Electronic Supplementary Material (ESI) for RSC Advances

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

Christelle Doebelin, Patrick Wagner, Isabelle Bertin, Frédéric Simonin, Martine Schmitt, Frédéric Bihel, Jean-Jacques Bourguignon

Content

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 ^{1}H NMR or HPLC/MS. The melting points are uncorrected. ^{1}H and ^{13}C 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.), Na_2CO_3 (3 eq.) were introduced in a process vial under nitrogen followed by the addition of a mixture of H_2O/CH_3CN (2/3). The mixture was nitrogen-flushed and $Pd(PPh_3)_2Cl_2$ (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 Na_2SO_4, 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.), Na_2CO_3 (3 eq.) were introduced in a process vial under nitrogen followed by the addition of a mixture of DME/H_2O (3/1). The mixture was nitrogen-flushed and $Pd(PPh_3)_4$ (0.1eq.) 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.), Cs_2CO_3 (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.), Cs_2CO_3 (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 $Pd_2(dba)_3.CHCl_3$ (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.), Cs_2CO_3 (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:

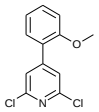
Boc-β-Ala-OH (1.1 eq.) was pre-activated with HATU (1.2 eq.) and DIEA (1.3 eq.) in CH_2Cl_2/DMF: 1/2. Aniline derivative (1 eq.) was added after 10 min. at r.t. The solution was stirred overnight at r.t. The solvent was

evaporated and the crude product was purified by chromatography on silica gel to give the expected products: **7e**, **14a**$_2$, **14c**$_2$, **18**$_1$, **21**$_2$, **26**$_1$.

Reduction of nitro group:

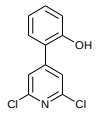
Method H:

To a solution of nitroaryl (1eq.) in EtOH/H_2O: 1/1 (0.02mmol/mL) was added NH_4Cl (6.4eq.) and Fe (6eq.). 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**$_1$, **14c**$_1$, **21**$_1$.



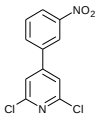
2,6-dichloro-4-(2-methoxyphenyl)pyridine 7a :

Following the general method A and starting from 2,6-dichloro-4-iodopyridine (300mg, 1.1mmol) and 2-methoxyphenylboronic acid (175mg, 1.15mmol), **7a** was obtained as a light yellow solid (274mg, 1.07mmol). Yield 98%. Eluent for the purification: heptane/EtOAc: 8/2. ^{1}H NMR (400 MHz, CDCl3): δ= 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)



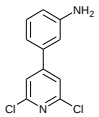
2-(2,6-dichloropyridin-4-yl)phenol 7b :

Following the general method A and starting from 2,6-dichloro-4-iodopyridine (300mg, 1.1mmol) and 2-hydroxyphenylboronic acid (159mg, 1.15mmol), **7b** was obtained as a white solid (254mg, 1.06mmol). Yield 97%. Eluent for the purification: heptane/EtOAc: 7/3. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 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).



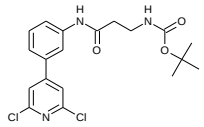
2,6-dichloro-4-(3-nitrophenyl)pyridine 7c :

Following the general method A and starting from 2,6-dichloro-4-iodopyridine (100mg, 0.365mmol) and 3-nitrophenylboronic acid (64mg, 0.385mmol), **7c** was obtained as a light yellow solid (80mg, 0.297mmol). Yield 81%. Eluent for the purification: heptane/EtOAc: 9/1. ^{1}H NMR (400MHz, $CDCl_3$): δ= 8.48 (t, *J* = 1.9 Hz, 1 H), 8.40 - 8.36 (m, 1 H), 7.96 - 7.92 (m, 1 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.53 (s, 2 H).



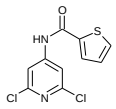
3-(2,6-dichloropyridin-4-yl) aniline 7d:

Following the general method A and starting from 2,6-dichloro-4-iodopyridine (1200mg, 4.38mmol) and 3-aminophenylboronic acid hydrochloride (836mg, 4.82mmol), **7d** was obtained as a light yellow solid (1008mg, 4.22mmol). Yield 96%. Eluent for the purification: heptane/EtOAc: 8/2. ^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.44 (s, 2 H), 7.26 (m, 1H), 7.00 - 6.95 (m, 1 H), 6.87 (t, *J* = 2.1 Hz, 1 H), 6.80 (dd, *J* = 2.4, 8.2 Hz, 1 H), 3.85 (br. s., 2 H).



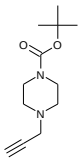
***tert*-butyl (3-{[3-(2,6-dichloropyridin-4-yl)phenyl]amino}-3-oxopropyl)carbamate 7e:**

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. ^{1}H NMR (400MHz ,$CDCl_3$): 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:**

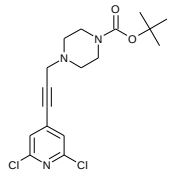
Following the general method C and starting from 2,6-dichloro-4-iodopyridine (100mg, 0.365mmol) and 2-thienylamide (46mg, 0.365mmol), **8** was obtained as a white solid (90mg, 0.329mmol). Yield: 90%. Eluent for the purification: heptane/EtOAc: 8/2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (br. s., 1H), 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:**

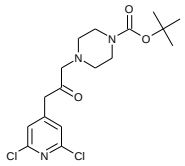
Step 1: Piperazine (3440mg, 39.94mmol)) was solubilized in CH_2Cl_2 (100mL) at r.t., then a solution of Boc_2O (4358mg, 19.97mmol) in CH_2Cl_2 (50mL) was added dropwise. The solution was stirred overnight at r.t. The solvent was evaporated and the residue was triturated in H_2O. The precipitate was filtered and the filtrate was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4, filtered and concentrated to give a white solid (2289mg, 12.29mmol). Yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$): 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), Cs_2CO_3(1,75g, 5.37mmol) and propargyl bromide (404µL, 5.37mmol) were solubilized in acetone (15mL) at 0°C. The solution was stirred overnight at r.t. The precipitated was filtered and washed with acetone. The filtrate was concentrated and the residue was extracted with EtOAc. The organic layer was washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4. Evaporation under reduce pressure afford the pure piperazine-1-carboxylate (**9**$_{\mathbf{alkyne}}$) derivative as an orange oil (1,14mg, 5.09mmol). Yield 95%.^{1}H NMR (300 MHz, $CDCl_3$): 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).



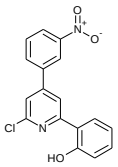
***tert*-butyl 4-[3-(2,6-dichloropyridin-4-yl)prop-2-yn-1-yl]piperazine-1-carboxylate 9:**

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_3N (1 mL, 7.30mmol) were added in a flamed dried microwave tube nitrogen. The reaction mixture was nitrogen-flushed then $Pd(PPh_3)_2Cl_2$ (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, 1.38mmol). Yield 95%. ^{1}H NMR (400MHz, $CDCl_3$): δ = 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).



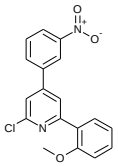
***tert*-butyl 4-[3-(2,6-dichloropyridin-4-yl)-2-oxopropyl]piperazine-1-carboxylate 10 :**

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 $Pd(PPh_3)_2Cl_2$ (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, $CDCl_3$): δ= 7.16 (s, 2H), 3.80 (s, 2H), 3.45 - 3.53 (m, 4H), 3.25 (s, 2H), 2.45 (t, *J* = 5.14 Hz, 4H), 1.47 (s, 9H).



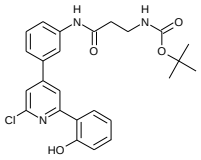
2-[6-chloro-4-(3-nitrophenyl)pyridin-2-yl]phenol 11a :

Following the general method B and starting from **7c** (100mg, 0.372mmol) and 2-hydroxyphenylboronic acid (51mg, 0.372mmol), **11a** was obtain as a light yellow solid (86mg, 0.263mmol). Yield 70%. Eluent for the purification: heptane/EtOAc: 8/2. ^{1}H NMR (400MHz , $CDCl_3$): δ = 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).



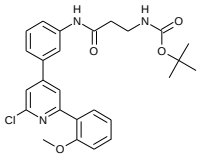
2-chloro-6-(2-methoxyphenyl)-4-(3-nitrophenyl)pyridine 11b :

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. ^{1}H NMR (300MHz, $CDCl_3$): δ = 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).



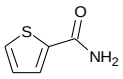
tert-butyl (3-((3-(2-chloro-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 11c :

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. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 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).



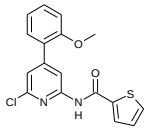
tert-butyl (3-((3-(2-chloro-6-(2-methoxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 11d :

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. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 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).



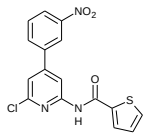
thiophene-2-carboxamide :

2-thiophenecarbonyl chloride (3g, 20.5mmol) was solubilized in H_20 (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, $CDCl_3$): δ= 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).



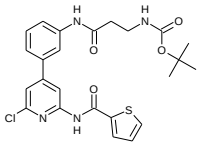
***N*-[6-chloro-4-(2-methoxyphenyl)pyridin-2-yl]thiophene-2-carboxamide 12a:**

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, $CDCl_3$): δ= 8.45 (s, 1H), 8.41 (br. s, 1H), 7.68 (dd, *J* = 1.00, 3.76 Hz, 1H), 7.58 - 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).



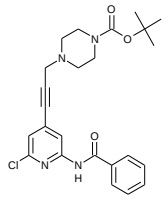
***N*-[6-chloro-4-(3-nitrophenyl)pyridin-2-yl]thiophene-2-carboxamide 12b:**

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, $CDCl_3$): δ = 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).



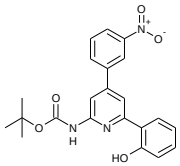
tert-butyl (3-((3-(2-chloro-6-(thiophene-2-carboxamido)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 12c:

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, $CDCl_3$): δ = 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).



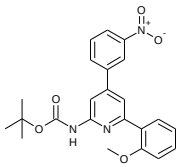
tert-butyl 4-(3-(2-benzamido-6-chloropyridin-4-yl)prop-2-yn-1-yl)piperazine-1-carboxylate 12d :

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, $CDCl_3$): δ = 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).



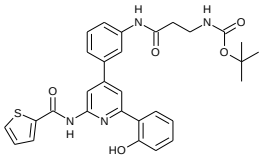
tert-butyl (6-(2-hydroxyphenyl)-4-(3-nitrophenyl)pyridin-2-yl)carbamate 13a:

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, $CDCl_3$): δ= 8.56 - 8.59 (m, 1H), 8.32 - 8.37 (m, 1H), 8.14 (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).



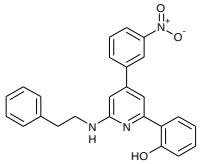
tert-butyl (6-(2-methoxyphenyl)-4-(3-nitrophenyl)pyridin-2-yl)carbamate 13b :

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 (400MHz, $CDCl_3$): δ = 8.55 (t, *J* = 2.0 Hz, 1 H), 8.32 - 8.27 (m, 1 H), 8.17 (s, 1 H), 8.06 (dd, *J* = 1.3, 8.0 Hz, 1 H), 7.77-7.75 (m, 2 H), 7.66 (t, *J* = 7.9 Hz, 1 H), 7.47 (br. s., 1 H), 7.44 - 7.38 (m, 1 H), 7.14 - 7.07 (m, 1 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 3.90 (s, 3 H), 1.56 (s, 9 H).



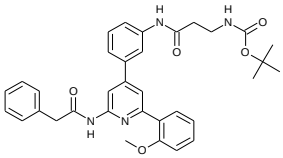
tert-butyl (3-((3-(2-(2-hydroxyphenyl)-6-(thiophene-2-carboxamido)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13c:

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. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 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).



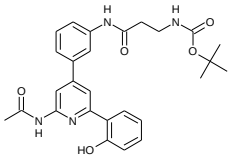
2-(4-(3-nitrophenyl)-6-(phenethylamino)pyridin-2-yl)phenol 13d:

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. ^{1}H NMR (400MHz, $CDCl_3$): δ = 14.20 (br. s., 1H), 8.48 (t, *J* = 1.9 Hz, 1 H), 8.34 - 8.28 (m, 1 H), 7.96 - 7.92 (m, 1 H), 7.85 (dd, *J* = 1.3, 8.0 Hz, 1 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.40 - 7.28 (m, 7 H), 7.03 (dd, *J* = 1.0, 8.0 Hz, 1 H), 6.96 - 6.89 (m, 1 H), 6.49 (d, *J* = 1.3 Hz, 1 H), 4.76 (t, *J* = 6.1 Hz, 1 H), 3.77 - 3.69 (m, 2 H), 3.04 (t, *J* = 6.8 Hz, 2 H).



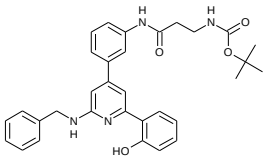
tert-butyl (3-((3-(2-(2-methoxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13e:

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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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).



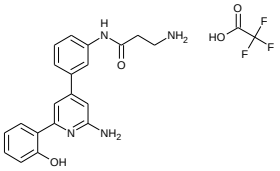
tert-butyl (3-((3-(2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)amino)-3-oxopropyl)carbamate 13f:

Following the general method C and starting from **11c** (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%. ^{1}H NMR (400 MHz, $CDCl_3$): 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* = 6.02 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 E and starting from **11c** (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. ^{1}H NMR (400 MHz, $CDCl_3$): 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), 2.66 (t, *J* = 6.02 Hz, 2H), 1.45 (s, 9H).



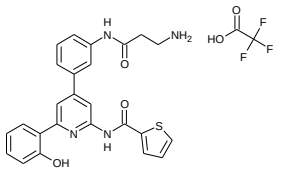
3-amino-N-(3-(2-amino-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)propanamide trifluoroacetic acid 14a :

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-metoxyphenyl)pyridin-2-yl)carbamate (**14a$_1$**) was obtained as a white solid (64mg, 0.163mmol). Yield 69%. Eluent for the purification: heptane/EtOAc: 7/3. ^{1}H NMR (400MHz, $CDCl_3$): 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 - 6.69 (m, 1 H), 3.79 (s, 3 H), 3.71 (br. s., 2 H), 1.47 (s, 9 H).

Step 2: Starting from **14a$_1$** (60mg, 0.153mmol) and following the general method G for coupling reaction tert-butyl N-{4-[3-(3-{[(tert-butoxy) carbonyl]amino}propanamido) phenyl]-6-(2-methoxyphenyl) pyridin-2-yl} carbamate (**14a$_2$**) was obtained as a white solid (69mg, 0.122mmol). Yield 80%. Eluent for the purification: heptane/EtOAc: 6/4. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.03 (s, 1H), 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).

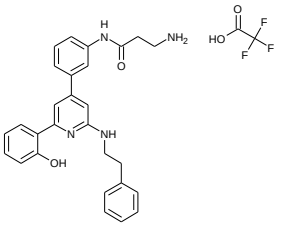
Step 3: The resulting solid **14a$_2$** and TFA (1mL) were mixed in CH_2Cl_2 (1 mL). After 1 hour at r.t., the volatiles were evaporated and 3-amino-N-{3-[2-amino-6-(2-methoxyphenyl)pyridin-4-yl]phenyl}propanamide; trifluoroacetic acid was obtained as a light yellow oil (68mg, 0.116mmol). Yield 95%. The resulting oil was directly submitted to deprotection of the methoxy group.

Step 4: The crude oil (68mg, 0.116mmol) and anhydrous CH_2Cl_2 (1.1mL) were introduced in a process vial followed by the addition of BBr_3 1M (CH_2Cl_2, 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 BBr_3 was hydrolyzed with MeOH and concentrated under vacuum. The crude product was purified on reverse phase using H_2O(0.05%TFA)/MeOH to afford **14a** after lyophilisation as a light yellow solid (38mg, 0.082mmol). Yield 71%. ^{1}H 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); ^{13}C 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-(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 CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated and the crude product was purified by chromatography on reverse phase using H_2O(0.05%TFA)/MeOH, to afford after trituration in ether **14b** as a white solid (35mg, 0.061mmol). Yield 98%. ^{1}H NMR (400MHz, MeOD): 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); ^{13}C NMR (101 MHz, MeOD): 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, 124.08, 122.15, 120.53, 120.44, 119.85, 119.08, 114.65, 111.38, 36.88, 33.78.

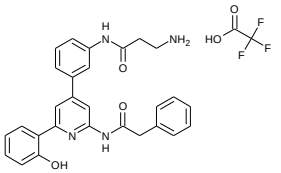


3-amino-N-{3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl}propanamide; trifluoroacetic acid 14c :

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$_1$**) was obtained as a white solid (28mg, 0.073mmol). Yield 60%. Eluent for the purification: heptane/EtOAc: 7/3. ^{1}H NMR (400 MHz, $CDCl_3$): 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).

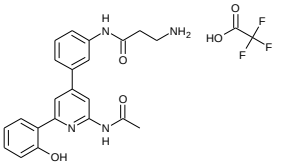
Step 2: Starting from **14c$_1$** (21mg, 0.055mmol) and following the general method G for coupling reaction, tert-butyl N-[2-({3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl}carbamoyl)ethyl]carbamate (**14c$_2$**) was obtained as a light yellow oil (21mg, 0.038mmol). Yield 70%. Eluent for the purification: heptane/EtOAc: 5/5. ^{1}H NMR (400 MHz, $CDCl_3$): 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 **14c$_2$** and TFA (1mL) were mixed in CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H_2O(0.05%TFA)/MeOH to afford after lyophilisation **14c** as a light yellow solid (15mg, 0.026mmol). Yield 70%. ^{1}H 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); ^{13}C 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.



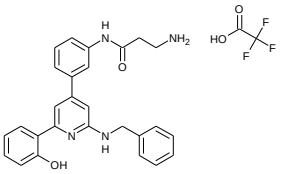
3-amino-N-{3-[2-(2-hydroxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl]phenyl}propanamide; trifluoroacetic acid 14d:

Step 1: **13e** (90mg, 0.155mmol) and TFA (1mL) were mixed in CH_2Cl_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 2: The crude oil and anhydrous CH_2Cl_2 (1mL) were introduced in a process vial followed by the addition of BBr_3 1M (CH_2Cl_2, 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 BBr_3 was hydrolyzed with MeOH and concentrated under vacuum. The crude product was purified by chromatography on reverse phase using H_2O(0.05%TFA)/MeOH to afford after lyophilisation **14d** as a light yellow solid (45mg, 0.077mmol). Yield 50%. ^{1}H 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); ^{13}C 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.



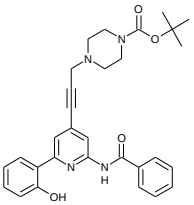
3-amino-N-{3-[2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide; trifluoroacetic acid 14e:

13f (59mg, 0.12mmol) and TFA (1mL) were mixed in CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H_2O(0.05%TFA)/MeOH to afford after lyophilisation **14e** as a light yellow solid (48mg, 0.095mmol). Yield 79%. ^{1}H 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). ^{13}C 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, 110.2, 36.9, 33.9, 24.2.



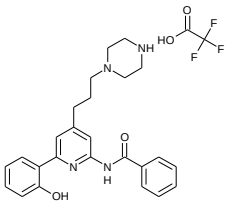
3-amino-N-{3-[2-(benzylamino)-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide; trifluoroacetic acid 14f:

13g (75mg, 0.139mmol) and TFA (1mL) were mixed in in CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H_2O(0.05%TFA)/MeOH to afford after lyophilisation **14f** as a light yellow solid (53mg, 0.096mmol). Yield 69%. ^{1}H 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); ^{13}C 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, $CDCl_3$): δ = 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).

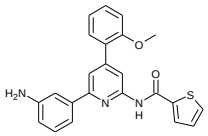


N-[6-(2-hydroxyphenyl)-4-[3-(piperazin-1-yl)propyl]pyridin-2-yl]benzamide; trifluoroacetic acid 16:

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 **16$_1$** as a colorless oil (90mg, 0.174mmol). Yield 82%.

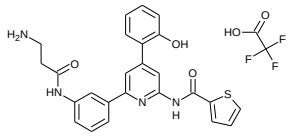
^{1}H NMR (400MHz, $CDCl_3$): δ = 13.14 (s, 1H), 8.36 (s, 1 H), 8.19 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 2 H), 7.83 - 7.77 (m, 1 H), 7.66 - 7.58 (m, 1 H), 7.58 - 7.50 (m, 3 H), 7.38 - 7.29 (m, 1 H), 7.02 (d, *J* = 8.5 Hz, 1 H), 6.95 (t, *J* = 7.3 Hz, 1 H), 3.52 - 3.40 (m, 4 H), 2.81 (t, *J* = 7.7 Hz, 2 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 **16$_1$** and TFA (1mL) were mixed in CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified by chromatography on reverse phase using H_2O(0.05%TFA)/MeOH to afford **16** as a yellow solid after lyophilisation (90mg, 0.170mmol). Yield 97%. ^{1}H NMR (400MHz, MeOD): δ = 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): δ = 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, $CDCl_3$): δ = 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).

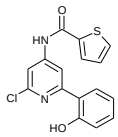


N-{6-[3-(3-aminopropanamido)phenyl]-4-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide; trifluoroacetic acid 18:

Step 1: Following the general method G and starting from **17** (80mg, 0.199mmol), tert-butylN-[2-({3-[4-(2-methoxyphenyl)-6-(thiophene-2-amido)pyridin-2-yl]phenyl}carbamoyl)ethyl]carbamate (**18$_1$**) was obtained as a a light yellow solid (102mg, 0.178mmol). Yield 89%. Eluent for the purification: heptane/EtOAc: 6/4. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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).

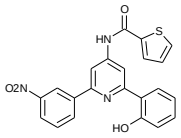
Step 2: The resulting solid **18$_1$** (95mg, 0.166mmol) and TFA (1mL) were mixed in CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The resulting oil was directly submitted to deprotection of the methoxy group.

Step 3: The crude oil and anhydrous CH_2Cl_2 (3mL) were introduced in a process vial followed by the addition of BBr_3 1M (CH_2Cl_2, 1.5mL, 1.5mmol). 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_2O(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): δ = 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): δ = 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.



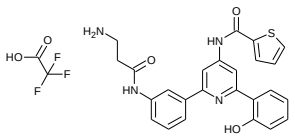
N-[2-chloro-6-(2-hydroxyphenyl)pyridin-4-yl]thiophene-2-carboxamide 19:

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, $CDCl_3$): δ = 12.80 (br. s., 1H), 8.17 (d, *J* = 1.76 Hz, 1H), 7.95 (br. s., 1H), 7.77 (dd, *J* = 1.63, 8.16 Hz, 1H), 7.72 (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 (ddd, *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 (ddd, *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 (52mg, 0.125mmol). Yield 82%. Eluent for the purification: heptane/EtOAc: 7/3. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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).



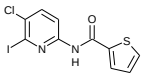
N-{2-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-4-yl}thiophene-2-carboxamide; trifluoroacetic acid 21:

Step 1: Following the general method H of the reduction of the nitro group and starting from **20** (52mg, 0.125mmol), *N*-[2-(3-aminophenyl)-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, $CDCl_3$): δ =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): δ = 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).

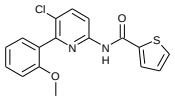
Step 3: The resulting **21$_2$** (31mg, 0.055mmol) and TFA (1mL) were mixed in CH_2Cl_2 (1mL). After 1 hour at r.t., the volatiles were evaporated. The crude product was purified on reverse phase using H_2O (0.05%TFA)/MeOH to afford, after lyophilisation, **21** as a white solid (25mg, 0.044mmol). Yield 80%. ^{1}H NMR (400 MHz, MeOD): δ = 8.38 (d, *J* = 2.01 Hz, 1H), 8.30 - 8.36 (m, 2H), 8.04 (dd, *J* = 1.26, 3.76 Hz, 1H), 7.88 - 7.95 (m, 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): δ = 170.7,

163.2, 160.5, 159.5, 156.7, 150.2, 140.6, 140.0, 133.9, 132.7, 131.1, 130.7, 129.2, 127.8, 123.6, 122.2, 120.3, 120.2, 119.3, 119.0, 110.9, 109.2, 36.8, 33.6.



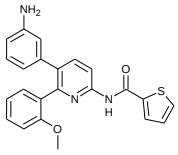
N-(5-chloro-6-iodopyridin-2-yl)thiophene-2-carboxamide 23:

Step 1: 2-amino-6-bromopyridine (2000mg, 11.56mmol), CuI (110mg, 0.578mmol), NaI (3465mg, 23.12mmol), N,N-dimethylethyldiamine (126µL, 1.156mmol), and 1,4-dioxane (16mL) were introduced in a process vial under nitrogen. The solution was nitrogen-flushed. The reaction mixture was then capped properly and heated at 110°C for 6h. The solvent was removed under vacuum and the obtained residue was diluted in CH_2Cl_2. The organic layer was washed with a concentrated solution of $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography on silica gel using CH_2Cl_2/MeOH: 99/1 to afford 2-amino-6-iodopyridine (**23_1**) as a white solid (2425mg, 11.072mmol). Yield 89%. ^{1}H NMR (300MHz, $CDCl_3$): δ = 7.13 - 6.99 (m, 2 H), 6.44 (d, *J* = 7.5 Hz, 1 H), 4.59 (br. s., 2 H).
Step 2: 2-amino-6-iodopyridine **23_1** (1115mg, 5.091mmol) was solubilized in DMF (15mL), following by the addition of NCS (748mg, 5.600mmol). The reaction mixture was stirred overnight at r.t. The solvent was removed under vacuum and the resulting residue was diluted in CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated under vaccum. The crude product was purified by chromatography on silica gel using CH_2Cl_2 to afford 2-iodo-3-chloro-6-aminopyridine (**23_2**) as a white solid (971mg, 3.818mmol). Yield 75%. ^{1}H NMR (300MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.4 Hz, 1 H), 6.41 (d, *J* = 8.4 Hz, 1 H), 4.59 (br. s., 2 H).
Step 3: Following the general method F and starting from **23_2** (200mg, 0.786mmol) and 2-thiophenecarbonyl chloride (101µL, 0.943mmol), **23** was obtained as a light orange solid (229mg, 0.628mmol). Yield 80%. Eluent for the purification: heptane/AcOEt: 10/0 to 8/2. ^{1}H NMR (400MHz, $CDCl_3$): 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).



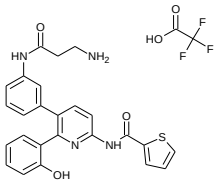
N-(5-chloro-6-(2-methoxyphenyl)pyridin-2-yl)thiophene-2-carboxamide 24:

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. ^{1}H NMR (400MHz, $CDCl_3$): 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-aminophenyl)-6-(2-methoxyphenyl)pyridin-2-yl)thiophene-2-carboxamide 25:

24 (100mg, 0.274mmol), 3-aminophenylboronic hydrochloride acid (52mg, 0.302mmol), K_2CO_3 (141mg, 1.10mmol), CH_3CN/H_2O: 4/1 (1mL) were introduced in a process vial under nitrogen. The reaction mixture was nitrogen-flushed followed by the addition of S-phos (11mg, 0.027mmol) and $Pd(OAc)_2$ (3mg, 0.014mmol). The reaction mixture was capped properly and heated under microwave irradiation at 110°C for 15min. Solvents were evaporated and the crude product was purified by chromatography on silica gel using heptane/EtOAc: 8/2 to 4/6 to afford **25** as a white solid (52mg, 0.13mmol). Yield 47%. ^{1}H NMR (400MHz, $CDCl_3$): δ = 8.93 (br. s., 1 H), 8.36 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 8.5 Hz, 1 H), 7.63 (d, *J* = 3.8 Hz, 1 H), 7.55 (dd, *J* = 1.0, 5.0 Hz, 1 H), 7.34 - 7.24 (m, 2 H), 7.09 (dd, *J* = 3.9, 4.9 Hz, 1 H), 6.96 (q, *J* = 7.4 Hz, 2 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 6.56 - 6.48 (m, 2 H), 6.47 - 6.44 (m, 1 H), 3.70 (br. s., 2 H), 3.37 (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 (**26$_1$**) was obtained as a white solid (65mg, 0.113mmol). Yield: 94%. Eluent for the purification: heptane/EtOAc: 5/5. ^{1}H NMR (400MHz , $CDCl_3$): 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 **26$_1$** and TFA (1mL) were mixed in CH_2Cl_2 (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 (**26$_2$**) was obtained as a white solid (66mg, 0.113mmol). Yield: 99%. ^{1}H 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 **26$_2$** (66mg, 0.113mmol) and anhydrous CH_2Cl_2 (1mL) were introduced in a process vial followed by the addition of BBr_3 1M (CH_2Cl_2, 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 BBr_3 was hydrolyzed with MeOH. The reaction mixture was concentrated under vacuum. The crude product was purified on reverse phase using H_2O(0.05%TFA)/MeOH to afford, after lyophilisation, **26** as a white solid (43mg, 0.079mmol). Yield 70%. ^{1}H 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); ^{13}C 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 Bruker 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, 5%B; 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.

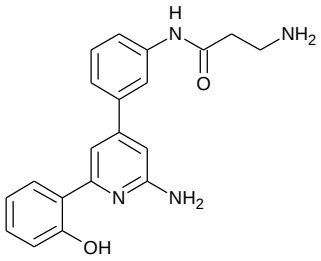
Method B : Analytical RP-HPLC-MS was performed using a LC-MSD 1200SL Agilent with a Thermo Hypersilgold® column (C18, 30 mm × 1 mm; 1.9 µm) using the following parameters : 1) The solvent system : A (acetonitrile) and B (0.05% TFA in H2O); 2) A linear gradient : t = 0 min, 98%B; t = 5 min, 5% B; t = 6 min, 5%B; t = 7 min, 98%B; t = 9 min, 98%B; 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:

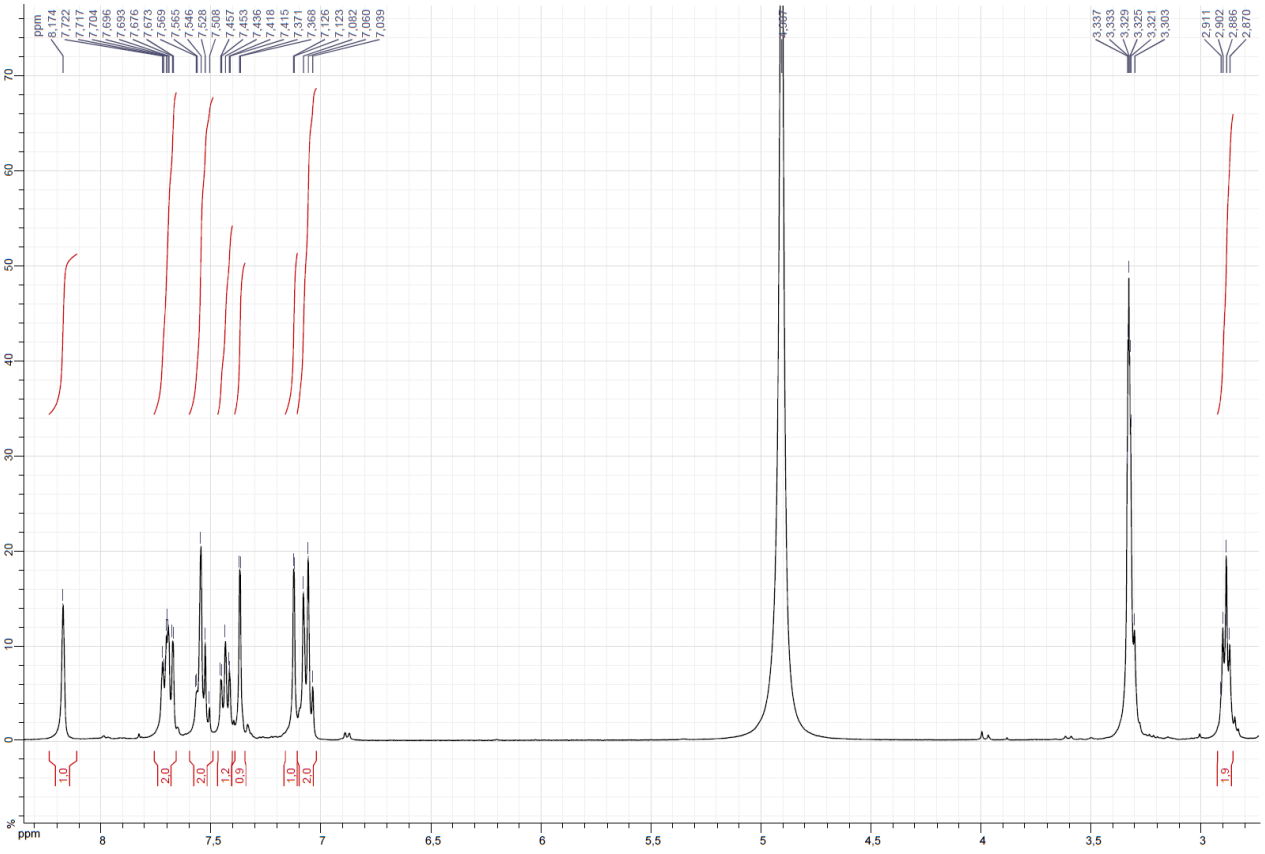
Compound	HPLC Method	t_R(min)	Calc. m/z	Exp. m/Z	Compound	HPLC Method	t_R(min)	Calc. m/z	Exp. m/Z
7a	B	4.75	254.0	254.0	**14b**	A	3.20	459.1	459.1
7b	B	3.13	240.0	240.0	**14c$_1$**	B	4.64	382.2	382.2
7c	B	4.45	269.0	269.0	**14c$_2$**	B	5.23	553.3	553.2
7d	B	3.67	239.0	239.0	**14c**	B	3.59	453.2	453.2
7e	B	4.59	410.1	410.0	**14d**	B	3.85	467.2	467.2
8	B	4.00	272.9	273.0	**14e**	B	3.18	391.2	391.2
9$_{alkyne}$	B	2.19	169.1[a]	169.2[a]	**14f**	B	3.69	439.2	439.2
9	A	3.60	370.1	370.1	**15**	B	4.52	513.2	513.2
10	A	3.00	388.1	388.1	**16$_1$**	B	3.91	517.3	517.2
11a	B	5.14	327.0	327.0	**16**	B	3.03	417.2	417.2
11b	B	5.12	341.1	341.0	**17**	B	4.35	402.2	402.2
11c	B	4.82	468.2	468.2	**18$_1$**	B	5.04	573.2	573.2
11d	B	4.96	482.2	482.2	**18**	B	3.89	459.1	459.0
12a	B	4.80	345.0	345.0	**19**	B	4.80	331.0	331.0
12b	B	4.55	360.0	360.0	**20**	B	5.13	418.1	418.0
12c	B	4.69	401.1[b]	401.0[b]	**21$_1$**	B	4.33	388.1	388.2
12d	B	4.23	399.1[a]	399.2[a]	**21$_2$**	B	5.00	559.2	559.2
13a	B	5.33	408.1	408.0	**21**	B	3.48	459.2	459.2
13b	B	5.38	422.2	422.1	**23$_1$**	B	1.38	221.0	221.0
13c	B	4.93	559.2	559.2	**23$_2$**	B	3.06	254.9	255.0
13d	B	5.48	412.2	412.2	**23**	B	4.39	365.0	364.9
13e	B	4.82	581.3	581.2	**24**	B	4.77	345.0	345.0
13f	B	4.43	491.2	491.2	**25**	B	3.80	402.1	402.1
13g	B	5.08	539.3	539.2	**26$_1$**	B	4.86	573.2	573.2
14a$_1$	B	4.22	336.1[a]	336.2[a]	**26$_2$**	B	3.54	473.2	473.2
14a$_2$	B	4.92	563.3	563.2	**26**	B	3.47	459.2	459.0
14a	B	2.47	349.2	349.2	a: [m-tBu]/z; b: [m-Boc]/z				

- NMR spectra:

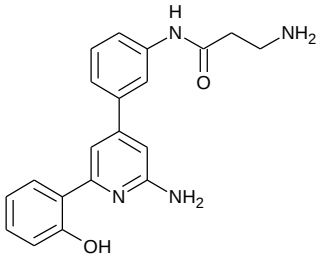
3-amino-N-(3-(2-amino-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)propanamide 14a :



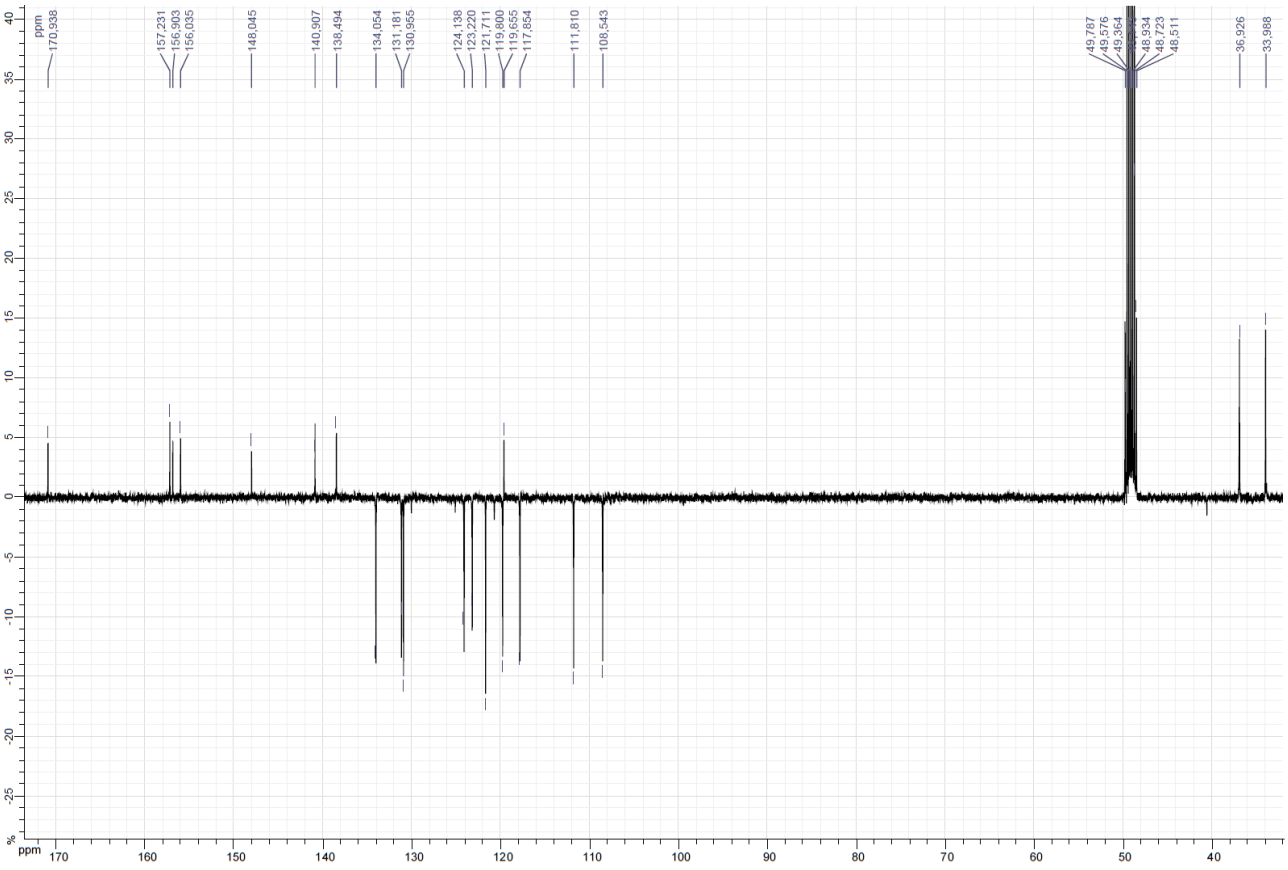
H-NMR (MeOD) :



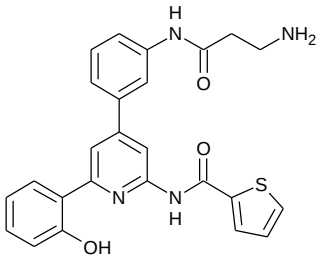
3-amino-N-(3-(2-amino-6-(2-hydroxyphenyl)pyridin-4-yl)phenyl)propanamide 14a :



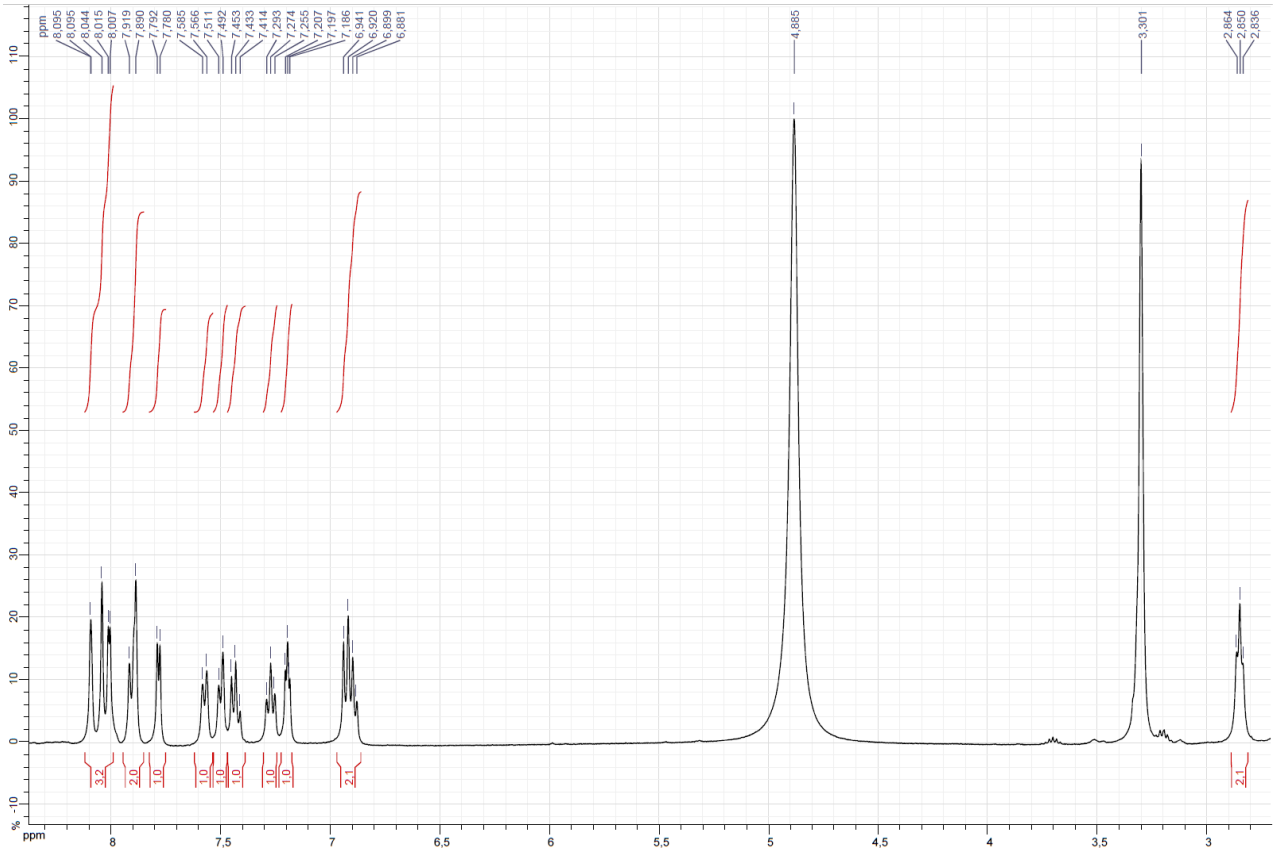
^{13}C-NMR (MeOD) :



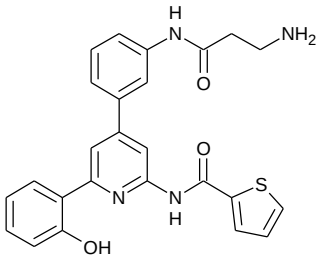
N-{4-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 14b:



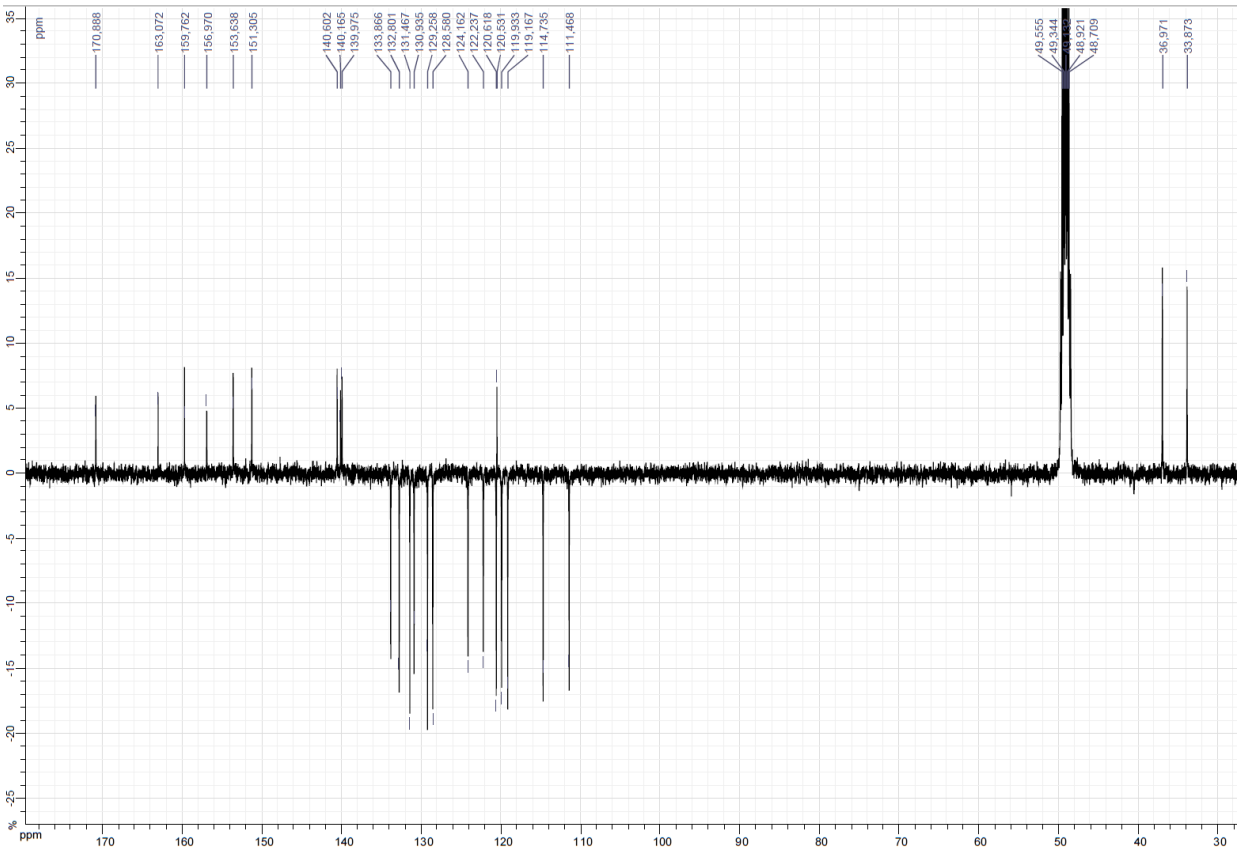
H-NMR (MeOD) :



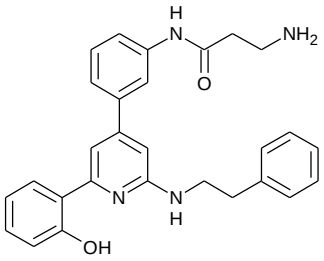
N-{4-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 14b:



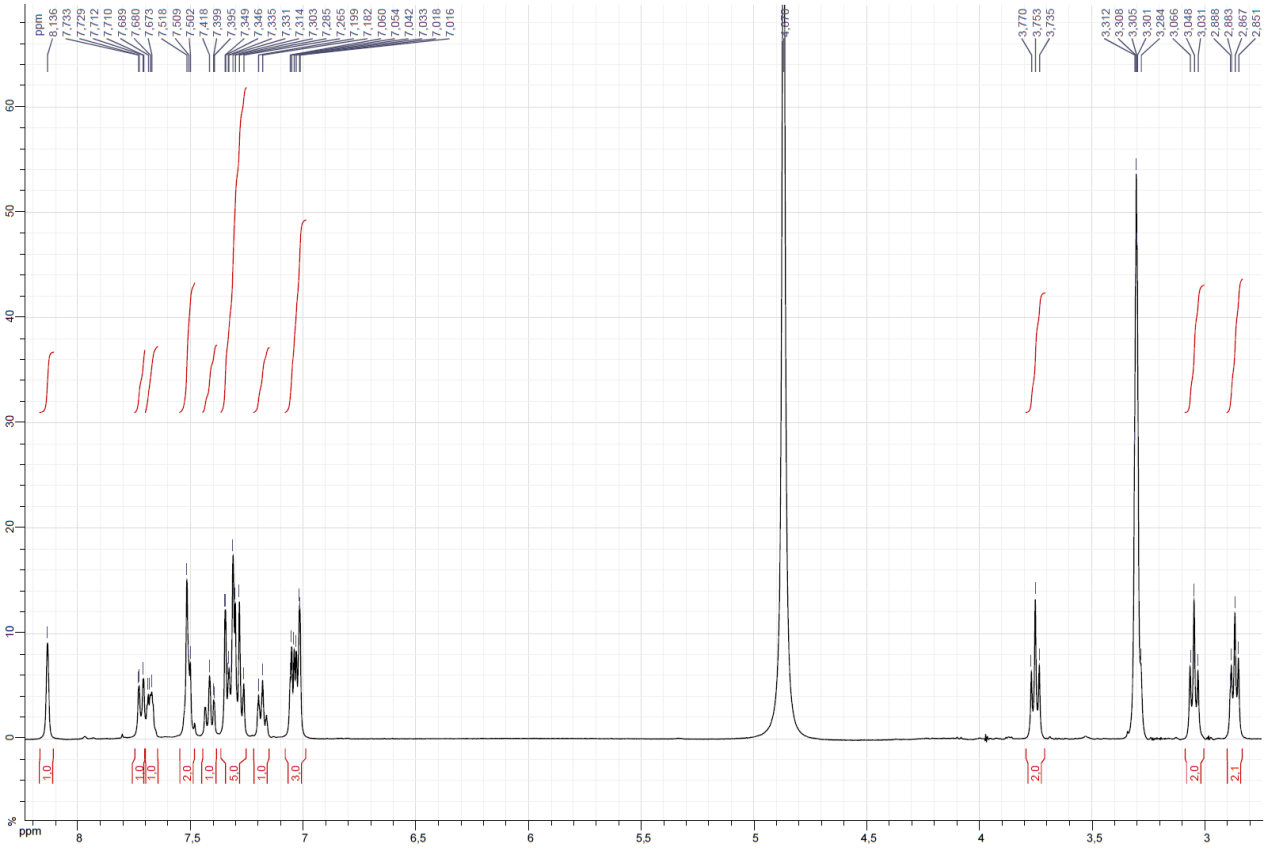
^{13}C-NMR (MeOD) :



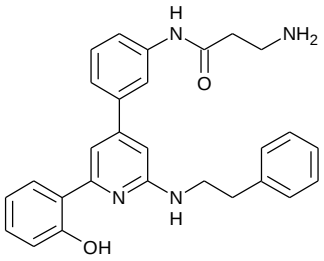
3-amino-N-{3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl}propanamide 14c :



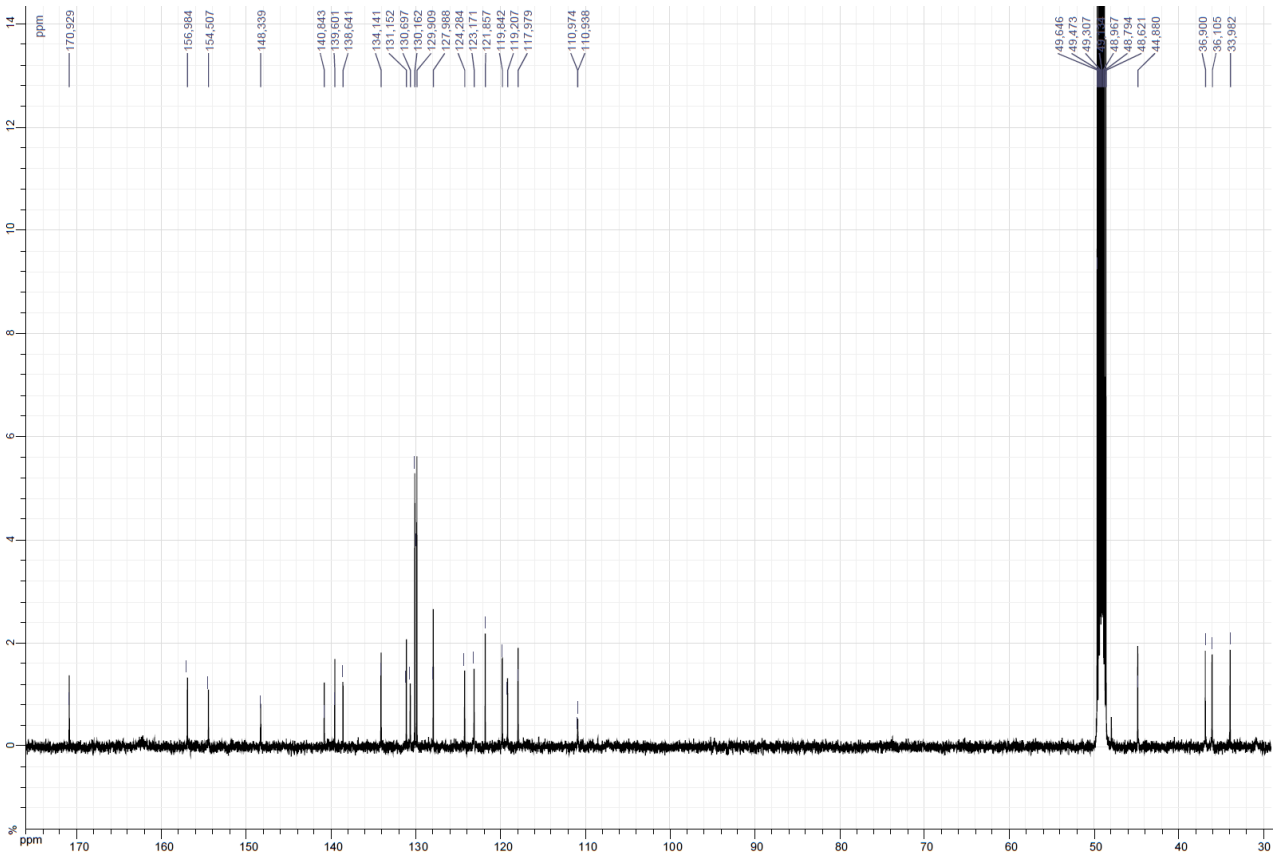
H-NMR (MeOD) :



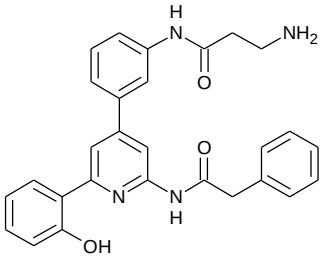
3-amino-N-{3-[2-(2-hydroxyphenyl)-6-[(2-phenylethyl)amino]pyridin-4-yl]phenyl}propanamide 14c :



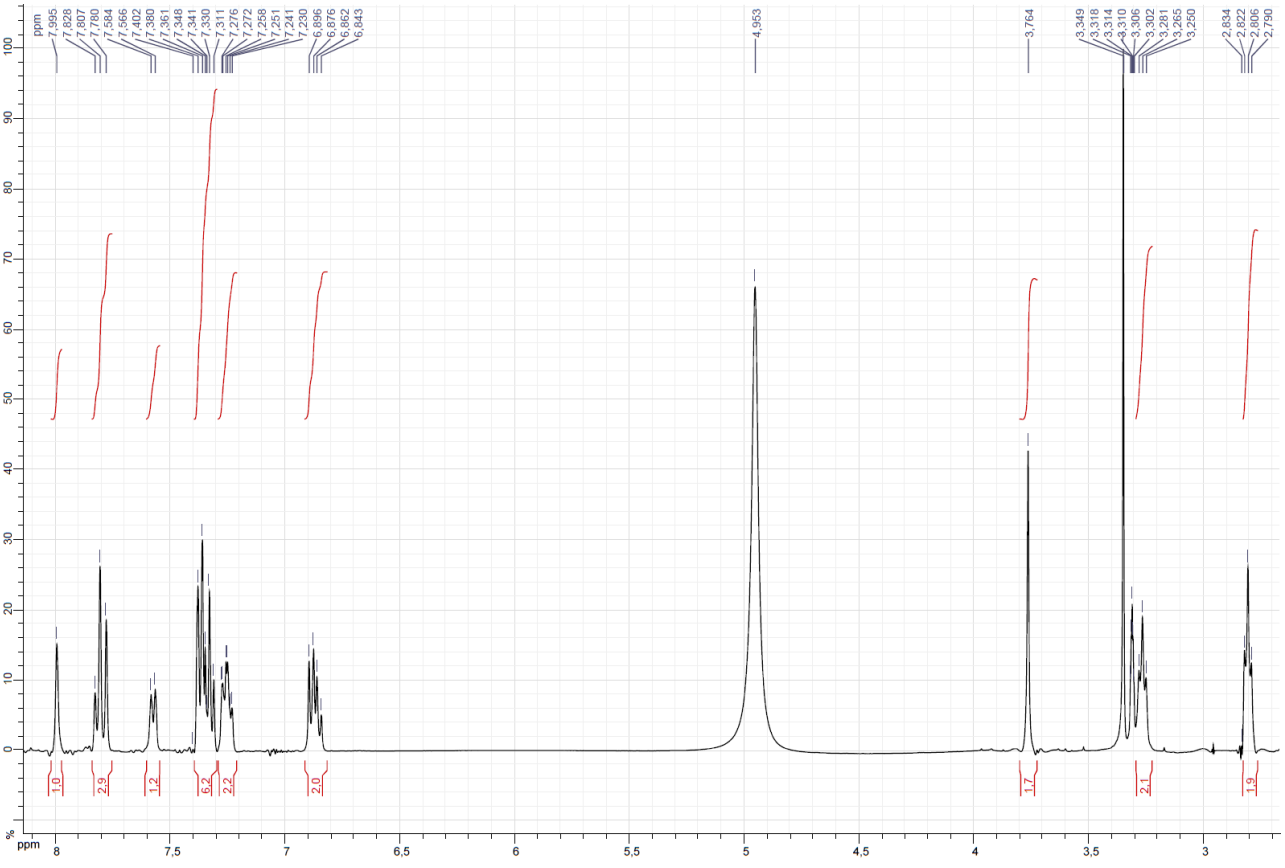
^{13}C-NMR (MeOD) :



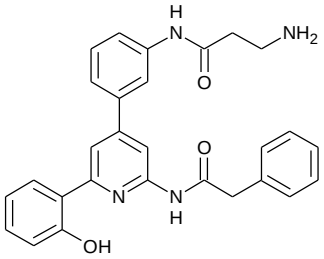
3-amino-N-{3-[2-(2-hydroxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl]phenyl}propanamide 14d:



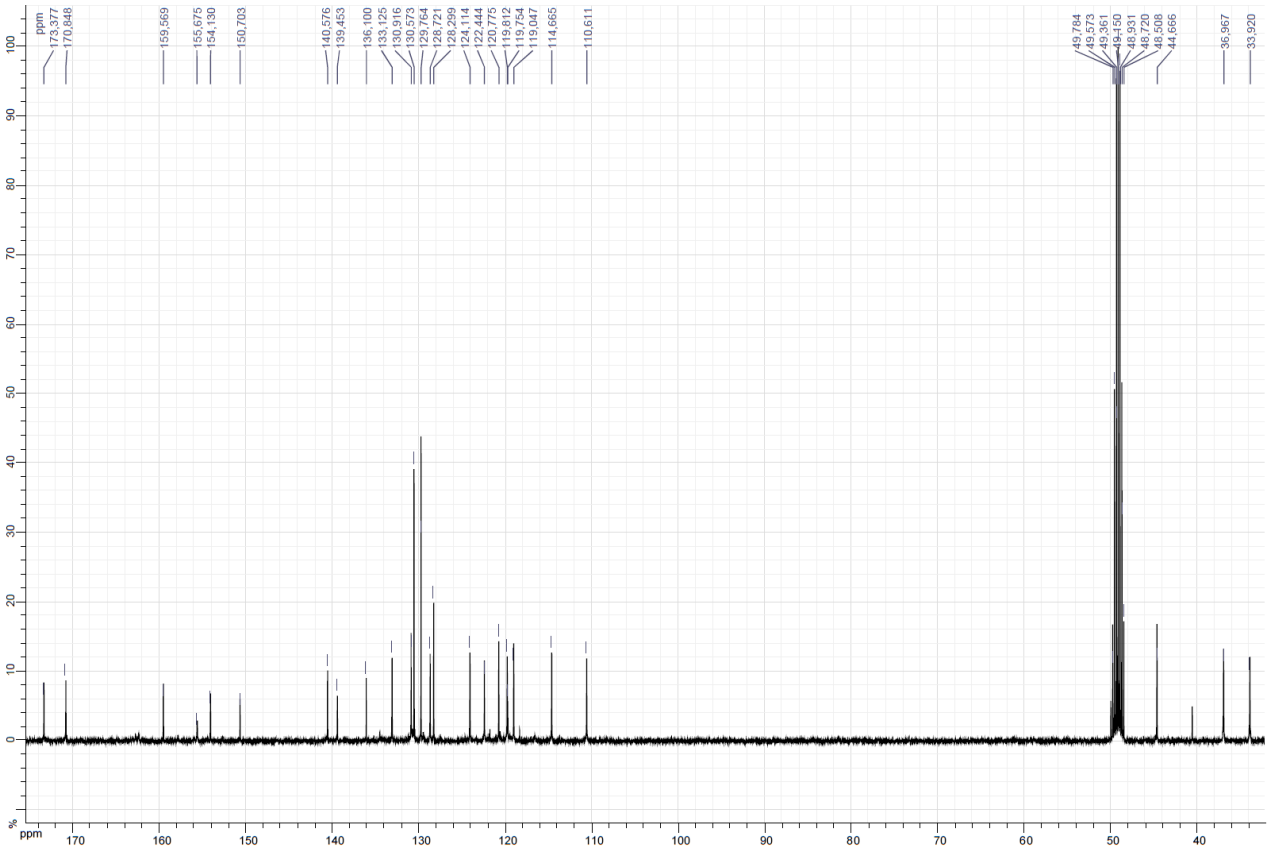
H-NMR (MeOD) :



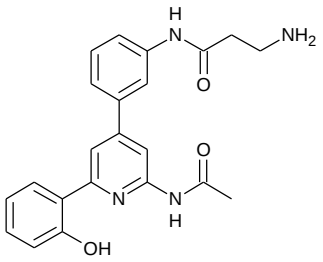
3-amino-N-{3-[2-(2-hydroxyphenyl)-6-(2-phenylacetamido)pyridin-4-yl]phenyl}propanamide 14d:



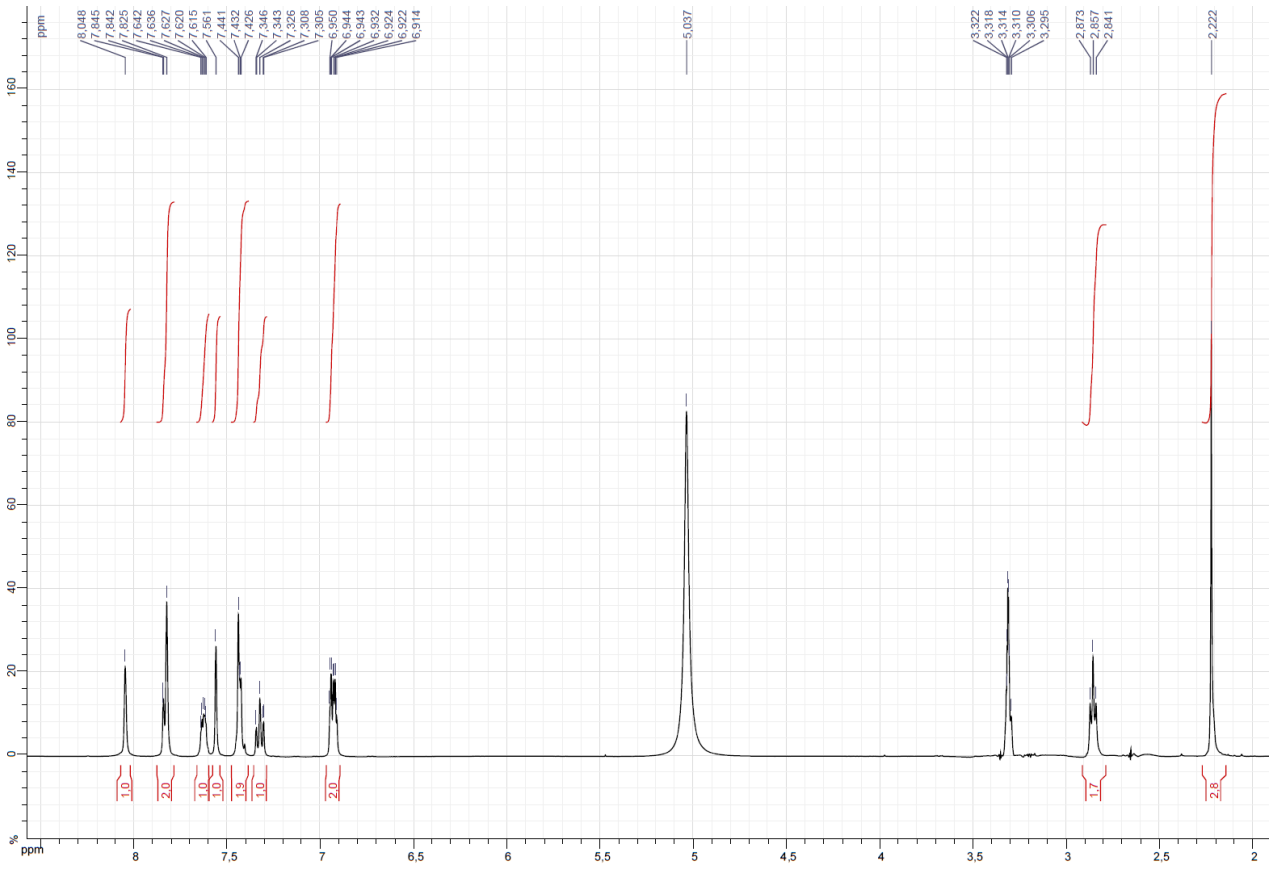
^{13}C-NMR (MeOD) :



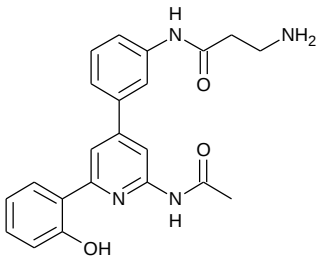
3-amino-N-{3-[2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide 14e:



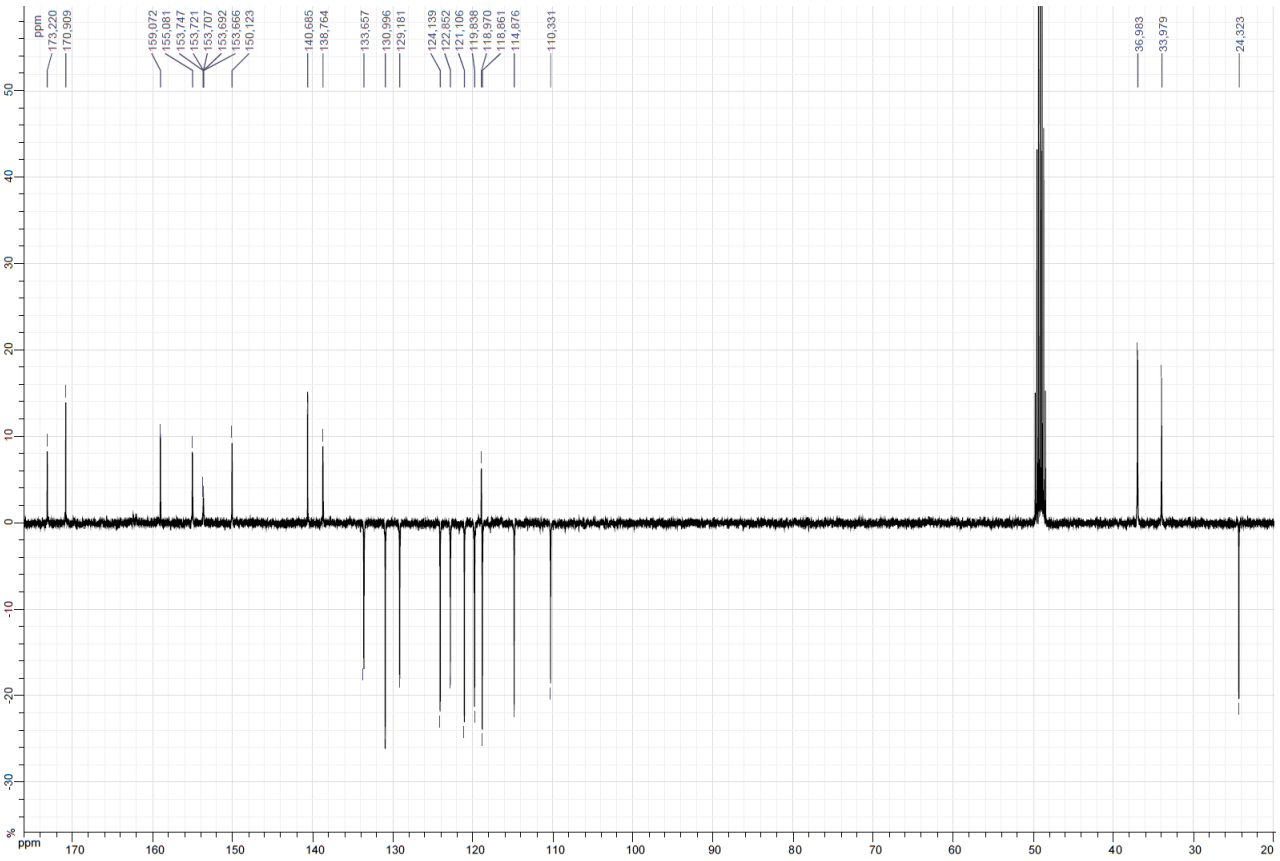
H-NMR (MeOD) :



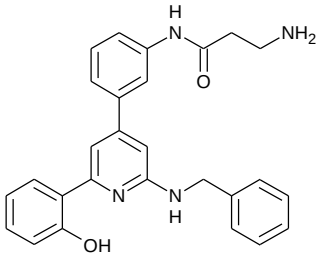
3-amino-N-{3-[2-acetamido-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide 14e:



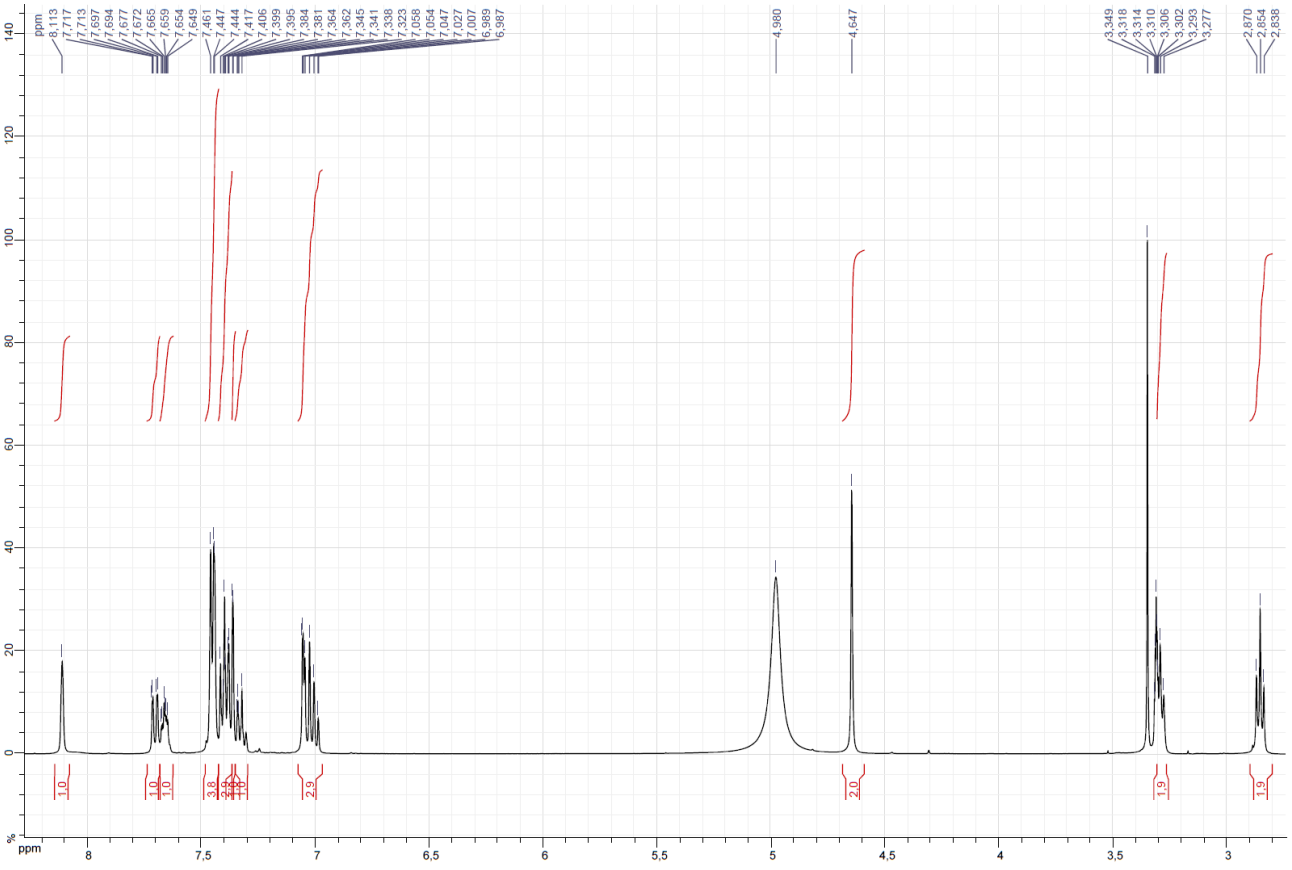
^{13}C-NMR (MeOD) :



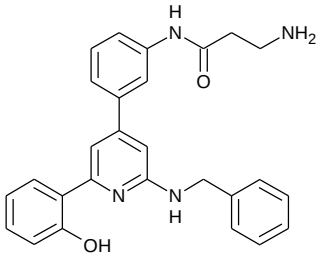
3-amino-N-{3-[2-(benzylamino)-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide 14f:



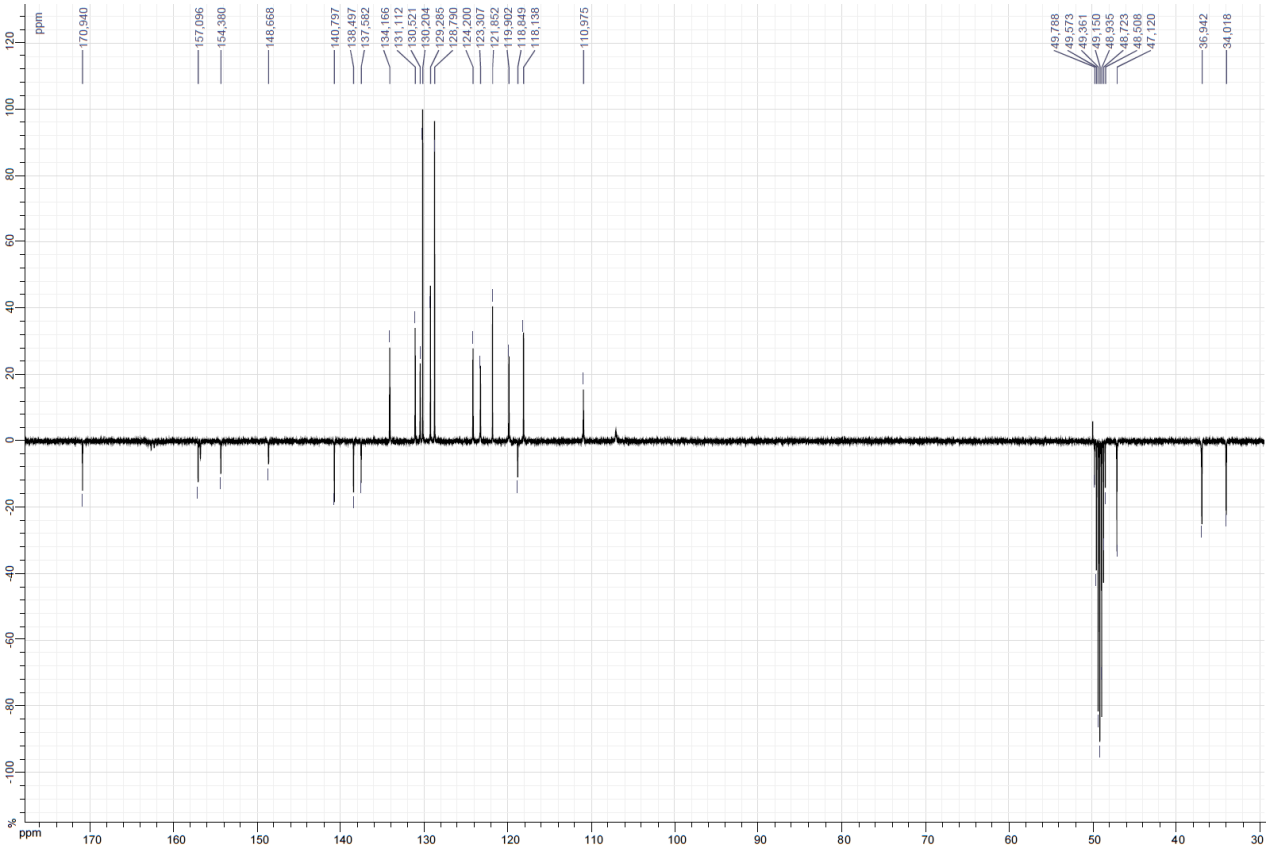
H-NMR (MeOD) :



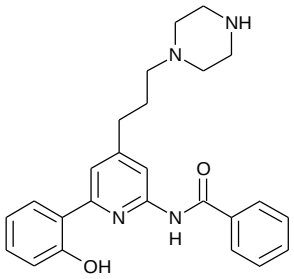
3-amino-N-{3-[2-(benzylamino)-6-(2-hydroxyphenyl)pyridin-4-yl]phenyl}propanamide 14f:



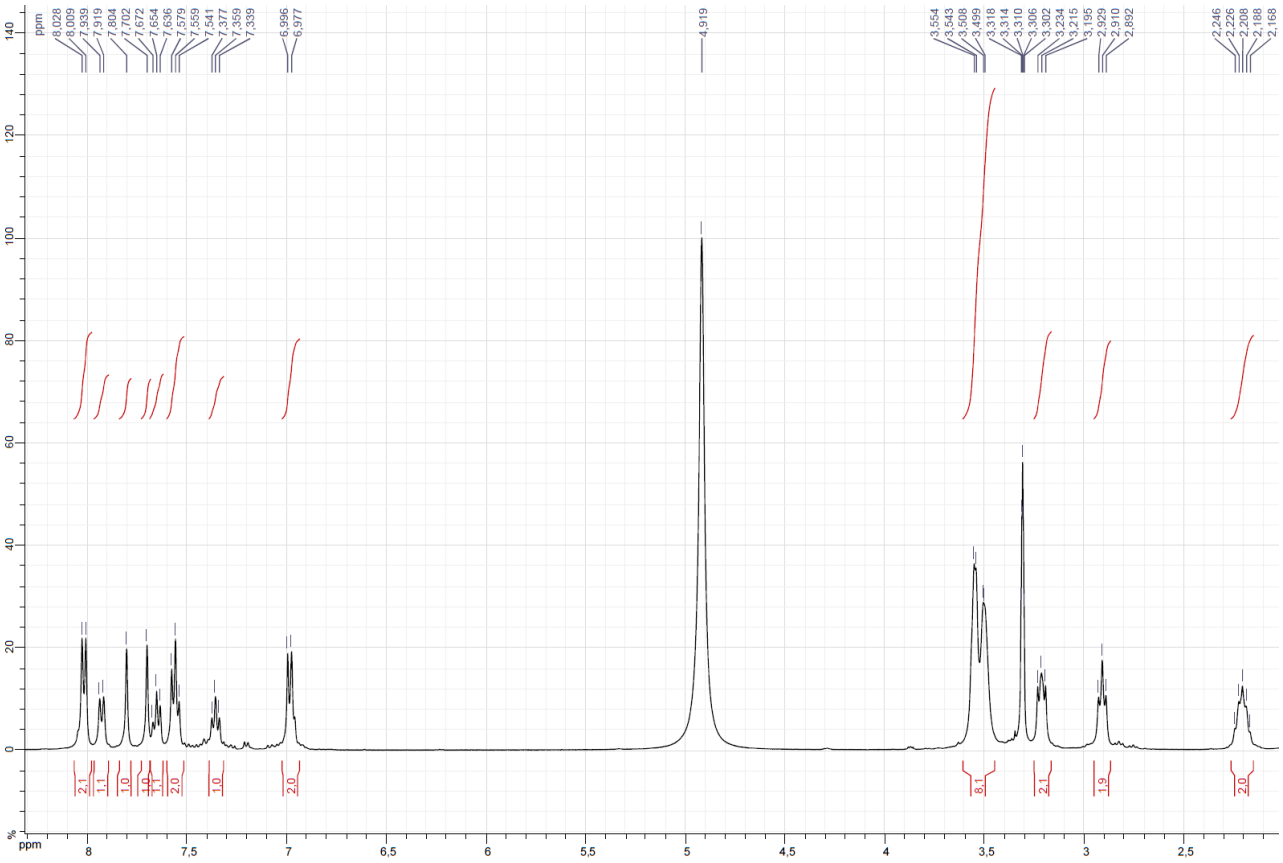
^{13}C-NMR (MeOD) :



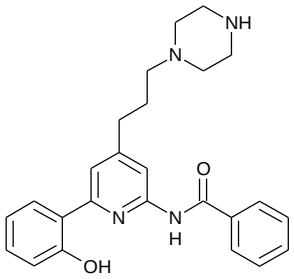
N-[6-(2-hydroxyphenyl)-4-[3-(piperazin-1-yl)propyl]pyridin-2-yl]benzamide 16:



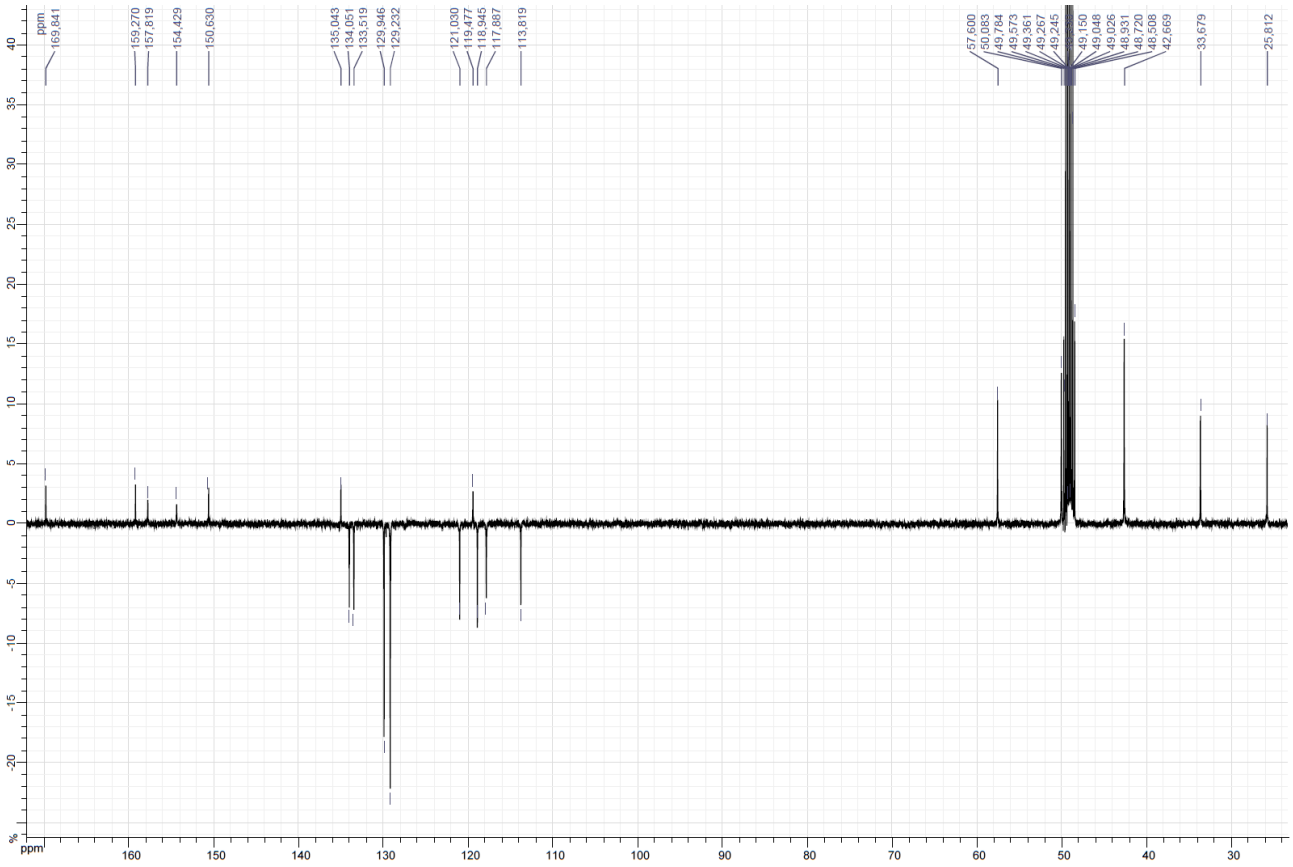
H-NMR (MeOD) :



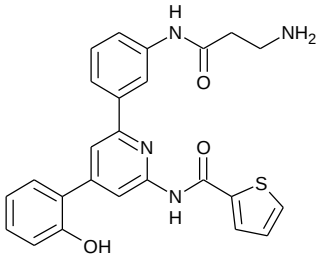
N-[6-(2-hydroxyphenyl)-4-[3-(piperazin-1-yl)propyl]pyridin-2-yl]benzamide 16:



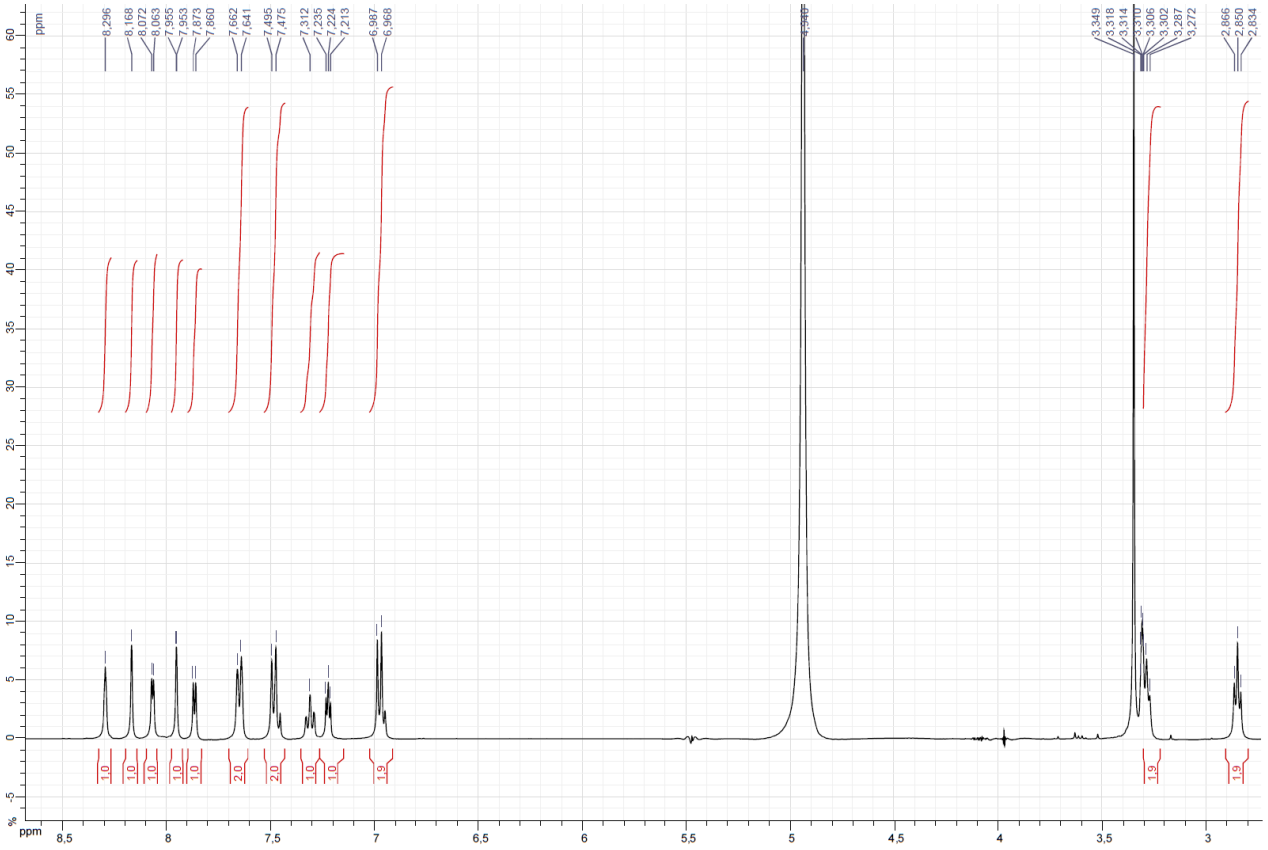
^{13}C-NMR (MeOD) :



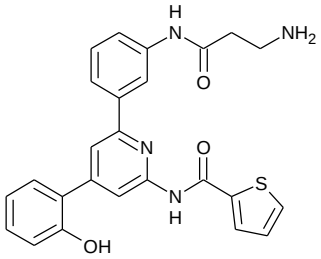
N-{6-[3-(3-aminopropanamido)phenyl]-4-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 18:



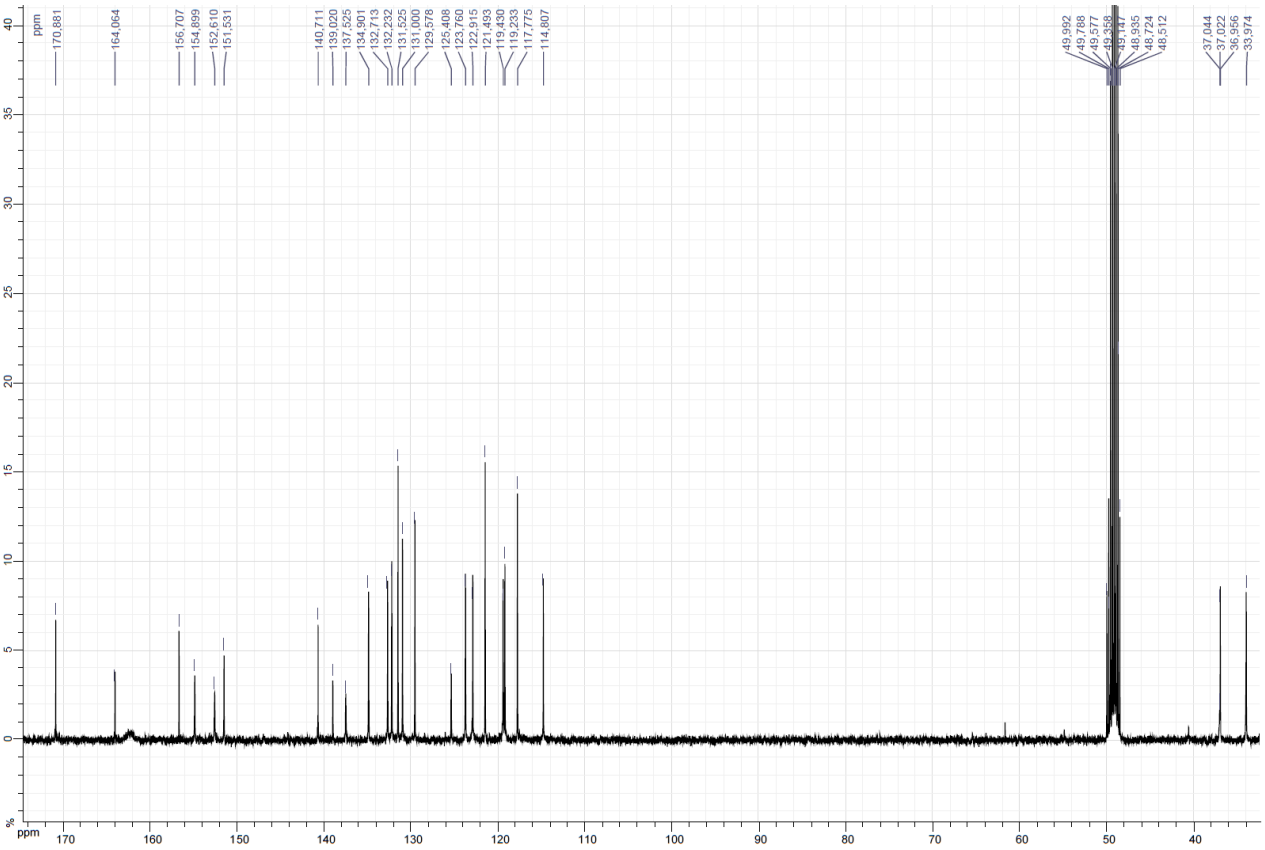
H-NMR (MeOD) :



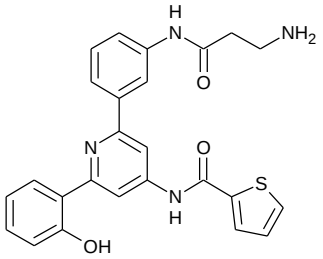
N-{6-[3-(3-aminopropanamido)phenyl]-4-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 18:



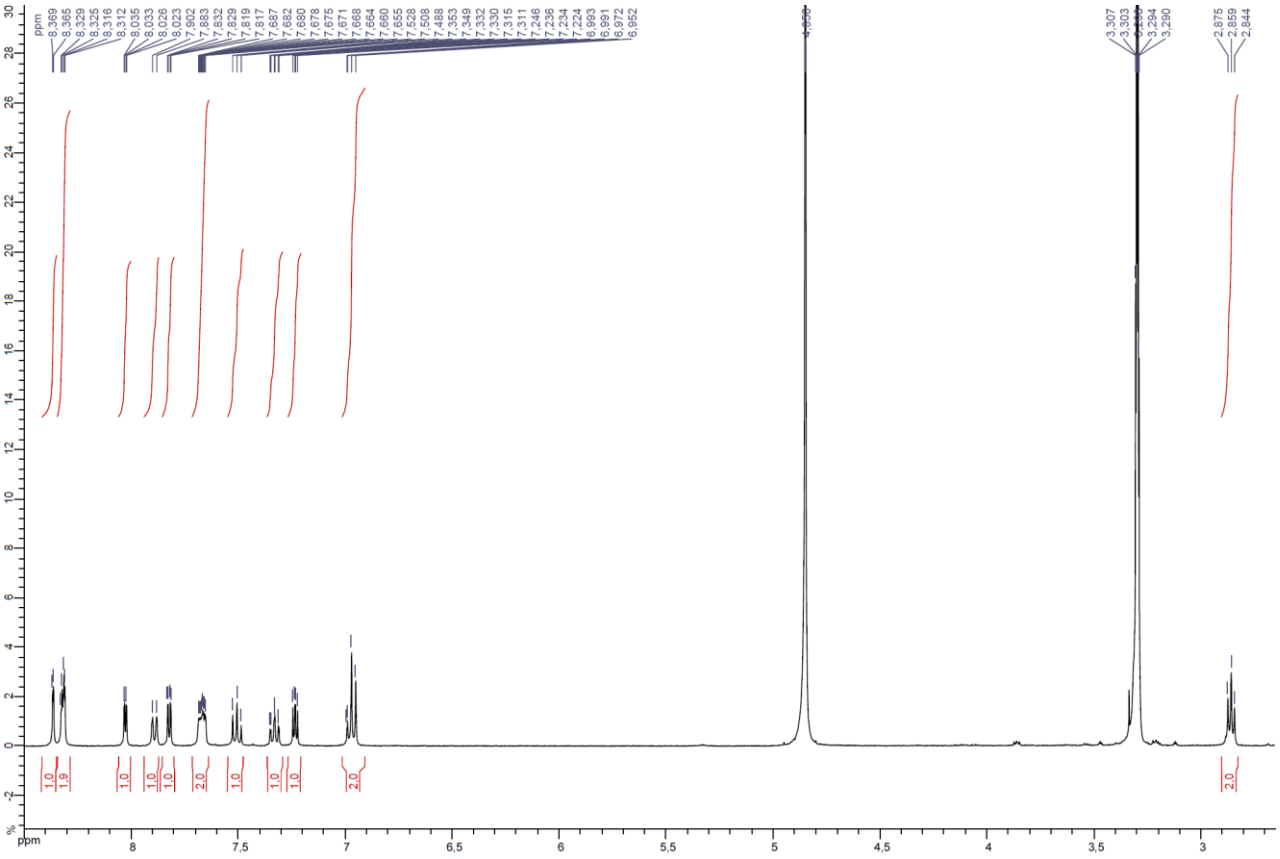
^{13}C-NMR (MeOD) :



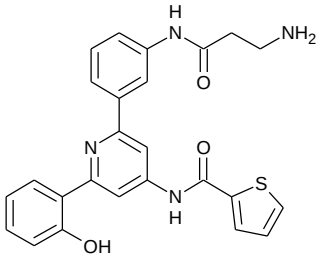
N-{2-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-4-yl}thiophene-2-carboxamide 21:



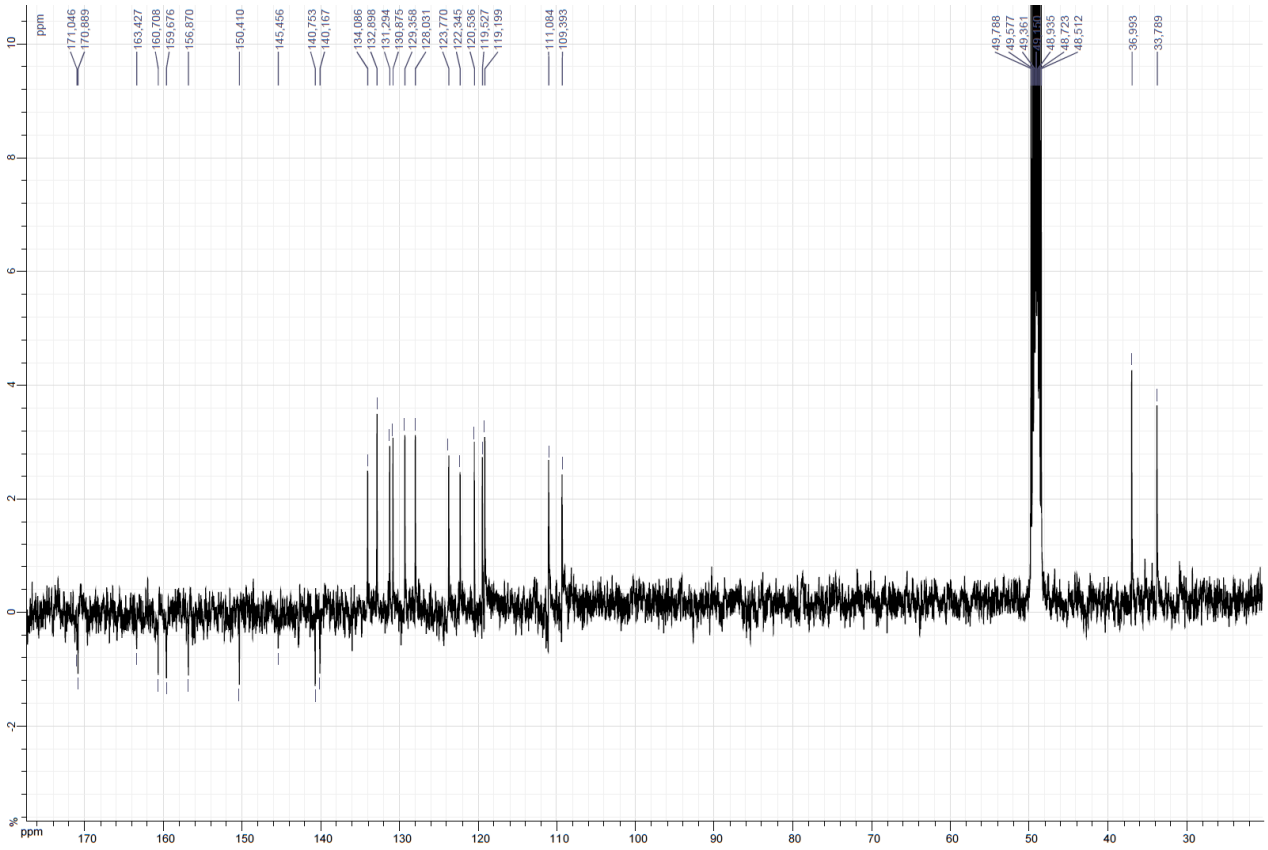
H-NMR (MeOD) :



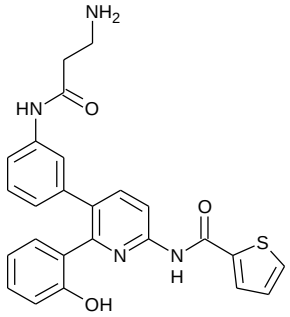
N-{2-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-4-yl}thiophene-2-carboxamide 21:



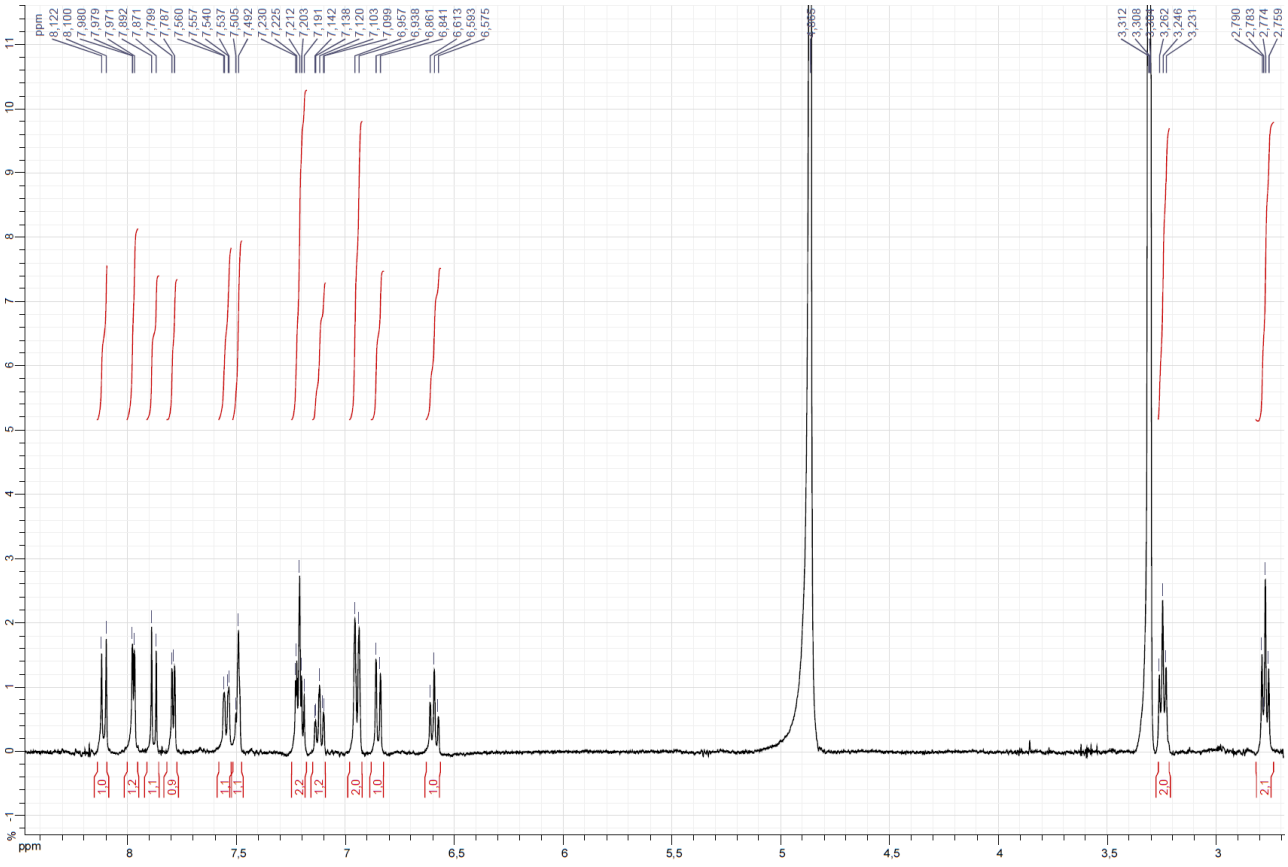
^{13}C-NMR (MeOD) :



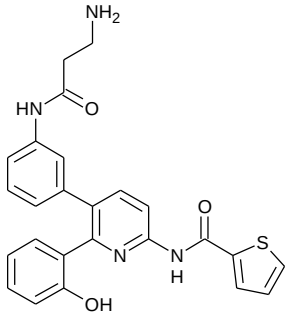
N-{5-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 26:



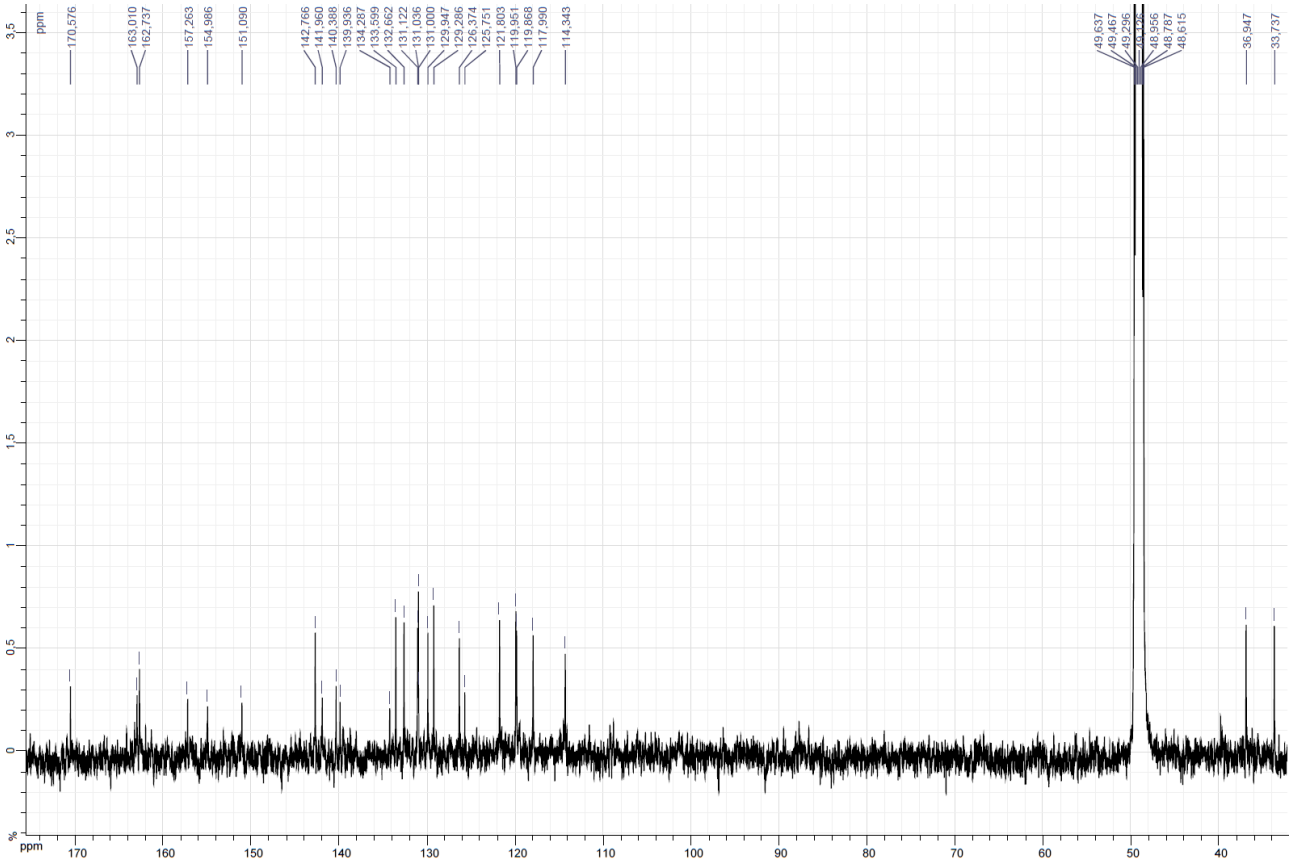
H-NMR (MeOD) :



N-{5-[3-(3-aminopropanamido)phenyl]-6-(2-hydroxyphenyl)pyridin-2-yl}thiophene-2-carboxamide 26:



^{13}C-NMR (MeOD) :



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 eptitope (Guan et al., 1992). The resulting contruct (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 $MgCL_2$, 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 $MgCL_2$, 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 $MgCl_2$, EDTA 1mM, 0.5% bovine serum albumin, 0.02 nM [^{125}I]-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 where then dryied 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).