J = 3.9$, 4.9 Hz, 1 H), 5.15 (br. s., 1H), 3.54 (t, $J = 6.3$ Hz, 2 H), 2.72 - 2.61 (m, 2 H), 1.46 (s, 9 H).
tert-butyl 4-(3-(2-benzamido-6-chloropyridin-4-yl)prop-2-yn-1-yl)piperazine-1-carboxylate 12d:
Following the general method C and starting from 9 (513mg, 1.38mmol) and benzamide (269mg, 2.22mmol), 12d was obtained as a light yellow oil (300mg, 0.659mmol). Yield 48%. Eluent for the purification: heptane/EtOAc: 6/4. $^1$H NMR (400MHz, CDCl$_3$): $\delta = 8.52$ (s, 1 H), 8.37 (d, $J = 1.0$ Hz, 1 H), 7.95 - 7.88 (m, 2 H), 7.64 - 7.57 (m, 1 H), 7.57 - 7.49 (m, 2 H), 7.12 (d, $J = 1.0$ Hz, 1 H), 3.60 (s, 2 H), 3.53 (m, 4 H), 2.62 (m, 4 H), 1.48 (s, 9 H).

tert-butyl (6-(2-hydroxyphenyl)-4-(3-nitrophenyl)pyridin-2-yl)carbamate 13a:
Following the general method C and starting from 11a (50mg, 0.153mmol) and tert-butyl carbamate (27mg, 0.23mmol), 13a was obtained as a light yellow solid (50mg, 0.123mmol). Yield 80%. Eluent for the purification: heptane/EtOAc: 7/3. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.56 - 8.59$ (m, 1H), 8.32 - 8.37 (m, 1H), 8.17 (s, 1H), 8.06 (d, $J = 8.03$ Hz, 1H), 7.88 (dd, $J = 1.51$, 7.78 Hz, 1H), 7.77 (s, 1H), 7.71 (t, $J = 8.03$ Hz, 1H), 7.32 - 7.39 (m, 1H), 7.05 (d, $J = 8.28$ Hz, 1H), 6.92 - 7.01 (m, 1H), 5.27 (br. s., 1H), 1.59 (s, 9H).

tert-butyl (6-(2-methoxyphenyl)-4-(3-nitrophenyl)pyridin-2-yl)carbamate 13b:
Following the general method C and starting from 11b (83mg, 0.244mmol) and tert-butyl carbamate (43mg, 0.365mmol), 13b was obtained as a light yellow solid (92mg, 0.22mmol). Yield 90%. Eluent for the purification: heptane/EtOAc: 7/3. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.55$ (t, $J = 2.0$ Hz, 1H), 8.32 - 8.27 (m, 1H), 8.17 (s, 1H), 8.06 (dd, $J = 1.3$, 8.0 Hz, 1H), 7.77-7.75 (m, 2H), 7.66 (t, $J = 7.9$ Hz, 1H), 7.47 (br. s., 1H), 7.44 - 7.38 (m, 1H), 7.14 - 7.07 (m, 1H), 7.04 (d, $J = 8.5$ Hz, 1H), 3.90 (s, 3H), 1.56 (s, 9H).
tert-butyl (3-((3-(2-(2-hydroxyphenyl)-6-(thiophene-2-carboxamido)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13c:
Following the general method C and starting from 11c (150mg, 0.459mmol) and thiophene-2-carboxamide (88mg, 0.689mmol), 13c was obtained as a light yellow solid (109mg, 0.261mmol). Yield 57%. Eluent for the purification: heptane/EtOAc: 7/3.

1H NMR (400 MHz, CDCl$_3$): $\delta$= 12.99 (br. s., 1H), 8.52 (br. s., 1H), 8.43 (s, 1H), 7.91 (br. s., 1H), 7.84 (dd, $J = 1.6, 8.2$ Hz, 1H), 7.81 - 7.79 (m, 1H), 7.77 (dd, $J = 0.9, 3.6$ Hz, 1H), 7.65 (dd, $J = 1.1, 4.9$ Hz, 2H), 7.50 - 7.41 (m, 3H), 7.36 - 7.30 (m, 1H), 7.19 (dd, $J = 3.8, 4.8$ Hz, 1H), 7.05 (dd, $J = 1.0, 8.3$ Hz, 1H), 6.93 (t, $J = 7.5$ Hz, 1H), 5.28 (br. s., 1H), 3.57 (m, 2H), 2.69 (t, $J = 6.0$ Hz, 2H), 1.46 (s, 9H).

2-(4-(3-nitrophenyl)-6-(phenethylamino)pyridin-2-yl)phenol 13d:
Following the general method E and starting from 11a (80mg, 0.245mmol) and phenethylamine (45µL, 0.367mmol), 13d was obtained as a light yellow solid (57mg, 0.139mmol). Yield 57%. Eluent for the purification: heptane/EtOAc: 8/2.

1H NMR (400MHz, CDCl$_3$): $\delta$ = 14.20 (br. s., 1H), 8.48 (t, $J = 1.9$ Hz, 1H), 8.34 - 8.28 (m, 1H), 7.96 - 7.92 (m, 1H), 7.85 (dd, $J = 1.3, 8.0$ Hz, 1H), 7.68 (t, $J = 7.9$ Hz, 1H), 7.40 - 7.28 (m, 7H), 7.03 (dd, $J = 1.0, 8.0$ Hz, 1H), 6.96 - 6.89 (m, 1H), 6.49 (d, $J = 1.3$ Hz, 1H), 4.76 (t, $J = 6.1$ Hz, 1H), 3.77 - 3.69 (m, 2H), 3.04 (t, $J = 6.8$ Hz, 2H).

tert-butyl (3-((3-(2-(2-methoxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13e:
Following the general method C and starting from 11d (100mg, 0.201mmol) and phenylacetamide (42mg, 0.311mmol), 13e was obtained as a light yellow solid (72mg, 0.124mmol). Yield 60%. Eluent for the purification: heptane/EtOAc: 6/4.

1H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.59 (s, 1H), 8.35 (s, 1H), 8.22 (br. s., 1H), 7.88 (dd, $J = 1.76, 7.53$ Hz, 1H), 7.75 (br. s., 1H), 7.69 (d, $J = 1.51$ Hz, 1H), 7.57 - 7.66 (m, 2H), 7.28 - 7.39 (m, 6H), 7.24 - 7.26 (m, 1H), 6.95 - 7.03 (m, 2H), 5.31 (t, $J = 5.90$ Hz, 1H), 3.78 (s, 3H), 3.65 (s, 2H), 3.38 - 3.53 (m, 2H), 2.50 - 2.61 (m, 2H), 1.40 (s, 9H).
tert-butyl (3-((3-(2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13f:
Following the general method C and starting from 11e (80mg, 0.171mmol) and acetamide (15mg, 0.256mmol), 13f was obtained as a light yellow solid (62mg, 0.126mmol). Yield 74%. Eluent for the purification: heptane/AcOEt: 7/3. Yield 74%. 1H NMR (400 MHz, CDCl3): δ= 8.31 (br. s., 1H), 8.27 (s, 1H), 7.97 - 8.03 (m, 1H), 7.88 - 7.93 (m, 1H), 7.76 - 7.81 (m, 1H), 7.72 (s, 1H), 7.62 (dd, J = 3.64, 7.15 Hz, 1H), 7.44 (d, J = 5.27 Hz, 2H), 7.29 (d, J = 6.78 Hz, 1H), 7.01 - 7.06 (m, 1H), 6.88 (t, J = 7.53 Hz, 1H), 5.41 (br. s., 1H), 3.57 (q, J = 4.02 Hz, 2H), 2.69 (t, J = 5.77 Hz, 2H), 2.21 (s, 3H), 1.46 (s, 9H).

**tert-butyl (3-((3-(2-benzylamino)-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13g:**
Following the general method F and starting from 11e (89mg, 0.19mmol) and benzylamine (31µL, 0.285mmol), 13g was obtained as a light yellow solid (81mg, 0.15mmol). Yield 79%. Eluent for the purification: heptane/EtOAc: 7/3. 1H NMR (400 MHz, CDCl3): δ= 14.22 (s, 1H), 7.88 - 7.97 (m, 2H), 7.80 - 7.86 (m, 1H), 7.57 (d, J = 7.53 Hz, 1H), 7.29 - 7.43 (m, 9H), 6.94 - 7.02 (m, 1H), 6.89 (t, J = 7.53 Hz, 1H), 6.51 - 6.58 (m, 1H), 5.10 - 5.21 (m, 1H), 5.00 (br. s., 1H), 4.60 (d, J = 5.27 Hz, 2H), 3.54 (q, J = 6.11 Hz, 2H), 2.06 (t, J = 6.02 Hz, 2H), 1.45 (s, 9H).

3-amino-N-(3-(2-amino-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)propanamide trifluoroacetic acid 14a:

**Step 1:** Following the general method H for the reduction of the nitro group and starting from 13b (100mg, 0.237mmol), tert-butyl (4-(3-aminophenyl)-6-(2-methoxyphenyl)pyridin-2-yl)carbamate (14a1) was obtained as a white solid (64mg, 0.163mmol). Yield 69%. Eluent for the purification: heptane/EtOAc: 7/3. 1H NMR (400MHz, CDCl3); δ = 8.01 (s, 1 H), 7.63 (dd, J=7.7, 1.9 Hz, 1 H), 7.60 (d, J=1.5 Hz, 1 H), 7.24 - 7.34 (m, 2 H), 7.12 - 7.18 (m, 1 H), 6.92 - 7.05 (m, 4 H), 6.64 - 6.96 (m, 1 H), 3.79 (s, 3 H), 3.71 (br. s., 2 H), 1.47 (s, 9 H).

**Step 2:** Starting from 14a1 (60mg, 0.153mmol) and following the general method G for coupling reaction tert-butyl N-[4-[3-3-{{(tert-butoxy) carbonylamino}propanamido} phenyl]-6-(2-methoxyphenyl) pyridin-2-yl) carbamate (14a2) was obtained as a white solid (69mg, 0.122mmol). Yield 80%. Eluent for the purification: heptane/EtOAc: 6/4. 1H NMR (400 MHz, CDCl3); δ = 8.03 (s, 1 H), 7.70 (br. s., 1H), 7.59 - 7.67 (m, 3H), 7.27 - 7.46 (m, 4H), 6.97 - 7.02 (m, 1H), 6.92 - 6.96 (m, 1H), 5.10 (br. s., 1H), 4.97 (br. s., 1H), 3.80 (s, 3H), 3.45 (q, J = 6.44 Hz, 2H), 2.57 (t, J = 5.90 Hz, 2H), 1.47 (s, 9H), 1.36 (s, 9H).

**Step 3:** The resulting solid 14a3 and TFA (1mL) were mixed in CH2Cl2 (1 mL). After 1 hour at r.t., the volatiles were evaporated and 3-amino-N-[3-[2-amino-6-(2-methoxyphenyl)pyridin-4-yl]phenyl]propanamide; trifluoroacetic acid was obtained as a light yellow oil (68mg, 0.116mmol). Yield 95%. The resulting oil was directly submitted to deprotection of the methoxy group.

**Step 4:** The crude oil (68mg, 0.116mmol) and anhydrous CH2Cl2 (1.1mL) were introduced in a process vial followed by the addition of BBr3 1M (CH2Cl2, 0.9mL, 0.92mmol). The reaction mixture was capped properly and heated at 110°C under microwave irradiation for 10min. The reaction mixture was then cooled at r.t. and excess of BBr3 was hydrolyzed with MeOH and concentrated under vacuum. The crude product was purified on reverse phase using H2O(0.05%TFA)/MeOH to afford 14a after lyophilisation as a light yellow solid (38mg, 0.082mmol). Yield 71%. 1H NMR (400 MHz, MeOD): δ = 8.17 (s, 1H), 7.65 - 7.76 (m, 2H), 7.50 - 7.60 (m, 2H), 7.40 - 7.50 (m, 1H), 7.37 (s, 1H), 7.12 (s, 1H), 7.02 - 7.10 (m, 2H), 3.30 - 3.33 (m, 2H), 2.89 (t, J = 6.40 Hz, 2H). 13C NMR (101 MHz, MeOD): δ = 170.8, 157.1, 156.8, 155.9, 147.9, 140.8, 138.4, 133.9, 131.1, 130.8, 124.0, 123.1, 121.6, 119.7, 119.5, 117.7, 111.7, 108.4, 36.8, 33.9.
N-[4-[3-(aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl]thiophene-2-carboxamide; trifluoroacetic acid 14b:

13c (35mg, 0.063mmol) and TFA (1mL) were mixed in CH2Cl2 (1mL). After 1 hour at r.t., the volatiles were evaporated and the crude product was purified by chromatography on reverse phase using H2O(0.05%TFA)/MeOH, to afford after triturations with ether 14b as a white solid (35mg, 0.061mmol). Yield 98%.

1H NMR (400MHz, CDCl3): δ = 8.08 (d, J = 1.3 Hz, 1 H), 8.05 (s, 1 H), 7.96 (dd, J = 1.1, 3.9 Hz, 1 H), 7.91 - 7.86 (m, 2 H), 7.71 (dd, J = 1.0, 5.0 Hz, 1 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.50 - 7.45 (m, 1 H), 7.44 - 7.37 (m, 1 H), 7.25 - 7.19 (m, 1 H), 7.13 (dd, J = 4.0, 5.0 Hz, 1 H), 6.90 - 6.82 (m, 2 H), 3.20 (m, 2H), 2.77 (t, J = 6.0 Hz, 2 H); 13C NMR (101 MHz, CDCl3): δ = 170.81, 162.99, 159.68, 156.89, 153.55, 151.22, 140.52, 140.08, 139.89, 133.78, 132.72, 131.38, 130.85, 129.17, 128.49, 124.2, 123.1, 121.8, 119.7, 119.1, 117.9, 44.8, 36.8, 36.0, 33.9.

3-amino-N-[3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl]propionamide; trifluoroacetic acid 14c:

Step 1: Following the general method H for the reduction of the nitro group and starting from 13d (50mg, 0.122mmol), 2-[4-(3-aminophenyl)-6-[(2-phenylethyl)amino]pyridin-2-yl]phenol (14c) was obtained as a white solid (28mg, 0.073mmol). Yield 60%. Eluent for the purification: heptane/EtOAc 7/3. 1H NMR (400 MHz, CDCl3): δ = 14.37 (br. s., 1H) 7.82 - 7.90 (m, 1H), 7.32 - 7.39 (m, 3H), 7.21 - 7.32 (m, 5H), 7.01 (d, J = 8.03 Hz, 2H), 6.86 - 6.95 (m, 2H), 6.77 (td, J = 1.35, 7.84 Hz, 1H), 6.47 (s, 1H), 4.62 (br. s., 1H), 3.64 - 3.74 (m, 2H), 3.02 (t, J = 6.78 Hz, 2H).

Step 2: Starting from 14c (21mg, 0.055mmol) and following the general method G for coupling reaction, tert-butyl N-[2-[3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl]carbamoyl]ethyl]carbamate (14c2) was obtained as a light yellow oil (21mg, 0.038mmol). Yield 70%. Eluent for the purification: heptane/EtOAc: 5/5. 1H NMR (400 MHz, CDCl3): δ = 7.98 (br. s., 1H), 7.91 (br. s., 1H), 7.84 (d, J = 8.03 Hz, 1H), 7.55 - 7.61 (m, 1H), 7.43 (t, J = 7.78 Hz, 1H), 7.31 - 7.39 (m, 4H), 7.22 - 7.31 (m, 5H), 7.01 (d, J = 8.28 Hz, 1H), 6.90 (t, J = 7.53 Hz, 1H), 6.49 (s, 1H), 5.15 (br. s., 1H), 3.65 - 3.72 (m, 2H), 3.50 - 3.59 (m, 2H), 3.01 (t, J = 7.03 Hz, 2H), 2.66 (t, J = 6.02 Hz, 2H), 1.49 (s, 9H).

Step 3: The resulting oil 14c3 and TFA (1mL) were mixed in CH2Cl2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H2O(0.05%TFA)/MeOH to afford after lyophilisation 14c as a light yellow solid (15mg, 0.026mmol). Yield 70%. 1H NMR (400 MHz, MeOD): δ = 8.16 (s, 1H), 7.72 - 7.78 (m, 1H), 7.68 - 7.72 (m, 1H), 7.52 - 7.57 (m, 2H), 7.40 - 7.50 (m, 1H), 7.28 - 7.39 (m, 5H), 7.16 - 7.26 (m, 1H), 6.99 - 7.13 (m, 3H), 3.78 (t, J = 7.03 Hz, 2H), 3.33 - 3.30 (m, 2H), 3.07 (t, J = 7.03 Hz, 2H), 2.89 (t, J = 6.27 Hz, 2H); 13C NMR (126 MHz, MeOD): δ = 170.8, 156.9, 154.4, 148.2, 140.7, 139.5, 138.5, 134.0, 131.0, 130.6, 130.1, 129.8, 127.9, 124.2, 123.1, 121.8, 119.7, 119.1, 117.9, 44.8, 36.8, 36.0, 33.9.
3-amino-N-[3-[2-(2-hydroxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl]phenyl]propanamide; trifluoroacetic acid 14d:
Step 1: 13e (90mg, 0.155mmol) and TFA (1mL) were mixed in CH₂Cl₂ (1mL). After 1 hour at r.t., the volatiles were evaporated. The resulting oil was directly submitted to deprotection of the methoxy group.
Step 2: The crude oil and anhydrous CH₂Cl₂ (1mL) were introduced in a process vial followed by the addition of BBr₃ 1M (CH₂Cl₂, 1.2mL, 1.24mmol). The reaction mixture was then capped properly and heated at 110°C under microwave irradiation for 10min. The reaction mixture was then cooled at r.t. and excess of BBr₃ was hydrolyzed with MeOH and concentrated under vacuum. The crude product was purified by chromatography on reverse phase using H₂O(0.05%TFA)/MeOH to afford after lyophilisation 14d as a light yellow solid (45mg, 0.077mmol). Yield 50%. ¹H NMR (400 MHz, MeOD): δ = 7.98 - 8.02 (m, 1H), 7.76 - 7.85 (m, 3H), 7.58 (td, J = 1.94, 7.40 Hz, 1H), 7.30 - 7.39 (m, 6H), 7.22 - 7.29 (m, 2H), 6.83 - 6.92 (m, 2H), 3.76 (s, 2H), 3.27 (t, J = 6.27 Hz, 2H), 2.81 (t, J = 6.40 Hz, 2H); ¹³C NMR (101 MHz, MeOD): δ = 173.3, 170.8, 159.5, 154.1, 150.6, 140.5, 139.4, 136.0, 133.0, 130.8, 130.5, 129.7, 128.6, 128.2, 124.0, 122.4, 120.7, 119.7, 119.7, 119.0, 114.6, 110.5, 44.6, 36.9, 33.8.

3-amino-N-[3-[2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl]propanamide; trifluoroacetic acid 14e:
13f (59mg, 0.12mmol) and TFA (1mL) were mixed in CH₂Cl₂ (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H₂O(0.05%TFA)/MeOH to afford after lyophilisation 14e as a light yellow solid (48mg, 0.095mmol). Yield 79%. ¹H NMR (400 MHz, MeOD): δ = 8.06 (s, 1H), 7.81 - 7.88 (m, 2H), 7.64 (td, J = 2.67, 5.96 Hz, 1H), 7.58 (s, 1H), 7.41 - 7.50 (m, 2H), 7.29 - 7.39 (m, 1H), 6.91 - 6.99 (m, 2H), 3.31 - 3.32 (m, 2H), 2.87 (t, J = 6.40 Hz, 2H), 2.24 (s, 3H); ¹³C NMR (101 MHz, MeOD): δ = 173.1, 170.8, 159.0, 155.0, 153.6, 150.0, 140.6, 138.7, 133.6, 130.9, 129.1, 124.1, 122.8, 121.0, 119.8, 118.9, 118.8, 114.8, 36.9, 33.9, 24.2.

3-amino-N-[3-[2-(benzylamino)-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl]propanamide; trifluoroacetic acid 14f:
13g (75mg, 0.139mmol) and TFA (1mL) were mixed in in CH₂Cl₂ (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H₂O(0.05%TFA)/MeOH to afford after lyophilisation 14f as a light yellow solid (53mg, 0.096mmol). Yield 69%. ¹H NMR (400 MHz, MeOD): δ = 8.07 (s, 1H), 7.67 (dd, J = 1.76, 8.03 Hz, 1H), 7.61 - 7.65 (m, 1H), 7.38 - 7.44 (m, 4H), 7.32 - 7.38 (m, 4H), 7.25 - 7.32 (m, 1H), 6.94 - 7.03 (m, 3H), 4.61 (s, 2H), 3.22 - 3.25 (m, 2H), 2.81 (t, J = 6.40 Hz, 2H); ¹³C NMR (101 MHz, MeOD): δ = 170.9, 157.0, 156.7, 154.3, 148.6, 140.7, 138.4, 137.5, 134.1, 131.0, 130.4, 130.1, 129.2, 128.7, 124.1, 123.2, 121.8, 119.8, 118.8, 118.1, 110.9, 47.0, 36.9, 33.9.
tert-butyl 4-(3-(2-benzamido-6-(2-hydroxyphenyl)pyridin-4-yl)prop-2-yn-1-yl)piperazine-1-carboxylate 15:
Following the general method B and starting from 12d (162mg, 0.355mmol) and 2-hydroxyphenylboronic acid (59mg, 0.426mmol), 15 was obtained as a white solid (114mg, 0.22mmol). Yield 62%. Eluent for the purification: heptane/EtOAc: 6/4. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ = 12.74 (s, 1 H), 8.37 (s, 1 H), 8.35 - 8.32 (m, 1 H), 7.96 - 7.90 (m, 2 H), 7.78 (dd, $J$ = 1.4, 7.9 Hz, 1 H), 7.71 - 7.68 (m, 1 H), 7.66 - 7.61 (m, 1 H), 7.59 - 7.52 (m, 2 H), 7.38 - 7.32 (m, 1 H), 7.03 (dd, $J$ = 1.0, 8.3 Hz, 1 H), 6.99 - 6.99 (m, 1 H), 3.68 (s, 2 H), 3.58 (m, 4 H), 2.70 (m, 4 H), 1.49 (s, 9 H).

N-[6-(2-hydroxyphenyl)-4-[3-(piperazin-1-yl)propyl]pyridin-2-yl]benzamide; trifluoroacetic acid 16:
Step 1: The alkyne 15 (110mg, 0.212mmol) was dissolved in MeOH (0.05mmol/mL). The solution was nitrogen-flushed followed by the addition of Pd/C (10%w, 11mg). The hydrogenation was carried out at H$_2$-pressure of 60psi at r.t. for 30min, whereupon HPLC showed the reaction was complete. The solid was filtered off, and the MeOH was removed in vacuum. The crude product was purified by chromatography on silica gel using heptane/EtOAc: 6/4 to afford tert-butyl 4-[3-(2-benzamido-6-(2-hydroxyphenyl)pyridin-4-yl)propyl]piperazine-1-carboxylate 16i as a colorless oil (90mg, 0.174mmol). Yield 82%.
$^1$H NMR (400MHz, CDCl$_3$): $\delta$ = 13.14 (s, 1H), 8.36 (s, 1 H), 8.19 (s, 1 H), 7.93 (d, $J$ = 7.5 Hz, 2 H), 7.83 - 7.77 (m, 1H), 7.66 - 7.58 (m, 1 H), 7.58 - 7.50 (m, 3 H), 7.38 - 7.29 (m, 1 H), 7.02 (d, $J$ = 8.5 Hz, 1 H), 6.95 (t, $J$ = 7.3 Hz, 1 H), 3.52 - 3.40 (m, 4 H), 2.81 (t, $J$ = 7.7 Hz, 2 H), 2.49 - 2.35 (m, 4 H), 1.94 (quin, $J$ = 7.4 Hz, 2 H), 1.47 (s, 9 H), 1.27 (t, $J$ = 7.0 Hz, 2 H).

Step 2: The resulting oil 16i and TFA (1mL) were mixed in CH$_2$Cl$_2$ (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H$_2$O(0.05%TFA)/MeOH to afford 16 as a yellow solid after lyophilisation (90mg, 0.170mmol). Yield 97%. $^1$H NMR (400MHz, MeOD): $\delta$ = 7.79 - 7.73 (m, 2 H), 7.67 - 7.63 (m, 1 H), 7.60 (s, 1 H), 7.42 - 7.35 (m, 1 H), 7.31 - 7.25 (m, 2 H), 7.16 - 7.09 (m, 1 H), 6.77 - 6.71 (m, 2 H), 3.57 - 3.53 (m, 8 H), 2.66 (t, $J$ = 7.7 Hz, 2 H), 2.02 - 1.91 (m, 2 H), 1.86 - 1.81 (m, 2 H); $^{13}$C NMR (101MHz, MeOD): $\delta$ = 169.7, 159.2, 157.7, 154.3, 150.5, 134.9, 133.9, 133.4, 129.8, 129.1, 120.9, 119.4, 118.8, 117.8, 113.7, 57.5, 49.2, 48.8, 33.6, 25.7.
N-[6-(3-aminophenyl)-4-(2-methoxyphenyl)pyridin-2-yl]thiophene-2-carboxamide 17:
Following the general method B and starting from 12a (70mg, 0.203mmol) and 3-aminophenylboronic acid hydrochloride (53mg, 0.305mmol), 17 was obtained as a light yellow solid (73mg, 0.183mmol). Yield 90%. Eluent for the purification: heptane/EtOAc: 5/5. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.57\) (br. s., 1H), 8.46 (d, \(J = 1.25\) Hz, 1H), 7.73 (dd, \(J = 1.13, 3.89\) Hz, 1H), 7.68 (d, \(J = 1.51\) Hz, 1H), 7.60 (dd, \(J = 1.13, 4.89\) Hz, 1H), 7.46 (dd, \(J = 1.76, 7.53\) Hz, 1H), 7.38 - 7.44 (m, 1H), 7.36 - 7.35 (m, 2H), 7.28 (t, \(J = 8.20\) Hz, 1H), 7.17 (dd, \(J = 3.51, 5.02\) Hz, 1H), 7.08 (dt, \(J = 1.13, 7.47\) Hz, 1H), 7.04 (d, \(J = 8.28\) Hz, 1H), 6.77 (ddd, \(J = 1.13, 2.38, 7.78\) Hz, 1H), 3.88 (s, 3H), 3.80 (br. s., 2H).

N-[6-[3-(3-aminopropanamido)phenyl]-4-(2-hydroxyphenyl)pyridin-2-yl]thiophene-2-carboxamide; trifluoroacetic acid 18:

**Step 1:** Following the general method G and starting from 17 (80mg, 0.199mmol), tert-butylN-[2-[(3-[4-(2-methoxyphenyl)-6-(thiophene-2-amino)pyridin-2-yl]phenyl]carbamoyl]ethyl]carbamate (18) was obtained as a light yellow solid (102mg, 0.178mmol). Yield 89%. Eluent for the purification: heptane/EtOAc: 6/4. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.63\) (br. s., 1H), 8.46 (s, 1H), 8.19 (s, 1H), 7.84 (br. s., 1H), 7.76 (dd, \(J = 1.00, 3.76\) Hz, 1H), 7.68 - 7.75 (m, 2H), 7.58 - 7.67 (m, 2H), 7.39 - 7.51 (m, 3H), 7.17 (dd, \(J = 3.64, 5.14\) Hz, 1H), 7.05 - 7.11 (m, 1H), 7.03 (d, \(J = 8.28\) Hz, 1H), 5.18 (br. s., 1H), 3.88 (s, 3H), 3.45 - 3.59 (m, 2H), 2.65 (t, \(J = 6.27\) Hz, 2H), 1.38 - 1.49 (m, 9H).

**Step 2:** The resulting solid 18 (95mg, 0.166mmol) and TFA (1mL) were mixed in CH\(_2\)Cl\(_2\) (1mL). After 1 hour at r.t., the volatiles were evaporated. The resulting oil was directly submitted to deprotection of the methoxy group.

**Step 3:** The crude oil and anhydrous CH\(_2\)Cl\(_2\) (3mL) were introduced in a process vial followed by the addition of BBr\(_3\) 1M (CH\(_2\)Cl\(_2\), 1.5mL, 15mmol). The reaction mixture was then capped properly and heated at 110°C under microwave irradiation for 10min. The reaction mixture was then cooled to r.t. and excess of BBr\(_3\) was hydrolyzed with MeOH and concentrated under vacuum. The crude product was purified by chromatography on reverse phase using H\(_2\)O(0.05%TFA)/MeOH to afford, after lyophilisation, 18 as a light yellow solid (62mg, 0.108mmol). Yield 65%. \(^1\)H NMR (400 MHz, MeOD): \(\delta = 8.27 - 8.33\) (m, 1H), 8.17 (s, 1H), 8.07 (dd, \(J = 0.75, 3.76\) Hz, 1H), 7.96 (s, 1H), 7.87 (dd, \(J = 0.88, 4.89\) Hz, 1H), 7.66 (d, \(J = 8.28\) Hz, 2H), 7.44 - 7.54 (m, 2H), 7.28 - 7.37 (m, 1H), 7.20 - 7.26 (m, 1H), 6.98 (d, \(J = 7.78\) Hz, 2H), 3.28 - 3.33-(m, 2H), 2.85 (t, \(J = 6.40\) Hz, 2H); \(^{13}\)C NMR (101 MHz, MeOD): \(\delta = 170.8, 164.0, 156.6, 154.8, 152.5, 151.5, 140.6, 138.9, 137.4, 134.8, 132.6, 132.1, 131.4, 130.9, 129.5, 125.3, 123.7, 122.8, 121.4, 119.3, 119.1, 117.7, 114.7, 36.9, 33.9.

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**N-[2-chloro-6-(2-hydroxyphenyl)pyridin-4-yl]thiophene-2-carboxamide 19:**
Following the general method B and starting from 8 (476mg, 1.74mmol) and 2-hydroxyphenylboronic acid (240mg, 1.74mmol), 19 was obtained as a white solid (416mg, 1.26mmol). Yield 72%. Eluent for the purification: heptane/EtOAc: 8/2. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 12.80 (br. s., 1H), 8.17 (d, J = 1.76 Hz, 1H), 7.95 (br. s., 1H), 7.77 (dd, J = 1.25, 3.76 Hz, 1H), 7.67 (dd, J = 1.25, 5.02 Hz, 1H), 7.60 (d, J = 1.76 Hz, 1H), 7.34 (dd, J = 1.63, 6.96, 8.47 Hz, 1H), 7.20 (dd, J = 3.64, 5.14 Hz, 1H), 7.04 (dd, J = 1.25, 8.28 Hz, 1H), 6.92 (dd, J = 1.38, 7.03, 8.16 Hz, 1H).

**N-[2-(2-hydroxyphenyl)-6-(3-nitrophenyl)pyridin-4-yl]thiophene-2-carboxamide 20:**
Following the general method B and starting from 19 (50mg, 0.15mmol) and 3-nitrophenylboronic acid (27mg, 0.196mmol), 20 was obtained as a white solid (32mg, 0.125mmol). Yield 82%. Eluent for the purification: heptane/EtOAc: 7/3. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 14.08 (s, 1H), 8.68 (t, J = 2.01 Hz, 1H), 8.26 - 8.29 (m, 2H), 8.25 (s, 1H), 7.98 (br. s., 1H), 7.97 (d, J = 2.01 Hz, 1H), 7.78 - 7.83 (m, 1H), 7.70 (dd, J = 1.13, 3.64 Hz, 1H), 7.65 (t, J = 8.03 Hz, 1H), 7.59 - 7.63 (m, 1H), 7.27 - 7.33 (m, 1H), 7.15 (dd, J = 3.51, 5.02 Hz, 1H), 6.97 - 7.02 (m, 1H), 6.89 (t, J = 8.16 Hz, 1H).

**N-[2-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-4-yl]thiophene-2-carboxamide; trifluoroacetic acid 21:**
Step 1: Following the general method H of the reduction of the nitro group and starting from 20 (52mg, 0.125mmol), N-[2-(3-aminopropanamido)-6-(2-hydroxyphenyl)pyridin-4-yl]thiophene-2-carboxamide 21$_1$ was obtained as a white solid (30mg, 0.077mmol). Yield 60%. Eluent for the purification: heptane/EtOAc: 6/4. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 14.37 (br. s., 1H), 8.20 - 8.23 (m, 1H), 8.00 (br. s., 1H), 7.90 - 7.93 (m, 1H), 7.86 (dd, J = 1.76, 8.03 Hz, 1H), 7.76 (dd, J = 0.75, 4.02 Hz, 1H), 7.66 (dd, J = 1.00, 5.02 Hz, 1H), 7.29 - 7.37 (m, 3H), 7.24 - 7.26 (m, 1H), 7.21 (dd, J = 3.76, 5.02 Hz, 1H), 7.03 - 7.07 (m, 1H), 6.93 (t, J = 7.53 Hz, 1H), 6.76 - 6.81 (m, 1H).

Step 2: Starting from 21$_1$ (28mg, 0.072mmol) and following the general method G of coupling reaction, tert-butyl N-[2-((3-[6-(2-hydroxyphenyl)-4-(thiophene-2-amido)pyridin-2-yl)phenyl]carbamoyl)ethyl]carbamate (21$_2$) was obtained as a light yellow solid (34mg, 0.061mmol). Yield 84%. Eluent for the purification: heptane/EtOAc: 5/5. $^1$H NMR (400 MHz, MeOD): $\delta$ = 8.49 (s, 1H), 8.04 (br. s., 1H), 7.92 (s, 1H), 7.88 (d, J = 3.01 Hz, 1H), 7.83 (d, J = 7.78 Hz, 1H), 7.62 (d, J = 8.53 Hz, 1H), 7.56 - 7.60 (m, 2H), 7.38 (t, J = 8.03 Hz, 1H), 7.21 - 7.26 (m, 1H), 7.10 (t, J = 4.27 Hz, 1H), 6.92 (d, J = 8.78 Hz, 1H), 6.87 (t, J = 7.78 Hz, 1H), 3.37 (t, J = 6.40 Hz, 2H), 2.52 (t, J = 6.15 Hz, 2H), 1.34 (s, 9H).

Step 3: The resulting 21$_2$ (31mg, 0.055mmol) and TFA (1mL) were mixed in CH$_2$Cl$_2$ (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified on reverse phase using H$_2$O (0.05%TFA)/MeOH to afford, after lyophilisation, 21 as a white solid (25mg, 0.044mmol). Yield 80%. $^1$H NMR (400 MHz, MeOD): $\delta$ = 8.38 (d, J = 2.01 Hz, 1H), 8.30 - 8.36 (m, 2H), 8.04 (dd, J = 1.26, 5.02 Hz, 1H), 7.84 (dd, J = 1.26, 5.02 Hz, 1H), 7.65 - 7.73 (m, 2H), 7.48 - 7.58 (m, 1H), 7.30 - 7.39 (m, 1H), 7.21 - 7.29 (m, 1H), 6.94 - 7.04 (m, 2H), 3.30 - 3.33 (m, 2H), 2.87 (t, J = 6.15 Hz, 2H); $^{13}$C NMR (101 MHz, MeOD): $\delta$ = 170.7,
The reaction mixture was stirred overnight at r.t. Yield 89%.

Following the general method F and starting from 23 (200mg, 0.786mmol) and 2-thiophencarbonyl chloride (101µL, 0.943mmol), 24 was obtained as a light orange solid (229mg, 0.628mmol). Yield 80%. Eluent for the purification: heptane/AcOEt: 10/0 to 8/2. 1H NMR (400MHz, CDCl₃): δ = 8.40 (br. s., 1 H), 8.28 (d, J = 8.8 Hz, 1 H), 7.70 - 7.66 (m, 2 H), 7.63 (dd, J = 1.1, 4.9 Hz, 1 H), 7.17 (dd, J = 3.8, 5.0 Hz, 1 H).

Following the general method B and starting from 23 (220mg, 0.603mmol) and 2-methoxyphenylboronic acid (110mg, 0.724mmol), 24 was obtained as a light yellow solid (197mg, 0.578mmol). Yield 95%. Eluent for the purification: heptane/EtOAc: 6/4. 1H NMR (400MHz, CDCl₃): δ = 8.51 (br. s., 1 H), 8.32 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 7.59 (dd, J = 1.1, 4.9 Hz, 1 H), 7.45 (dt, J = 1.8, 7.9 Hz, 1 H), 7.29 (dd, J = 1.6, 7.4 Hz, 1 H), 7.15 - 7.12 (m, 1 H), 7.12 - 7.07 (m, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 3.83 (s, 3 H).

Following the general method B and starting from 23 (220mg, 0.603mmol) and 2-methoxyphenylboronic acid (110mg, 0.724mmol), 24 was obtained as a light yellow solid (197mg, 0.578mmol). Yield 95%. Eluent for the purification: heptane/EtOAc: 6/4. 1H NMR (400MHz, CDCl₃): δ = 8.51 (br. s., 1 H), 8.32 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 7.59 (dd, J = 1.1, 4.9 Hz, 1 H), 7.45 (dt, J = 1.8, 7.9 Hz, 1 H), 7.29 (dd, J = 1.6, 7.4 Hz, 1 H), 7.15 - 7.12 (m, 1 H), 7.12 - 7.07 (m, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 3.83 (s, 3 H).

Following the general method B and starting from 23 (220mg, 0.603mmol) and 2-methoxyphenylboronic acid (110mg, 0.724mmol), 24 was obtained as a light yellow solid (197mg, 0.578mmol). Yield 95%. Eluent for the purification: heptane/EtOAc: 6/4. 1H NMR (400MHz, CDCl₃): δ = 8.51 (br. s., 1 H), 8.32 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 7.59 (dd, J = 1.1, 4.9 Hz, 1 H), 7.45 (dt, J = 1.8, 7.9 Hz, 1 H), 7.29 (dd, J = 1.6, 7.4 Hz, 1 H), 7.15 - 7.12 (m, 1 H), 7.12 - 7.07 (m, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 3.83 (s, 3 H).

N-(5-chloro-6-(2-methoxyphenyl)pyridin-2-yl)thiophene-2-carboxamide 24:

Following the general method B and starting from 23 (220mg, 0.603mmol) and 2-methoxyphenylboronic acid (110mg, 0.724mmol), 24 was obtained as a light yellow solid (197mg, 0.578mmol). Yield 95%. Eluent for the purification: heptane/EtOAc: 6/4. 1H NMR (400MHz, CDCl₃): δ = 8.51 (br. s., 1 H), 8.32 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 7.59 (dd, J = 1.1, 4.9 Hz, 1 H), 7.45 (dt, J = 1.8, 7.9 Hz, 1 H), 7.29 (dd, J = 1.6, 7.4 Hz, 1 H), 7.15 - 7.12 (m, 1 H), 7.12 - 7.07 (m, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 3.83 (s, 3 H).

N-(5-Lysino-6-(2-methoxyphenyl)pyridin-2-yl)thiophene-2-carboxamide 25:

Following the general method B and starting from 23 (220mg, 0.603mmol) and 2-methoxyphenylboronic acid (110mg, 0.724mmol), 24 was obtained as a light yellow solid (197mg, 0.578mmol). Yield 95%. Eluent for the purification: heptane/EtOAc: 6/4. 1H NMR (400MHz, CDCl₃): δ = 8.51 (br. s., 1 H), 8.32 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 7.59 (dd, J = 1.1, 4.9 Hz, 1 H), 7.45 (dt, J = 1.8, 7.9 Hz, 1 H), 7.29 (dd, J = 1.6, 7.4 Hz, 1 H), 7.15 - 7.12 (m, 1 H), 7.12 - 7.07 (m, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 3.83 (s, 3 H).
N-[5-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl]thiophene-2-carboxamide; trifluoroacetic acid 26:

Step 1: Following the general method G for coupling reaction and starting from 25 (48mg, 0.12mmol), tert-butyl-N-[2-[(3-[2-(2-methoxyphenyl)]-6-(thiophene-2-amido)pyridin-3-yl]phenyl]carbamoyl]ethyl]carbamate (261) was obtained as a white solid (65mg, 0.113mmol). Yield: 94%. Eluent for the purification: heptane/EtOAc: 5/5.

1H NMR (400MHz, CDCl3): δ = 8.84 (br. s., 1H), 8.33 (d, J = 8.3 Hz, 1 H), 7.89 (br. s., 1H), 7.75 (d, J = 8.3 Hz, 1 H), 7.65 (d, J = 3.5 Hz, 1 H), 7.56 (d, J = 5.0 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.32 - 7.21 (m, 3 H), 7.13 - 7.08 (m, 2 H), 6.95 (t, J = 7.0 Hz, 1 H), 6.79 (d, J = 7.3 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 5.23 (br. s., 1 H), 3.50 - 3.39 (m, 2 H), 3.33 (s, 3 H), 2.54 (br. s., 2 H), 1.43 (s, 9 H).

Step 2: The obtained compound 261 and TFA (1mL) were mixed in CH2Cl2 (1mL). After 1 hour at r.t., the volatiles were evaporated and N-[5-[3-(3-aminopropanamido)phenyl]-6-(2-methoxyphenyl)pyridin-2-yl]thiophene-2-carboxamide; trifluoroacetic acid (262) was obtained as a white solid (66mg, 0.113mmol). Yield: 99%.

1H NMR (400MHz, MeOD): δ = 8.19 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 8.8 Hz, 1 H), 8.06 (dd, J = 0.5, 3.8 Hz, 1 H), 7.92 (dd, J = 0.8, 5.0 Hz, 1 H), 7.58 (d, J = 1.3 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 1 H), 7.47 - 7.40 (m, 1 H), 7.32 (dd, J = 1.8, 7.3 Hz, 1 H), 7.30 - 7.26 (m, 1 H), 7.21 (t, J = 7.9 Hz, 1 H), 7.01 (m, 2 H), 6.90 (d, J = 7.8 Hz, 1 H), 3.60 (s, 3 H), 3.27 (t, J = 5.9 Hz, 2 H), 2.80 (t, J = 6.3 Hz, 2 H). The resulting solid was directly submitted to deprotection of the methoxy group.

Step 3: The obtained compound 262 (66mg, 0.113mmol) and anhydrous CH2Cl2 (1mL) were introduced in a process vial followed by the addition of BBr3 1M (CH2Cl2, 955µL, 0.955mmol). The reaction mixture was capped properly and heated at 110°C under microwave irradiation for 10min. The reaction mixture was then cooled at r.t. and excess of BBr3 was hydrolyzed with MeOH. The reaction mixture was concentrated under vacuum. The crude product was purified on reverse phase using H2O(0.05%TFA)/MeOH to afford, after lyophilisation, 26 as a white solid (43mg, 0.079mmol). Yield 70%. 1H NMR (400MHz, MeOD): δ = 7.96 - 7.91 (m, 3 H), 7.75 (d, J = 5.0 Hz, 1 H), 7.49 - 7.42 (m, 2 H), 7.18 - 7.11 (m, 2 H), 7.08 (t, J = 8.2 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 2 H), 6.80 (d, J = 8.3 Hz, 1 H), 6.57 - 6.49 (m, 1 H), 3.15 (t, J = 6.0 Hz, 2 H), 2.68 (t, J = 6.3 Hz, 2 H);

13C NMR (126 MHz, MeOD): δ = 170.6, 162.8, 162.8, 157.3, 157.3, 155.8, 151.1, 142.8, 140.0, 133.6, 132.7, 131.2, 131.1, 130.0, 129.3, 126.4, 125.8, 125.8, 121.8, 120.0, 119.9, 118.0, 114.4, 37.0, 33.8.
Analytical characterization:

- **HPLC-MS methods:**

Method A: Analytical RP-HPLC-MS was performed using a LC Agilent 1200SL–Trappe Brucker HCT ultra with a Thermo Hypersilgold® column (C18, 30 mm × 1 mm; 1.9 μm) using the following parameters: 1) the solvent system: A (0.01% formic acid in acetonitrile) and B (0.01% formic acid in H2O); 2) a linear gradient: t = 0 min, 95%B; t = 7 min, 5% B; t = 9 min, 95%; t = 9.50 min, 95%B; 3) flow rate of 0.5 mL/min; 4) Column temperature: 60°C; 5) The ratio of products was determined by integration of spectra recorded at 210 nm or 254 nm; 6) Ionization mode: ESI.

Method B: Analytical RP-HPLC-MS was performed using a LC-MSD 1200SL Agilent with a Thermo Hypersilgold® column (C18, 30 mm × 1 mm; 1.9 μm) using the following parameters: 1) The solvent system: A (acetonitrile) and B (0.05% TFA in H2O); 2) A linear gradient: t = 0 min, 98%B; t = 5 min, 5% B; t = 6 min, 5%B; t = 7 min, 98%B; t = 9 min, 98%; 3) Flow rate of 0.3 mL/min; 4) Column temperature: 50°C; 5) The ratio of products was determined by integration of spectra recorded at 210 nm or 254 nm; 6) Ionization mode: MM-ES+APCI.

- **HPLC-MS data:**

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a: [m-tBu]/z; b: [m-Boc]/z
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3-amino-N-(3-(2-amino-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)propanamide 14a:

\[
\text{H-NMR (MeOD):}
\]
3-amino-N-(3-(2-amino-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)propanamide 14a:

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\[ \text{N} \quad \text{H} \quad \text{2} \]

\[ \text{N} \quad \text{H} \quad \text{2} \]

$^{13}$C-NMR (MeOD):

Electronic Supplementary Material (ESI) for RSC Advances
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N-[4-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl]thiophene-2-carboxamide 14b:

H-NMR (MeOD):

![H-NMR Spectrum](image_url)
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3-amino-N-[3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl]propanamide 14c:

H-NMR (MeOD):

![NMR spectrum image]
3-amino-N-[3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl]propanamide 14c :

\[
\begin{array}{c}
\text{\includegraphics[width=0.5\textwidth]{structure.png}}
\end{array}
\]

\[\text{13}^\text{C}-\text{NMR (MeOD)}:\]

Electronic Supplementary Material (ESI) for RSC Advances
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3-amino-N-[3-[2-(2-hydroxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl]phenyl]propanamide 14d:

H-NMR (MeOD):

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3-amino-N-[3-[2-(2-hydroxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl]phenyl]propanamide 14d:

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{O} & \\
\end{align*}
\]

\[13^C\text{-NMR (MeOD)}: \]

![13C-NMR (MeOD) spectrum](image)
3-amino-N-[3-[2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl]propanamide 14e:

H-NMR (MeOD):

- 27
3-amino-N-{[2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide 14e:

\[
\begin{array}{c}
\text{HO} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{NH}_2 \\
\text{O} \\
\end{array}
\]

$^{13}$C-NMR (MeOD):

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3-amino-N-[3-[2-(benzylamino)-6-(2-hydroxyphenyl)pyridin-4-y]phenyl]propanamide 14f:

H-NMR (MeOD):

[Image of NMR spectrum]
3-amino-N-{3-[2-(benzylamino)-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide 14f:

\[
\begin{align*}
&\text{13C-NMR (MeOD):} \\
&\text{(Graph of 13C-NMR spectrum)}
\end{align*}
\]
N-[6-(2-hydroxyphenyl)-4-[3-(piperazin-1-yl)propyl]pyridin-2-yl]benzamide 16:

H-NMR (MeOD):

![H-NMR spectrum diagram]
N-[6-(2-hydroxyphenyl)-4-[3-(piperazin-1-yl)propyl]pyridin-2-yl]benzamide 16:

$\begin{align*}
N- & \text{O} \\
O- & \text{NH} \\
N- & \text{H} \\
N & \text{OH} \\
O & \text{N} \\
N & \text{H} \\
N & \text{O}
\end{align*}$

$^{13}$C-NMR (MeOD):

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N-{6-[3-(3-aminopropanamido)phenyl]-4-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 18:

H-NMR (MeOD):

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N-{6-[3-(3-aminopropanamido)phenyl]-4-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 18:

\[
\begin{align*}
\text{H} & \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{H} \\
& \quad \text{O} \\
& \quad \text{H} \\
& \quad \text{S} \\
& \quad \text{O}
\end{align*}
\]

\[^{13}\text{C-NMR (MeOD)}: \]

![C-NMR spectrum](image)
**N-[2-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-4-yl]thiophene-2-carboxamide 21:**

H-NMR (MeOD):

![NMR Spectrum](image)
N-[2-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-4-yl]thiophene-2-carboxamide 21:

\[\text{Structure Image}\]

$^{13}$C-NMR (MeOD):

**Figure Image**
N-[5-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl]thiophene-2-carboxamide 26:

H-NMR (MeOD):

Electronic Supplementary Material (ESI) for RSC Advances
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N-{5-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 26:

\[\text{N-H} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{S} \quad \text{O} \quad \text{N-H} \quad \text{O} \quad \text{NH}_2\]

\[\text{13C-NMR (MeOD)}:\]

![NMR spectrum]

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Cell membrane preparation and receptor binding assay

Wild-type human GPR54 receptor cDNA was cloned into pCDNA3.1 (in vitrogen) expression vector in fusion at its 5’ end with a sequence encoding a signal sequence and a flag epitope (Guan et al., 1992). The resulting construct (SF-hGPR54) was then stably transfected into CHO cells. For membrane preparations, cell pellets were homogenized in 15 mM Tris-HCl pH 7.5, 2mM MgCl₂, 0.3 mM EDTA and 1mM EGTA using a glass homogenizer and centrifuge at 4°C for 30 min. at 100 000 X g. The pellets were resuspended in the same buffer, centrifuge again in the same conditions and membrane pellets were finally resuspended in 75 mM Tris-HCl pH 7.5, 12.5 mM MgCl₂, 0.3 mM EDTA, 1mM EGTA and 250 mM sucrose. GPR54 membranes (10µg) were incubated for 60 min at 25 °C in a final volume of 0.25 ml containing 50 mM Tris-HCl pH 7.4, 10 mM MgCl₂, EDTA 1mM, 0.5% bovine serum albumin, 0.02 nM [¹²⁵I]-Tyr-Kiss10 (Perkin Elmer, Courtaboeuf, France; specific activity, 2200 Ci/mmol) and the ligands to be tested. Non-specific binding was determined in presence of 1 µM Kiss-10. Typical total and nonspecific binding were around 1200 and 200 cpm, respectively. Incubation mixtures were rapidly filtered and washed with the binding buffer, on 96 wells GF/B unifilter (Perkin Elmer). Unifilter plates were then dried for 1hr at 65°C and bound radioactivity was determined by scintillation counting with 30 µl of scintillation cocktail (O-scint, Perkin Elmer) per well on a Topcount scintillation apparatus (Perkin Elmer).