Supporting Information

Modulation of Peripheral Serotonin Level by Novel Tryptophan Hydroxylase Inhibitors for the Potential Treatment of Functional Gastrointestinal Disorders

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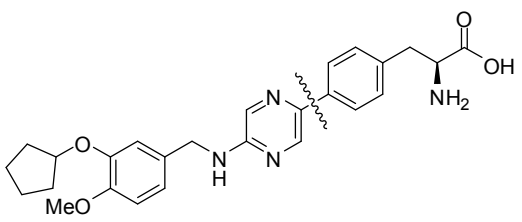
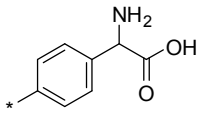
Contents:

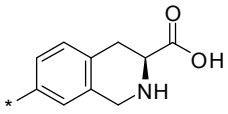
I. Compound 11 – 15 and their in-vitro potencies.



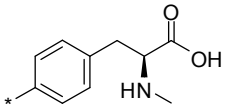
Compound 6h
TPH1 IC50 = 0.045 μM



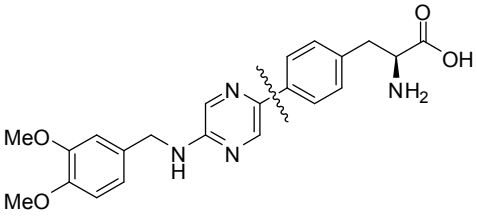
Compound 11
TPH1 IC50 > 50 μM



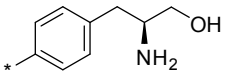
Compound 12
TPH1 CI50 = 5.1 μM



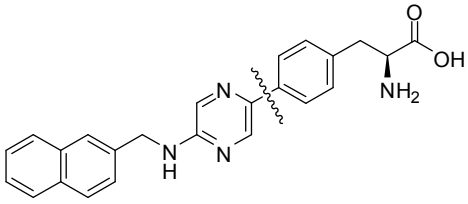
Compound 13
TPH1 IC50 = 2.9 μM



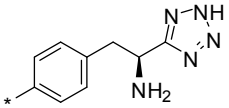
Compound 6j
TPH1 IC50 = 0.069 μM



Compound 14
TPH1 IC50 > 50 μM



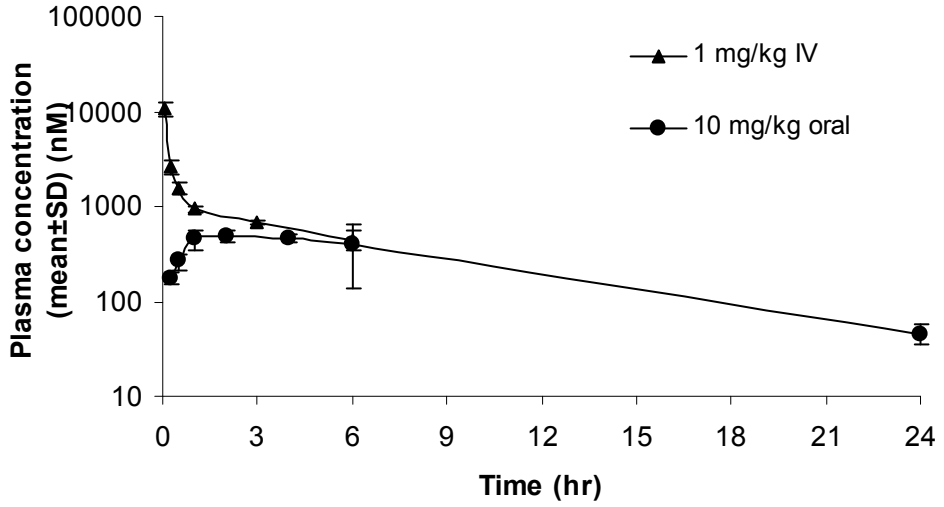
Compound 6g
TPH1 IC50 = 0.013 μM



Compound 15
TPH1 IC50 > 50 μM

II: In-vivo Mouse PK data of compound 21

Compound 21 was dosed to C57 albino mice at 1 mg/kg IV or 10 mg/kg PO to assess its *in-vivo* pharmacokinetic properties. Following intravenous injection, LP-533401 plasma concentration decreased in a bi-exponential fashion. The compound showed a low plasma clearance (3.33±0.56 ml/min/kg) and a small volume of distribution (0.73±0.07 L/kg). After oral administration, compound 21 was slowly absorbed. C_{max} (641±172 nM) appeared at 3.25±2.20 hours post-dosing. Overall oral absorption is poor with a low oral bioavailability (7.6±1.6%). The compound level in the brain (<7 nM) is negligible following oral administration, indicating no penetration of the blood-brain barrier.



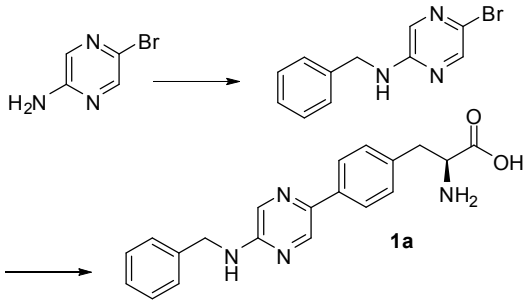
	1 mg/kg IV	10 mg/kg PO	Brain exposure		
			2hr	6hr	24hr
CL (ml/min/kg)	3.33±0.56	-	-	-	-
Vss (L/kg)	0.73±0.07	-	-	-	-
Half life (hr)	3.26±0.56	5.98±0.60	-	-	-
T_{max} (hr)	-	3.25±2.2	-	-	-
C_{max} (nM)	-	641±172	-	-	-
$AUC_{0\text{-}6hr}$ (hr*nM)	6200±1259	-	-	-	-
$AUC_{0\text{-}24hr}$ (hr*nM)	-	6087±1380	-	-	-
$AUC_{0\text{-}\infty}$ (hr*nM)	8543±1541	6497±1426	-	-	-
%F	-	7.6±1.7	-	-	-
Brain concentration (nM)	-	-	6.05±2.70	6.15±2.90	BLLOQ
Ratio of brain-to-plasma	-	-	0.01±0.01	0.01±0.01	-

BLLOQ: below the low limit of quantitation (0.38nM)

III: Experimental

Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Reactions involving air- or moisture-sensitive reagents were run under nitrogen atmosphere. Flash column chromatography was carried out using pre-packed silica gel column from Biotage or ISCO. ^{1}H NMR spectra were collected on Bruker ARX300, DRX400 or DPX400, or Varian Mercury 400 MHz NMR Spectrometers. Values in ppm relative to tetramethylsilane were given. Analytical HPLC spectra were collected on Shimadzu HPLC system equipped with an auto-sampler and a UV detector (220 and 254 nm). Mass spectra were obtained on Waters ZQ or ZMD LCMS system equipped with an auto-sampler, an ELSD detector, a UV detector (220 and 254 nm) and a Mass detector. The elemental analysis was done by Robertson Microlit Laboratory, Madison, NJ. High Resolution Mass Spectra were done by M-Scan Inc., West Chester, PA.

1, Synthesis of (S)-2-amino-3-(4-(5-(benzylamino)pyrazin-2-yl)phenyl)propanoic acid (1a).

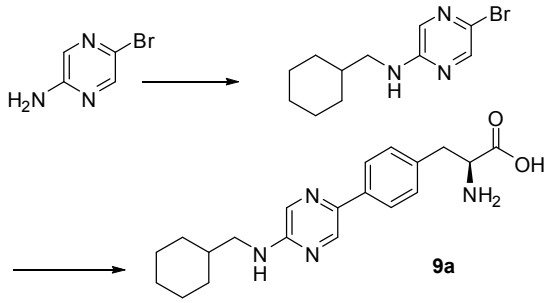


N-benzyl-5-bromopyrazin-2-amine. Benzaldehyde (122 mg, 1.15 mmol), 2-amino-5-bromopyrazine (200 mg, 1.15 mmol), borane trimethylamine complex (126 mg, 1.73 mmol) and glacial acetic acid (137 mg, 2.29 mmol) were added to anhydrous methanol (10 mL). The mixture was stirred at room temperature for 12h. Solvent was removed on the rotavap under reduced pressure. The resulting residue was diluted with ethyl acetate, washed with water, brine, dried (Na_2SO_4) and then filtered. The filtrate was concentrated to afford 300 mg of titled crude compound which was directly used in the following step.

(S)-2-amino-3-(4-(5-(benzylamino)pyrazin-2-yl)phenyl)propanoic acid (1a).

N-benzyl-5-bromopyrazin-2-amine (38 mg, 0.14 mmol), 4-borono-L-phenylalanine (30 mg, 0.14 mmol), dichlorobis(triphenylphosphine)palladium (2 mg, 0.02 mmol), and Na_2CO_3 (31 mg, 0.288 mmol) were added to a mixture of acetonitrile (2 mL) and water (2 mL) in a microwave vial. Vial was sealed and irradiated in a microwave reactor at 150 ^oC for 6 min. Reaction mixture was cooled to ambient temperature, filtered and purified by reverse phase preparative HPLC using MeOH/H_2O/TFA as the solvent system. Pure fractions were combined and concentrated, suspended in water (5 mL), frozen and lyophilized to afford 33 mg of **1a** as TFA salt. ^1H NMR (400 MHz, CD_3OD): δ 8.41 (d, *J* = 1.60 Hz, 1 H), 8.00 (d, *J* = 1.60 Hz, 1 H), 7.84 (m, 2 H), 7.29 - 7.39 (m, 6 H), 7.21 - 7.27 (m, 1 H), 4.59 (s, 2 H), 4.24 (dd, *J* = 7.96, 0.10 Hz, 1 H), 3.38-3.18 (m, 2 H); MS (EI) m/z: 349 (M+H). ^{13}C NMR (300 MHz, CD_3OD): δ 171.26, 155.31, 140.84, 140.50, 139.69, 138.09, 135.10, 133.74, 130.93, 129.54, 128.49, 128.14, 127.10, 55.08, 45.68, 37.05 Analysis calculated for $C_{20}H_{20}N_4O_2.2C_2HF_3O_2.0.75H_2O$: C 48.86 H 4.01 N 9.5 found: C 48.61 H 3.77 N 9.45.

2, **Synthesis of (S)-2-amino-3-(4-(5-(cyclohexylmethylamino)pyrazin-2-yl)phenyl) propanoic acid (9a).**

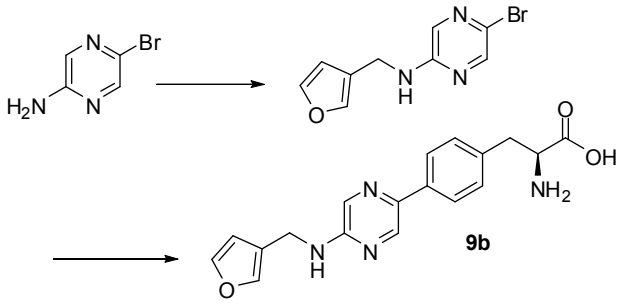


5-Bromo-*N*-(cyclohexylmethyl)pyrazin-2-amine. A mixture of (bromomethyl)cyclohexane (163 mg, 0.92 mmol), 2-amino-5-bromo pyrazine (160 mg, 0.92 mmol) and K_2CO_3 (254 mg, 1.84 mmol) in anhydrous DMF (5 mL) was heated at 100^oC for 12h. The mixture was diluted with ethyl acetate, washed with water, brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash silica gel column chromatography to afford 45 mg of the titled compound (Yield: 18 %). ^1H NMR (400 MHz, DMSO-d6): δ 8.05 (d, *J* = 1.36 Hz, 1H), 7.74 (d, *J* = 1.36 Hz, 1H), 7.32 -7.26 (m,

1H), 3.07 (t, *J* = 6.30 Hz, 2H), 1.76 -1.46 (m, 6H), 1.25 -1.09 (m, 3H), 0.98 -0.86 (m, 2H). MS (EI) m/z: 272 (M+H).

(S)-2-amino-3-(4-(5-(cyclohexylmethylamino)pyrazin-2-yl)phenyl)propanoic acid 9a. Compound **9a** was prepared using 5-bromo-*N*-(cyclohexylmethyl)pyrazin-2-amine (45 mg, 0.17 mmol), 4-borono-L-phenylalanine (35 mg , 0.17 mol), dichlorobis (triphenylphosphine)palladium (2 mg, 0.002 mmol), Na_2CO_3 (31 mg, 0.28 mmol), by following similar procedure described for compound **1a**. **9a (**TFA salt**,** 18 mg, 31 %). ^{1}H NMR (400 MHz, CD_3OD): δ 8.34 (d, *J* = 1.47 Hz, 1 H), 8.05 (d, *J* = 1.47 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.37 (d, *J* = 8 Hz, 2 H), 4.92 (d, *J* = 20, 2 H), 4.28 (dd, *J* = 7.79, 5.40 Hz, 1 H), 3.26-3.39 (m, 2 H), 1.59-1.90 (m, 6 H), 1.20 - 1.35 (m, 3 H), 1.09-1.95 (m, 2 H); MS (EI) m/z: 355 (M+H).

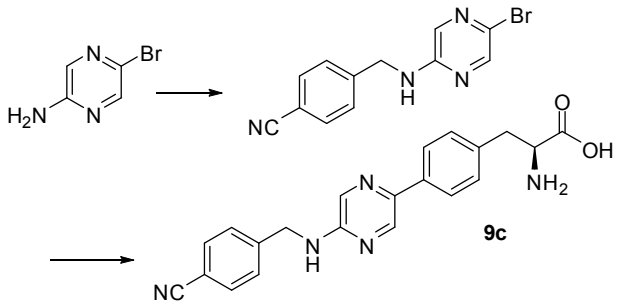
3, **Synthesis of** (S)**-2-amino-3-(4-(5-(furan-3-ylmethyl amino)pyrazin-2-yl) phenyl)propanoic acid (9b).**



5-Bromo-*N*-(furan-3-ylmethyl)pyrazin-2-amine. This compound was prepared from furan-3-carbaldehyde (166 mg, 1.73 mmol), 2-amino-5-bromopyrazine (300 mg, 1.72 mmol), borane trimethylamine complex (189 mg, 2.58 mmol) and glacial acetic acid (103.2 mg, 3.44 mmol) by following similar procedure used for the preparation of **1a.** Crude product was purified by silica gel column chromatography using ethyl acetate (10-30 %) in hexanes as eluent to afford 80 mg (18 %) of the titled product. ^{1}H NMR (400 MHz, CD_3OD): δ 8.06 (d, *J* = 1.37 Hz, 1H), 7.71 (d, *J* = 1.40 Hz, 1H), 7.49 -7.47 (m, 1H), 7.45 -7.44 (m, 1H), 6.44 -6.43 (m, 1H), 4.36 (s, 2H). MS (EI) m/z: 256 (M+H).

(S)-2-amino-3-(4-(5-(furan-3-ylmethyl amino)pyrazin-2-yl) phenyl)propanoic acid (9b). Compound **9b** was prepared using 5-bromo-*N*-(furan-3-ylmethyl)pyrazin-2-amine (36 mg, 0.14 mmol), 4-borono-L-phenylalanine (30 mg, 0.14 mol), dichlorobis(triphenylphosphine)palladium (2 mg, 0.02 mmol), and Na_2CO_3 (31 mg, 0.288 mmol), by following similar procedure described for the synthesis of **1a**. **9b (**TFA salt**,** 20 mg, 42%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.44 (d, *J* = 4 Hz, 1H), 8.05 (s, 1H), 7.86 (d, *J* = 8 Hz, 2H), 7.50 (dd, *J* = 0.59, 0.15 Hz, 1 H), 7.45 (d, *J* = 4 Hz, 1 H), 7.37 (d, *J* = 8.21 Hz, 2 H), 6.46 (s, 1H), 4.43 (s, 2H), 4.28 (q, *J* = 4 Hz, 1H), 3.15-3.40 (m, 2H); MS (EI) m/z: 339 (M+H). Analysis calculated for $C_{18}H_{18}N_4O_3.2C_2HF_3O_2.1.6H_2O$: C 44.39 H 3.93 N 9.41 Found : C 44.09 H 3.6 N 9.3

4, Synthesis of (S)-2-amino-3-(4-(5-(4-cyanobenzylamino)pyrazin-2-yl)phenyl) propanoic acid (9c).

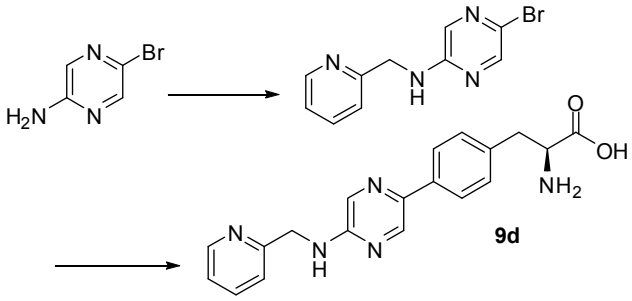


4-((5-Bromopyrazin-2-ylaminomethyl)benzonitrile. 4-formyl benzonitrile (151 mg, 1.15 mmol), 2-amino-5-bromopyrazine (200 mg, 1.15 mmol), sodium triacetoxy borohydride (366 mg, 1.72 mmol) and glacial acetic acid (207 mg, 3.45 mmol) were added to dichloromethane (15 mL). The mixture was stirred at room temperature for 12h. The reaction mixture was then diluted with dichloromethane (15 mL), washed with 1N NaOH, water, brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate) to afford the titled compound (355 mg). ^{1}H NMR (400 MHz, DMSO-d6): δ 8.08 (d, *J* = 1.37 Hz, 1H), 7.94 (t, *J* = 6.10 Hz, 1H), 7.85 (d, *J* = 1.37 Hz, 1H), 7.80 -7.77 (m, 2H), 7.50 (d, *J* = 8.32 Hz, 2H), 4.56 (d, *J* = 6.05 Hz, 2H). MS (EI) m/z: 291 (M+H).

(S)-2-amino-3-(4-(5-(4-cyanobenzylamino)pyrazin-2-yl)phenyl) propanoic acid (9c). Compound **9c** was prepared using 4-((5-bromopyrazin-2-

ylamino)methyl)benzonitrile (41 mg, 0.14 mmol), 4-borono-L-phenylalanine (30 mg, 0.14 mmol), dichloro bis(triphenylphosphine)palladium (2 mg, 0.02 mmol), and Na_2CO_3 (31 mg, 0.29 mmol) by following similar procedure described for the preparation of **1a**. **9c** (TFA salt, 5 mg, 10 %). ^{1}H NMR (400 MHz, CD_3OD): δ 8.40 (d, *J* = 1.51 Hz, 1 H), 8.04 (d, *J* = 1.51 Hz, 1 H), 7.82 - 7.86 (m, 2 H), 7.68 (dd, *J* = 8.21, 0.34 Hz, 2 H), 7.54 (dd, *J* = 8.23, 0.42 Hz, 2 H), 7.34 - 7.38 (m, 2 H), 4.69 (s, 2 H), 4.18 - 4.23 (m, 1 H), 3.12 - 3.39 (m, 2 H); MS (EI) m/z: 374 (M+H). Analysis calculated for $C_{21}H_{19}N_5O_2.1C_2HF_3O_2.0.2H_2O$: C 56.26 H 4.19 N 14.26 Found: C 56.08 H 4.28 N 14.49.

5, Synthesis of (S)-2-amino-3-(4-(5-(pyridine-2-ylmethylamino)pyrazin-2-yl)phenyl) propanoic acid (9d).

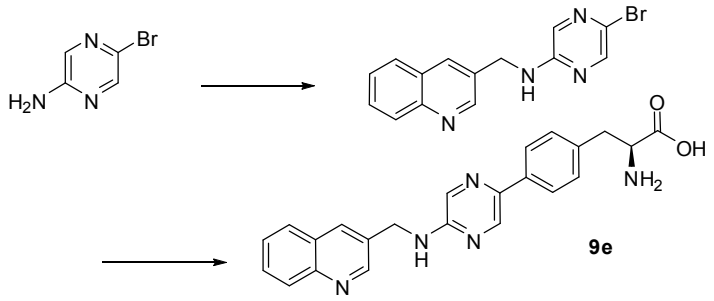


5-Bromo-*N*-(pyridine-2-ylmethyl)pyrazin-2-amine. This compound was prepared from picolinaldehyde (184 mg, 1.72 mmol), 2-amino-5-bromopyrazine (300 mg, 1.72 mmol), borane trimethylamine complex (189 mg, 2.58 mmol) and glacial acetic acid (206 mg, 3.44 mmol) by using similar procedure described for the preparation of **1a**. Crude product was purified by silica gel column chromatography using ethyl acetate (10-40 %) in hexanes as eluent to afford 70 mg (15 %) of the titled product. ^{1}H NMR (400 MHz, CD3OD): δ 8.49 (d, *J* = 4.75 Hz, 1H), 8.02 (d, *J* = 1.36 Hz, 1H), 7.82-7.76 (m, 2H), 7.42 (d, *J* = 7.94 Hz, 1H), 7.33 -7.28 (m, 1H), 4.66 (s, 2H). MS (EI) m/z: 267 (M+H).

(S)-2-amino-3-(4-(5-(pyridine-2-ylmethylamino)pyrazin-2-yl)phenyl)propanoic acid (9d). Compound **9d** was prepared from 5-bromo-*N*-(pyridine-2-ylmethyl)pyrazin-2-amine (38 mg, 0.14 mmol), 4-borono-L-phenylalanine (30 mg , 0.14 mmol), dichloro bis(triphenylphosphine)palladium (2 mg, 0.02 mmol), and Na_2CO_3

(31 mg, 0.288 mmol) by following similar procedure described for the preparation of **1a.** **9d** (TFA salt, 13 mg, 26 %). ^{1}H NMR (400 MHz, CD_3OD): δ 8.65 (m, 1 H), 8.40 (d, *J* = 4.0 Hz, 1 H), 8.30 - 8.35 (m, 1 H), 8.19 (s, 1 H), 7.83 - 7.92 (m, 3 H), 7.73 - 7.78 (m, 1 H), 7.35 - 7.39 (m, 2 H), 4.90 (s, 2 H), 4.24 - 4.29 (m, 1 H), 3.37 - 3.15 (m, 2 H); MS (EI) m/z: 350 (M+H).

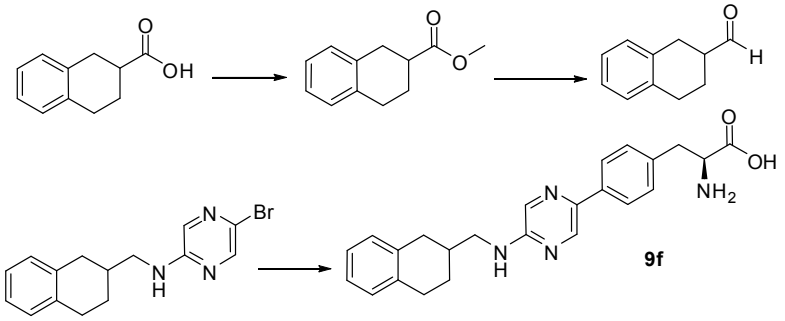
6, **Synthesis of (S)-2-amino-3-(4-{5-[(quinolin-3-ylmethyl)-amino]-pyrazin -2-yl} phenyl)propionic acid (9e).**



5-Bromo-pyrazin-2-yl)-quinolin-3-ylmethyl-amine. This compound was prepared using quinoline-3-carboxaldehyde (0.3 g, 1.91 mmol), 2-amino-5-bromopyrazine (0.28 g, 1.59 mmol), sodium triacetoxy borohydride (0.51g, 2.39 mmol), and acetic acid (0.25 mL), following similar procedure described for the preparation of **9c.** Crude product was purified by silica gel column chromatography using ethyl acetate (10-70 %) in hexanes as eluent to afford 0.18 g of the titled compound. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.99 (d, *J* = 2.14 Hz, 1H), 8.40 (s, 1H), 8.11 (d, *J* = 1.43 Hz, 1H), 8.07-7.98 (m, 3H), 7.89 (d, *J* = 1.46 Hz, 1H), 7.83 -7.78 (m, 1H), 7.69-7.64 (m, 1H), 4.71 (d, *J* = 5.35 Hz, 2H). MS (EI) m/z: 317 (M+H).

(S)-2-Amino-3-(4-{5-[(quinolin-3-ylmethyl)-amino]-pyrazin-2-yl}-phenyl)-propionic acid (9e). Compound **9e** was prepared using (5-bromo-pyrazin-2-yl)-quinolin-3-ylmethyl-amine (60 mg, 0.19 mmol), 4-borono-L-phenylalanine (40 mg, 0.1903 mmol), dichlorobis(triphenylphosphine)palladium (4 mg, 0.0057 mmol), sodium carbonate (40 mg, 0.38 mmol), following a similar procedure used for the preparation of **1a**. **9e** (TFA salt) ^{1}H NMR (300 MHz, CD_3OD): δ 7.67 (s, 1H), 7.46 (s, 1H), 6.87 (s, 1H), 6.7-6.26 (m, 7H), 5.8 (d, 2H, *J* = 7.1 Hz), 2.71 (t, 1H, *J* = 6.2 Hz), 1.75 (m, 3H), 1.61 (m, 1H); MS (EI) m/z: 400 (M+H).

7, Synthesis of (2S)-2-amino-3-(4-(5-((1,2,3,4-tetrahydronaphthalen-2-yl)methyl amino)pyrazin-2-yl)phenyl)propanoic acid (9f).

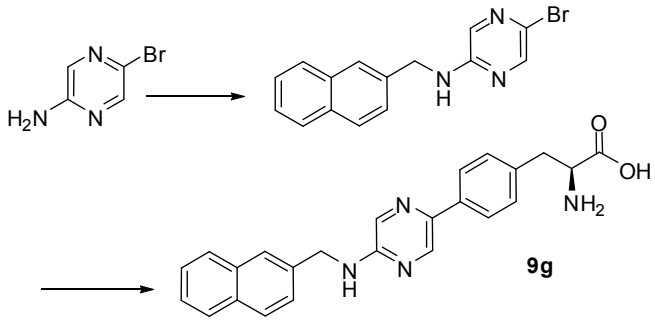


1,2,3,4-Tetrahydronaphthalene-2-carbaldehyde. 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (1.0 g, 5.58 mmol) was treated with thionyl chloride (1.35 g, 11.35 mmol) in methanol (30 mL) at reflux for 4 hours. The mixture was concentrated, dissolved in dichloromethane, washed with aqueous $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The resulting methyl ester was treated with DIBAL-H (6.1 mL, 1.0M) in toluene at -78^o C for 1 hour and quenched at -78^o C with aqueous NH_4Cl solution. The mixture was warmed to room temperature, extracted with dichloromethane, dried over $MgSO_4$ and concentrated. Crude product was purified by silica gel column chromatography using ethyl acetate:hexanes (1: 9) as solvent to afford the titled compound(0.45 g). ^{1}H NMR (400 MHz , $CDCl_3$): δ 9.81 (d, J=1.14, 1H), 7.18-7.08(m, 4H), 3.03-2.97 (m, 2H), 2.92-2.86 (m, 2H), 2.76-2.67 (m, 1H), 2.28-2.19 (m, 1H), 1.86-1.74 (m, 1H)); MS (EI) m/z: 183 (M+Na).

(**5-Bromo-pyrazin-2-yl)-(1,2,3,4-tetrahydro-naphthalen-2-ylmethyl)-amine.** This compound was prepared using 1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (0.44 g, 2.746 mmol), 2-amino-5-bromopyrazine (0.40 g, 2.29 mmol), acetic acid (0.40 mL), sodium triacetoxy borohydride (0.73 g, 3.43 mmol), following a similar procedure described for the preparation of **9c**. Crude compound was purified by silica gel column chromatography using ethyl acetate/hexanes (1:9) as solvent system to give 0.33 g of the titled compound. ^{1}H NMR (400 MHz , $CDCl_3$): δ 8.09 (s, 1H), 7.71 (s, 1H), 7.19-7.04 (m, 4H), 4.83 (s, 1H), 3.38 (d, J=6.62, 2H), 3.01-2.78 (m, 3H), 2.62-2.51 (m, 1H), 2.22-1.83 (m, 2H), 1.59-1.46 (m, 1H); MS (EI) m/z: 322 (M+H).

(2S)-2-amino-3-(4-(5-((1,2,3,4-tetrahydronaphthalen-2-yl)methylamino)pyrazin-2-yl)phenyl)propanoic acid 9f. Compound **9f** was prepared using (5-bromo-pyrazin-2-yl)-(1,2,3,4-tetrahydro-naphthalen-2-ylmethyl)-amine (0.33 g, 1.04 mmol), (S)-2-amino-3-(4-boronophenyl)propanoic acid (0.26 g, 1.24 mmol), dichloro bis(triphenylphosphine)palladium (44 mg, 0.0622 mmol), sodium carbonate (0.24 g, 2.28 mmol), following a similar procedure described for the preparation of **1a**. **9f** (TFA salt, 151 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.36 (s, 1H), 8.12 (s, 1H), 7.86 (d, 2H, *J* = 7.4 Hz), 7.38 (d, 2H, *J* = 8.9 Hz), 7.05 (s, 4H), 4.29 (t, 1H, *J* = 6.4 Hz), 3.42 (d, 1H, *J* = 6.6 Hz), 3.35 (s, 1H), 3.19 (m, 1H), 2.96 (m, 1H), 2.84 (m, 2H), 2.54 (m, 1H), 2.11 (m, 1H), 1.51 (m, 1H). MS (EI) m/z: 403 (M+H).

8, Synthesis of (S)-2-amino-3-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl) phenyl)propanoic acid (9g).

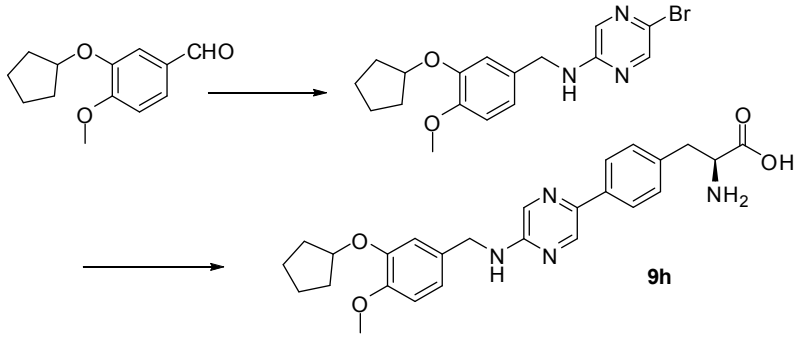


(**5-Bromo-pyrazin-2-yl)-naphthalen-2-ylmethyl-amine.** This compound was prepared using 2-napthaldehyde (3.0 g, 19.21 mmol), 2-amino-5-bromopyrazine (2.79 g, 16.01 mmol), acetic acid (2.5 mL) and sodium triacetoxyborohydride (5.09 g, 24.02 mmol) following a similar procedure described for the preparation of **9c**. Crude product (3.5 g) obtained was partially used in the following step.

(S)-2-amino-3-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)propanoic acid 9g. (5-Bromo-pyrazin-2-yl)-naphthalen-2-ylmethyl-amine (0.4 g, 1.27 mmol), (S)-2-amino-3-(4-boronophenyl)propanoic acid (0.32 g, 1.53 mmol), dichloro bis(triphenylphosphine)palladium (54 mg, 0.076 mmol), sodium carbonate (0.30 g, 2.8 mmol), acetonitrile (10 mL) and water (10 mL) were charged to a microwave vial. Vial was sealed and irradiated in a microwave reactor at 150^o C for 6 minutes. The mixture was cooled to room temperature, concentrated. The residue was taken into 1.0 N

HCl aq., then washed with ether (3x). The acidic aqueous solution was concentrated and dissolved in methanol, filtered. The filtrate was then concentrated. The residue was redissolved in 1.0 N HCl, filtered, and concentrated. The resulting solid was triturated with dichloromethane, and then dried to give the title compound **9g** as HCl salt. ^{1}H NMR (400 MHz,CD_3OD): δ 8.51 (s, 1H), 8.35 (s, 1H), 7.97-7.83 (m, 5H), 7.57-7.47 (m, 4H), 7.43 (d, 2H, *J* = 8.7 Hz), 4.84 (s, 2H), 4.31 (t, 1H), 3.4-3.19 (m, 2H); ^{13}C NMR(400 MHz, CD_3OD): δ 171.15, 149.75, 140.30, 139.32, 136.75, 135.53, 134.94, 134.58, 131.28, 129.91, 128.92, 128.82, 127.69, 127.62, 127.43, 127.38, 126.78, 54.98, 47.03, 37.10. MS (EI) m/z: 399 (M+H); Analysis calculated for $C_{24}H_{25}C_{l3}N_4O_2$: C 56.76 H 4.96 N 11.03 Found: C = 55.81, H = 4.62, N = 10.81

9, Synthesis of (S)-2-amino-3-{4-[5-(3-cyclopentyloxy-4-methoxy- benzyl amino)-pyrazin-2-yl]-phenyl}-propionic acid (9h).

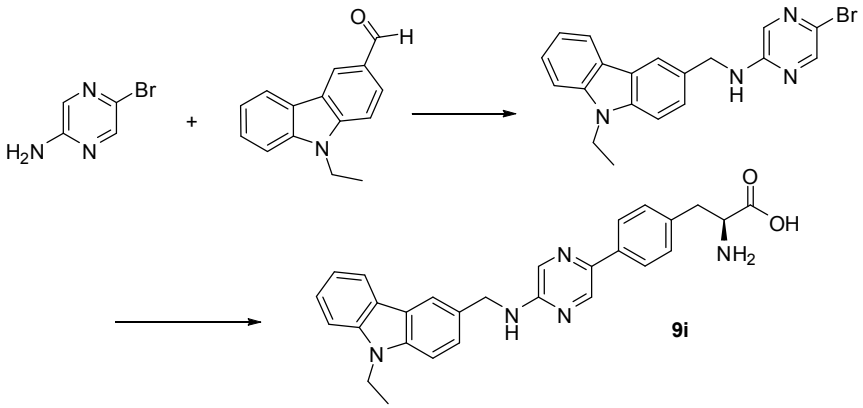


(6-bromo-pyrazin-2-yl)-(3-cyclopentyloxy-4-methoxy-benzyl)amine. This compound was prepared using 3-cyclopentyloxy-4-methoxy-benzaldehyde (417 mg, 1.72 mmol), 2-amino-5-bromo pyrazine (300 mg, 1.72 mmol), sodium triacetoxyborohydride (549 mg, 2.58 mmol) and glacial acetic acid (310 mg, 5.16 mmol), following a similar procedure described for the preparation of **9c**. Crude product was purified by silica gel flash column chromatography (hexanes/ethyl acetate) to afford 400 mg of the titled compound (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.65 (s, 1H), 6.87-6.80 (m, 3H), 5.22 (s, 1H), 4.73 (m, 1H), 4.41 (d, *J* = 6.47 Hz 2H), 3.82 (s, 3H), 1.93-1.76 (m, 6H), 1.64-1.54 (m, 2H). MS (EI) m/z: 380 (M+H).

(S)-2-amino-3-{4-[5-(3-cyclopentyloxy-4-methoxy-benzyamino)-pyrazin-2-yl]

-phenyl }-propionic acid (9h). Compound **9h** was prepared using (6-bromo-pyrazin-2-yl)-(3-cyclopentyloxy-4-methoxy-benzyl)-amine (50 mg, 0.13 mmol), 4-borono-L-phenyl alanine (30 mg, 0.14 mmol), dichlorobis(triphenylphosphine)palladium (5 mg, 0.007 mmol), and Na_2CO_3 (31 mg, 0.29 mmol) by following a similar procedure described for the preparation of **1a. 9h (**TFA salt**,** 12 mg, 20%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.41 (d, *J* = 4 Hz, 1H), 7.99 (s, 1H), 7.83 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 6.0 Hz, 2H), 6.90-6.95 (m, 3H), 4.78 (m, 1H), 4.50 (s, 2H), 4.22-4.26 (m, 1H), 3.79 (s, 3H), 3.12-3.39 (m, 2H), 1.80-1.81 (m, 6H), 1.60 (m, 2H); MS (EI) m/z: 463 (M+H).

10, Synthesis of (S)-2-amino-3-(4-(5-((9-ethyl-9H-carbazol-3-yl)methylamino)pyrazin-2-yl)phenyl)propanoic acid (9i).

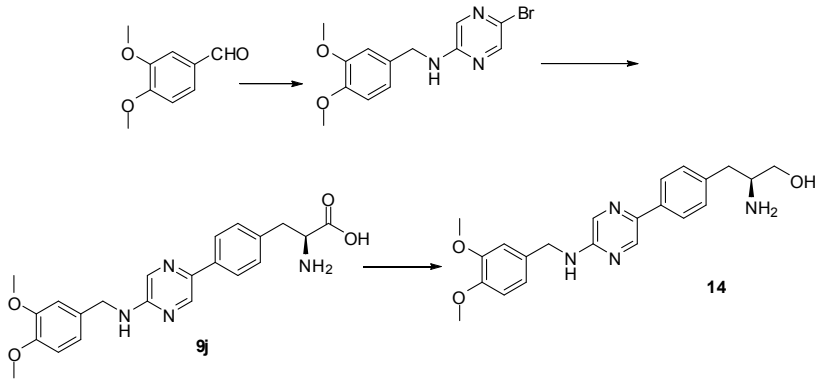


5-bromo-N-((9-ethyl-9H-carbazol-3-yl)methyl)pyrazin-2-amine. This compound was prepared using 2-amino-5-bromopyrazine (900 mg, 5.2 mmol), 9-ethyl-9H-carbazole-carbaldehyde (1.39 g, 6.22 mmol), sodium triacetoxyborohydride (1.65 g, 7.78 mmol) and acetic acid (0.5 mL) following the similar procedure described for the preparation of **9c**. The crude was purified by silica gel column chromatography (hexanes/ethyl acetate) to afford 1.06 g of the titled compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 1H, *J* = 1.3 Hz), 8.09 (m, 2H), 7.73 (d, 1H, *J* = 1.3 Hz)), 7.5-7.39 (m, 4H), 7.25 (m, 1H), 5.02 (br, 1H), 4.70 (d, 2H, *J* = 5.6 Hz), 4.40 (q, 2H, *J* = 7.1Hz); 1.45 (t, 3H, *J* = 7.1 Hz); M+1 = 381 with bromine isotope pattern.

(S)-2-amino-3-(4-(5-((9-ethyl-9H-carbazol-3-yl)methylamino)pyrazin-2-yl)phenyl) propanoic acid 9i. Compound **9i** was prepared using 5-bromo-N-((9-ethyl-

9H-carbazol-3-yl)methyl) pyrazin-2-amine (47 mg, 0.12 mmol), (S)-2-amino-3-(4-borono phenyl) propanoic acid (25 mg, 0.12 mmol), dichloro bis(triphenylphosphine) palladium (4.3 mg, 0.006 mmol), and Na_2CO_3 (0.24 mL, 1M in water), following a similar procedure used for the preparation of **1a**. **9i** (TFA salt, 7.1 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.44 (d, *J* = 3 Hz, 1H), 8.12 (s, 1H), 8.05 (d, *J* = 3 Hz, 1H), 7.82 (d, *J* = 9 Hz, 2H), 7.40-7.50 (m, 4H), 7.36 (d, *J* = 9 Hz, 2H), 7.17 (t, *J* = 6 Hz, 1H), 4.75 (s, 2H), 4.44 (q, *J* = 6 Hz, 2H), 4.27 (m, 1H), 3.32 (m, 1H), 3.21 (m, 1H), 1.38 (t, *J* = 6 Hz, 3H); MS (EI) m/z: 466 (M+H).

11, **Synthesis of (S)-2-amino-3-(4-(5-(3,4-dimethoxybenzylamino)pyrazin-2-yl) phenyl) propan-l-ol (9j).**



5-Bromo-*N*-(3,4-dimethoxybenzyl)pyrazin-2-amine. This compound was prepared using 3,4-dimethoxybenzaldehyde (286 mg, 1.72 mmol), 2-amino-5-bromo pyrazine (300 mg, 1.72 mmol), sodium triacetoxyborohydride (548 mg, 1.72 mmol) and glacial acetic acid (309.6 mg, 5.16 mmol) by following a similar procedure described for **9c** to afford 300 mg of crude titled compound, which was partially used in the following step.

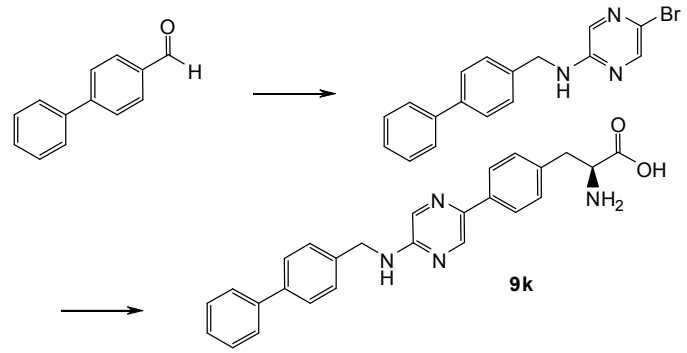
(S)-2-amino-3-(4-(5-(3,4-dimethoxybenzylamino)pyrazin-2-yl)phenyl)propanoic acid (9j). 5-bromo-*N*-(3,4-dimethoxybenzyl)pyrazin-2-amine (47 mg, 0.14 mmol), 4-borono-L-phenylalanine (30 mg , 0.14 mmol), dichlorobis(triphenylphosphine)palladium (2 mg, 0.002 mmol), Na_2CO_3 (31 mg, 0.28 mmol), acetonitrile (2 mL) and water (2 mL) were added to a microwave vial. Vial was sealed and irradiated at 150 ^oC for 5 min in a microwave reactor. Reaction mixture was cooled to room temperature, filtered through a syringe filter, diluted with 0.5 N NaOH

and extracted with Et_2O twice. The aqueous layer was then neutralized by 1 N HCl to pH ≈ 4-5. The precipitated product was filtered, washed with water and then dried. Small amount of crude product was purified by reverse phase preparative HPLC to give the titled compound **9j** (TFA salt). ^{1}H NMR (400 MHz, CD_3OD): δ 8.41 (d, *J* = 4.0 Hz, 1 H), 8.02 (d, *J* = 4.0 Hz, 1 H), 7.85 (dd, *J* = 8.45, 0.10 Hz, 2 H), 7.37 (d, *J* = 8.40 Hz, 2 H), 7.00 (d, *J* = 1.91 Hz, 1 H), 6.89 - 6.97 (m, 2 H), 4.52 (s, 2 H), 4.25 - 4.31 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.32 - 3.39 (m, 1 H), 3.14 - 3.21 (m, 1 H); MS (EI) m/z: 409 (M+H). Analysis calculated for $C_{22}H_{24}N_4O_4.2C_2HF_3O_2.1.15H_2O$: C 47.52,H 4.34 N 8.52 Found: C 47.08 H 3.84 N 8.44

12, Synthesis of (S)-2-amino-3-(4-(5-(3,4-dimethoxybenzylamino)pyrazin-2-yl)phenyl)propan-l-ol (14).

The crude acid (**9j**) was dissolved in anhydrous ethanol (10 mL) and $SOCl_2$ (1 mL) was added slowly. The mixture was refluxed for 1 hour. The solvent was removed at low pressure and the residue was dissolved in ethyl acetate and then washed with 1M Na_2CO_3, water, brine, dried ($MgSO_4$) and concentrated. The dried residue was dissolved in anhydrous THF (5 mL) and added to the flask charged with $LiAlH_4$ (16 mg, 0.42 mmol) in dry THF (30 mL) at 0^{o}C. After stirred at ambient temperature for 6 h, mixture was cooled to 0^{o}C and quenched by addition of sat. NH_4Cl solution. Resulting mixture was filtered and washed with MeOH. The filtrate was concentrated to give a crude product which was purified by a reverse phase preparative HPLC(MeOH/H_2O/TFA solvent system). The pure fractions were concentrated in vacuum. The product was then suspended in water (5 mL), frozen and lyophilized to afford **14** (TFA salt, 9 mg, 16 % for 3 steps). ^{1}H NMR (400 MHz, CD_3OD): δ 8.41 (d, *J* = 0.10 Hz, 1 H), 8.04 (d, *J* = 0.10 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.36 (d, *J* = 8 Hz, 2 H), 7.00 (s, 1 H), 6.89 - 6.96 (m, 2 H), 4.52 (s, 2 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.75 - 3.52 (m, 2 H), 3.31 (tt, *J* = 1.66, 0.83 Hz, 1 H), 2.97 (dd, *J* = 7.28, 5.52 Hz, 1 H); MS (EI) m/z: 395 (M+H)**.**

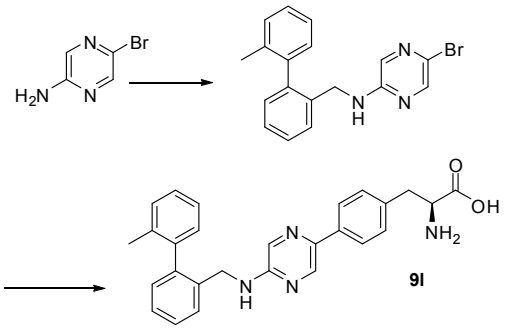
13, Synthesis of (S)-2-Amino-3-(4-{5-[(biphenyl-4-ylmethyl)-amino]-pyrazin-2-yl}-phenyl)-propionic acid 9k.



Biphenyl-4-ylmethyl-(5-bromo-pyrazin-2-yl)-amine. This compound was prepared using 4-phenylbenzaldehyde (0.3g, 1.65 mmol), 2-amino-5-bromopyrazine (0.24 g, 1.37 mmol), sodium triacetoxyborohydride (0.44 g, 2.06 mmol) and acetic acid (0.25 mL) by following a similar procedure used for the preparation of **9c**. Crude product was purified by silica gel column chromatography using ethyl acetate (10%) in hexanes to give 0.18 g of the titled product. ^{1}H NMR (400 MHz , DMSO-d6): δ 8.10 (d, J = 1.4 Hz, 1H), 7.86 (t, J=5.7 Hz, 1H), 7.8.3 (d, J=1.5 Hz, 1H), 7.63 (m, 4H), 7.48-7.32 (m, 5H) 4.51 (d, J=5.96 Hz, 2H); MS (EI) m/z: 342 (M+H).

(S)-2-Amino-3-(4-{5-[(biphenyl-4-ylmethyl)-amino]-pyrazin-2-yl}-phenyl)-propionic acid 9k. Compound **9k** was prepared using biphenyl-4-ylmethyl-(5-bromo-pyrazin-2-yl)-amine (60 mg, 0.176 mmol), 4-borono-L-phenylalanine (37 mg, 0.176 mmol), dichloro bis(triphenylphosphine)palladium(II) (3.6 mg, 0.0052 mmol) and sodium carbonate (37 mg, 0.353 mmol), by following a similar procedure used for the preparation of **1a**. 9**k** (TFA salt, 41 mg). ^{1}H NMR (400 MHz, CD_3OD). δ 8.4 (s, 1H), 8.05 (s, 1H), 7.8 (d, 2H), 7.6 (m, 4H), 7.5-7.2 (m, 7H), 4.6 (s, 2H), 4.25 (m, 1H), 3.2 (m, 2H). MS (EI) m/z: 425 (M+H)**.**

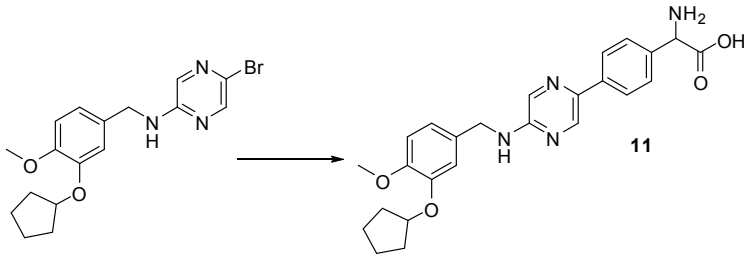
14, Synthesis of (S)-2-amino-3-(4-(5-((2'-methylbiphenyl-2-yl)methylamino)pyrazin-2-yl)phenyl)propanoic acid (9l).



5-Bromo-N-((2'-methylbiphenyl-2-yl)methyl)pyrazin-2-amine. This compound was prepared using sodium tiracetoxy borohydride (243 mg, 1.15 mmol), 2'-methyl biphenyl -2-carbaldehyde (112 mg, 0.58 mmol), 5-bromopyrazin-2-amine (100 mg, 0.58 mmol), and HOAc (0.1 mL) following a similar procedure described for **9c**. Crude product was purified by silica gel column chromatography (hexanes:EtOAc = 6:1) to give 90 mg (43%) of the titled compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J*=1.26 Hz, 1 H), 7.42 - 7.53 (m, 2 H), 7.37 (dd, *J*=5.68, 3.41 Hz, 2 H), 7.11 - 7.31 (m, 4 H), 4.31 - 4.43 (m, 1 H), 4.14 - 4.30 (m, 1 H), 2.08 (s, 3 H); MS (EI) m/z: 353 (M +H)

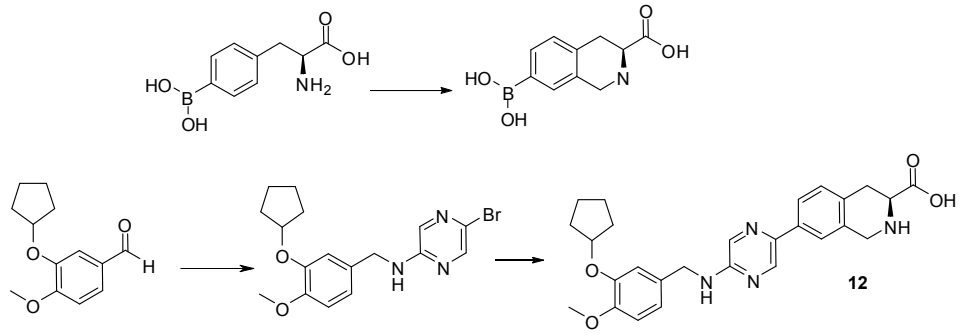
(S)-2-amino-3-(4-(5-((2'-methylbiphenyl-2-yl)methylamino)pyrazin-2-yl)phenyl) propanoic acid (9l). Compound 9**l** was prepared using 5-bromo-N-((2'-methylbiphenyl-2-yl)methyl)pyrazin-2-amine (45 mg, 0.13 mmol), (S)-2-amino-3-(4-boronophenyl) propanoic acid (53 mg, 0.25 mmol), aqueous sodium carbonate (1 mL, 1M), dichloro bis(triphenylphosphine)palladium(II) (4.6 mg, 0.0069 mmol), following a similar procedure described for **1a. 9l** (TFA salt, 12.8 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.24 (d, *J* = 1.37 Hz, 1 H), 7.90 (t, *J* = 1.37 Hz, 1 H), 7.76 - 7.85 (m, 2 H), 7.47 (d, *J* = 1.76 Hz, 1 H), 7.29 - 7.41 (m, 4 H), 7.07 - 7.25 (m, 5 H), 4.28 (br. s., 3 H), 3.32 - 3.39 (m, 1 H), 3.17 (dd, 1 H), 2.08 (s, 3 H). MS (EI) m/z: 439 (M+H)**.**

15, Synthesis of 2-amino-2-(4-(5-(3-(cyclopentyloxy)-4-methoxybenzylamino)pyrazin-2-yl)phenyl)acetic acid (11).



To a microwave vial, 5-bromo-N-(3-(cyclopentyloxy)-4-methoxybenzyl)pyrazin-2-amine (50 mg, 0.13 mmol), 4-borono-L-phenylalanine (28 mg, 0.13 mmol), dichloro bis(triphenylphosphine)palladium(II) (5 mg), sodium carbonate (0.26 mL of 1 M aqueous solution), water (0.74 mL) and acetonitrile (1 mL) were added. The vial was sealed and irradiated in a microwave reactor at 180^{o}C for 10 minutes. The crude mixture was cooled to room temperature and purified by reverse phase preparative HPLC using MeOH/H_2O /TFA mobile phase to afford 27 mg of **11** as TFA salt. ^{1}H NMR (MHz, CD_3OD): δ 8.47 (s, 1H), 8.01 (s, 1H), 7.97 (d, J = 9 Hz, 2H), 7.55 (d, J = 9 Hz, 2H), 6.95 (s, 1H), 6.90 (s, 2H), 5.09 (s, 1H), 4.77 (m, 1H), 4.51 (s, 2H), 3.79 (s, 3H), 1.81 (m, 6H), 1.59 (m, 2H); MS (EI) m/z: 449 (M+H).

16, Synthesis of 7-[5-(3-cyclopentyloxy-4-methoxy-benzylamino)-pyrazin-2-yl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (12).

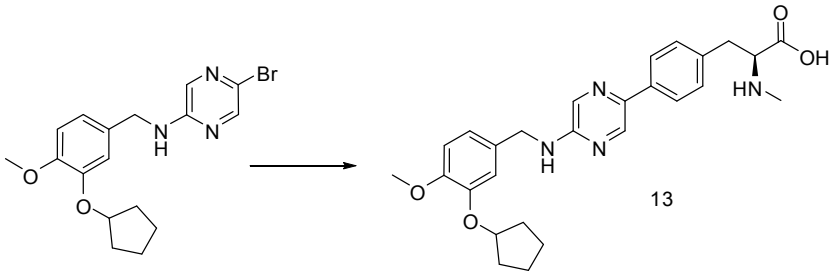


(5-Bromo-pyrazin-2-yl)-(3-cyclopentyloxy-4-methoxy-benzyl)-amine. This compound was prepared using 3-cyclopentyloxy-4-methoxy-benzaldehyde (1.0 g, 4.54 mmol), 2-amino-5-bromopyrazine, sodium triacetoxyborohydride (1.92 g, 9.08 mmol), acetic acid (0.75 mL) following a similar procedure described for **9c**. Crude product was purified by silica gel column chromatography to give 0.67 g of the titled compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.65 (s, 1H), 6.87-6.80 (m, 3H), 5.22 (s, 1H), 4.73 (m, 1H), 4.41 (d, J = 6.47 Hz 2H), 3.82 (s, 3H), 1.93-1.76 (m, 6H), 1.64-1.54 (m, 2H). MS (EI) m/z: 380 (M+H).

1,2,3,4-Tetrahydro-isoquinoline-3-carboxy-7-boronic acid. 4-Borono-L-phenylalanine(0.5g, 2.39 mmol) was treated with formaldehyde (37%, 1.2 mL) in concentrated HCl (3.2 mL) at 100 ^{o}C for 6 hours. The mixture was concentrated to give crude titled compound which was partially used in the following step.

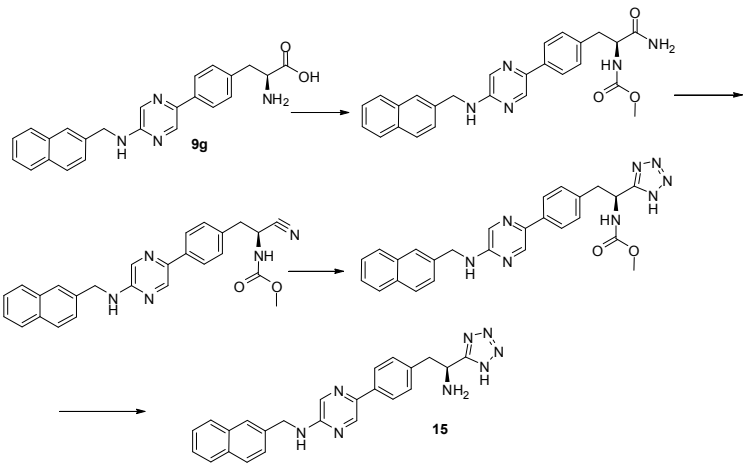
7-[5-(3-Cyclopentyloxy-4-methoxy-benzylamino)-pyrazin-2-yl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (12). Compound **12** was prepared using (5-bromo-pyrazin-2-yl)-(3-cyclopentyloxy-4-methoxy-benzyl)-amine (60 mg, 0.16 mmol), 1,2,3,4-tetrahydro isoquinoline-3-carboxy-7-boronic acid (41 mg, 0.16 mmol), dichloro bis(triphenylphosphine)palladium(II) (6 mg, 0.0079 mmol), sodium carbonate (67 mg, 0.63 mmol), by following a similar procedure described for **1a**. **12** (TFA salt, 21 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.42 (s, 1H), 8.02 (s, 1H), 7.85-7.75 (m, 2H), 7.38 (d, 1H), 6.95 (s, 1H) , 6.9 (s, 2H), 4.8 (m, 1H), 4.5 (s, 2H), 4.4 (m, 1H), 3.8 (s, 2H), 3.5 (m, 1H), 1.8 (m, 6H), 1.6 (m, 2H); MS (EI) m/z: 475 (M+H).

17. Synthesis of (S)-3-(4-(5-(3-(cyclopentyloxy)-4-methoxybenzylamino)pyrazin-2-yl)phenyl)-2-(methylamino)propanoic acid (13)



To a solution of 5-bromo-N-(3-(cyclopentyloxy)-4-methoxybenzyl)pyrazin-2-amine (60 mg, 0.16 mmol) in 3 mL of acetonitrile/water (1:1) was added (S)-2-(tert-butoxycarbonyl-methyl-amino)-3-[4-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-phenyl]-propionic acid methyl ester (50 mg, 0.16 mmol), dichlorobis(triphenylphosphine) palladium (II) (6 mg, 0.01 mmol) and sodium carbonate (33 mg, 0.32 mmol). The mixture was irradiated in a microwave reactor at 180^{o}C for 15 min. Solvent was removed in vacuo. The crude mixture was diluted with ethyl acetate (5 mL), filtered and acidified with 0.25 mL of conc. HCl. The residue was then evaporated at 50^{o}C on rotovap to give crude product which was purified by preparative HPLC to afford 49 mg (63%) of the titled compound. 1H NMR (400 MHz, MeOD) δ ppm 1.56 - 1.67 (m, 2 H) 1.74 - 1.89 (m, 6 H) 2.64 (s, 3 H) 3.17 - 3.25 (m, 1 H) 3.26 - 3.31 (m, 1 H) 3.78 (t, *J*=6.19 Hz, 1 H) 3.81 (s, 3 H) 4.52 (s, 2 H) 4.75 - 4.84 (m, 1 H) 6.93 (s, 2 H) 6.98 (s, 1 H) 7.41 (d, *J*=8.08 Hz, 2 H) 7.83 (d, *J*=8.08 Hz, 2 H) 8.00 (s, 1 H) 8.43 (s, 1 H). MS (EI) m/z: 477 (M+H).

18, Synthesis of 5-(4-((S)-2-amino-2-(1H-tetrazol-5-yl)-ethyl)-phenyl)-pyrazin-2-yl)-naphthalen-2-ylmethyl-amine (15).



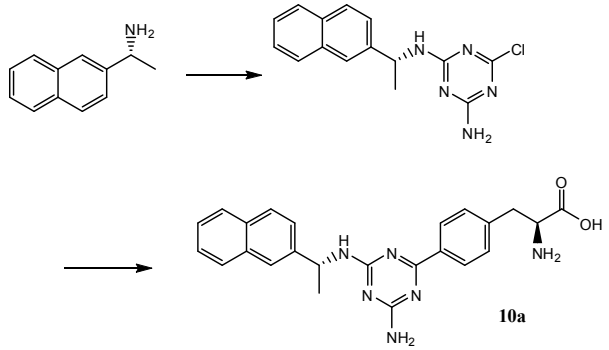
(S)-methyl 1-amino-3-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)-1-oxopropan-2-ylcarbamate. To a solution of (S)-2-amino-3-(4-(5-(naphthalene-2-ylmethyl)-amino)-pyrazin-2-yl)-phenyl)-propionic acid **9g** (300 mg, 0.75 mmol) in THF (10 mL) was added N,N-diisopropylethyl amine (387 mg, 3.0 mmol), chloromethyl formate (141 mg, 1.5 mmol) at 0^0C. After stirring for 1h, ammonia in 1,4-dioxane (1M, 2 mL) was added and the resulting mixture was stirred for 3h at room temperature. Solvent was removed on the rotavap under reduced pressure. To the residue was added sat. $NaHCO_3$ solution. The mixture was extracted with EtOAc (2 x 20 mL). Organic layer was dried (Na_2SO_4), filtered and concentrated to afford the crude titled compound which was directly used in the following step.

(S)-methyl 1-cyano-2-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)ethylcarbamate. To a solution of (S)-methyl 1-amino-3-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)-1-oxopropan-2-ylcarbamate (110 mg, 0.26 mmol) in 1,4-dioxane (15 mL) was added pyridine (65 mg, 0.78 mmol) and trifluoroacetic anhydride (107 mg, 0.52 mmol). The reaction mixture was stirred at room temperature for 12h. The progress of the reaction was monitored by LCMS. After completion of the reaction, solvent was removed in vacuo. To the residue was added sat. $NaHCO_3$ solution (20 mL). The reaction mixture was then extracted with ethyl acetate (2 x 20 mL), dried (Na_2SO_4) and concentrated to afford the titled crude product (95 mg) which was used in the following step.

(S)-methyl 2-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)-1-(1H-tetrazol-5-yl)ethylcarbamate. To a solution of (S)-methyl 1-cyano-2-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)ethylcarbamate (120 mg, 0.25 mmol) in DMF (5 mL) was added NaN_3 (33 mg, 0.5 mmol) and NH_4Cl (14 mg, 0.25 mmol). The mixture was heated at 120^0C for 12h. The progress of the reaction was monitored by LCMS. After completion of the reaction, solvent (DMF) was removed on the rotavap under reduced pressure. To the residue was added H_2O (20 mL) and the reaction mixture was extracted with ethyl acetate (2 x 20 mL), dried (Na_2SO_4) and concentrated to give the titled crude product which was used in the following step.

(S)-5-(4-(2-amino-2-(1H-tetrazol-5-yl)ethyl)phenyl)-N-(naphthalen-2-ylmethyl)pyrazin-2-amine (15). To a solution of (S)-methyl 2-(4-(5-(naphthalen-2-ylmethylamino)pyrazin-2-yl)phenyl)-1-(1H-tetrazol-5-yl)ethylcarbamate (110 mg, 0.24 mmol) in dry CH_3CN (10 mL) was added drop wise iodotrimethylsilane (98 mg, 0.48 mmol). Reaction mixture was stirred at room temperature for 6 h, and the solvent (CH_3CN) was removed. To the residue was added sat. $NaHCO_3$ (20 mL). The reaction mixture was then extracted with EtOAc (2 x 20 mL). Organic layer was dried (Na_2SO_4), filtered and the solvent was removed. Crude product was purified by reverse phase preparative HPLC to afford the titled compound **15** (20 mg, 20 %). ^{1}H-NMR (400 MHz, CD_3OD): δ 3.2 (m, 1H), 3.45(m, 1H), 4.85 (s, 2H), 5.05(m, 1H), 7.2 (m, 1H), 7.3-7.6(m, 4H), 7.9(m, 6H), 8.1(m, 1H), 8.5(m, 1H). MS (EI) m/z: 423 (M+H).

19, Synthesis of 2-amino-3-{4-[4-amino-6-(1-naphthalen-2-yl)-ethylamino)-[1,3,5] triazine-2-yl]-phenyl}-propionic acid (10a)

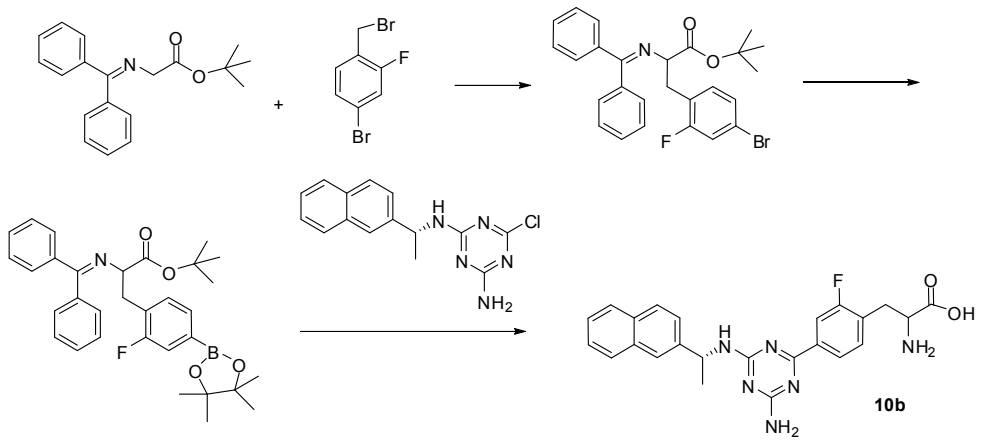


10a

(R)-6-chloro-N2-(1-(naphthalen-2-yl)ethyl)-1,3,5-triazine-2,4-diamine. A mixture of 2-amino-4,6-dichloro-[1,3,5]triazine (200 mg, 1.21 mmol), (R)-(+)-1-(2-naphthyl) ethylamine (207 mg, 1.21 mmol) and N,N-diisopropyl ethylamine (468 mg, 3.63 mmol) was dissolved in 150 mL of 1,4-dioxane. The solution was refluxed at 90^{o}C for 3 hours. After the completion of reaction (monitored by LCMS), solvent was removed and the reaction mixture was extracted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography to give 108 mg of titled compound. ^{1}H NMR (400 MHz, d6-DMSO): δ 8.40 (d, 1H, *J* = 8.4 Hz), 7.88 (d, 3H, *J* = 7.8 Hz), 7.80 (s, 1H), 7.55-7.45 (m, 3H), 7.25 (m, 2H), 5.27 (m, 1H), 1.49 (d, 3H, *J* = 6.9Hz); M+1 = 300.

2-Amino-3-{4-[4-amino-6-(1-naphthalen-2-yl)-ethylamino)-[1,3,5]triazin-2-yl]-phenyl}-propionic acid (10a). The above crude compound was dissolved in MeCN (5 mL) and H_2O (5 mL) in a 20 mL microwave vial. To this solution were added L-*p*-borono-phenylalanine (253 mg, 1.21 mmol), sodium carbonate (256 mg, 2.42 mmol) and dichloro bis(triphenylphosphine)palladium(II) (42.1 mg, 0.06 mmol). The vial was sealed and the mixture was irradiated in a microwave reactor at 150^{o}C for 5 min. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated and dissolved in MeOH and H_2O (1:1) and purified by reverse phase preparative HPLC using MeOH/H_2O/TFA solvent system. The combined pure fractions were evaporated *in vacuo* and further dried on lyophilizer to give 238 mg of **10a** (yield: 46%) as TFA salt. To compound **10a (TFA salt)** was added 1N HCl (2.1 eq) and diluted with water (3 mL). Resulting suspension was frozen and lyophilized to afford **10a** as 2 HCl salt. MS: ^{1}H NMR (300 MHz, CD_3OD) δ 8.20-8.07 (m, 2H), 7.81 -7.69 (m, 4H), 7.51-7.30 (m, 5H), 5.39 (q, J = 7.42 Hz, 1H), 4.30-4.20 (m, 1H), 3.38-3.13 (m, 2H), 1.60 (d, *J* = 6.92 Hz, 3H). ^{13}C NMR (300 MHz, CD_3OD) δ 170.98, 162.56, 142.81, 141.38, 134.83, 134.26, 131.47, 131.33, 130.32, 129.94, 129.53, 128.93, 128.65, 127.32, 127.07, 125.84, 125.74, 125.58, 125.46, 54.74, 52.38, 37.21, 22.19. MS (EI) m/z: 429 (M+H). Analysis calculated for $C_{24}H_{26}Cl_2N_6O_2.1.1H_2O$: C 55.3 H 5.45 N 16.12 Found C55.62 H 5.82 N 16.38.

20, Synthesis of 2-Amino-3-(4-(4-amino-6-(R)-1-(naphthalene-2-yl)ethylamino)-1, 3, 5-trizin-2-yl)-2-fluorophenyl)propanoic acid (10b).



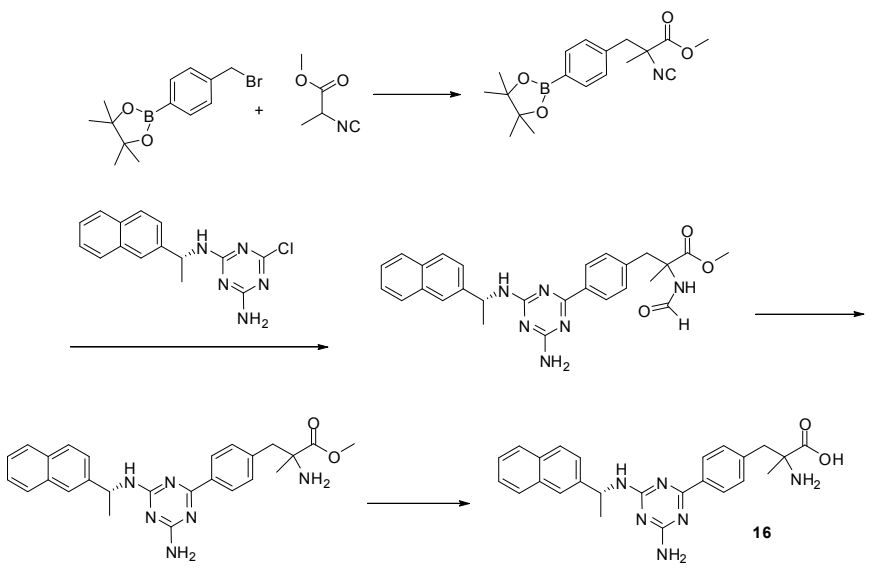
***tert*-Butyl 3-(4-bromo-2-fluorophenyl)-2-(diphenylmethyleneamino)propanoate**: To a solution of *tert*-butyl 2-(diphenylmethyleneamino) acetate (1.1g, 3.73 mmol) in THF (30 mL) was added a solution of LDA (2.13 mL, 1.8M in THF, 3.73 mmol) at -78^{0}C during 5 minutes. The mixture was stirred for 30 min at the same temperature. A solution of 4-bromo-1-(bromomethyl)-2-fluorobenezene (1g, 3.74 mmol) in THF (10 mL) was added drop wise to the reaction mixture during 5 min. Resulting mixture was stirred for 30 min at -78^{0}C. The reaction mixture was warmed to room temperature, quenched with sat. NH_4Cl solution and water (30 mL). The mixture was extracted with ethyl acetate (2 x 40 mL). Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford 600 mg of the titled compound (Yield: 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.67 (m, 2 H), 7.27 - 7.48 (m, 6 H), 7.00 - 7.23 (m, 3 H), 6.78 (d, *J*=6.57 Hz, 2 H), 4.21 (dd, *J*=9.09, 4.29 Hz, 1 H), 3.28 (d, *J*=4.29 Hz, 1 H), 3.16 (d, *J*=9.09 Hz, 1 H), 1.48 (s, 9 H); MS (EI) m/z: 484 (M+H).

***tert*-Butyl-2-(diphenylmethyleneamino)-3-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate**. A microwave reaction vial was charged with *tert*-butyl 3-(4-bromo-2-fluorophenyl)-2-(diphenylmethyleneamino)propanoate (600 mg, 1.24 mmol), $Pd(dba)_2$ (71 mg, 0.124 mmol), tricyclohexylphosphine (35 mg, 0.124 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'bi(1,3,2-dioxaborolane (346 mg, 1.36 mmol), KOAc (182 mg, 1.86 mmol) and DMF (20 mL). The reaction vessel was sealed and

irradiated at 160°C for 20 min in a microwave reactor. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. To the residue was added H_2O (30 mL) and extracted with EtOAc (2 x 40 mL). Solvent was removed and the residue was purified by preparative HPLC to give 220 mg of the titled product.

2-Amino-3-(4-(4-amino-6-(R)-1-(naphthalene-2-yl)ethylamino)-1, 3, 5-trizin-2-yl)-2-fluorophenyl)propanoic acid (10b). A microwave reaction vial (5 mL) was charged with (R)-6-chloro-N^2-(1-(naphthalene-2-yl)ethyl)-1,3,5-triazine-2,4-diamine (67 mg, 0.22 mmol), *tert*-butyl 2-(diphenylmethyleneamino)-3-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (120 mg, 0.22 mmol), acetonitrile (2 mL), aqueous sodium carbonate (2 mL, 1M), dichlorobis(triphenyl phosphine)palladium(II) (15 mg, 0.022 mmol). Reaction vessel was sealed and irradiated at 190°C for 10 min in a microwave reactor. The reaction mixture was cooled to room temperature and the solvents were removed. Residue was dissolved in THF (10 mL) and added 5N HCl (2 mL) and refluxed for 2 h. Resulting mixture was concentrated and the residue was dissolved in methanol (5 mL), and further purified by preparative HPLC to give the titled compound (**10b**) (10 mg) as TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 8.0 (m, 2H), 7.8-7.9 (m, 4H), 7.55 (m 1H), 7.46 (m, 3H), 5.51 (m, 1H), 4.27 (m, 1H), 3.46 (m, 1H), 3.27 (m, 1H), 1.68 (d, 3H, J = 8.01Hz). MS (EI) m/z: 447 (M +H).

21, Synthesis of 2-amino-3-(4-(4-amino-6-(R)-1-(naphthalene-2-yl)ethylamino)-(1,3,5-trizin-2-yl)-pheny)-2-propanoic acid (16).

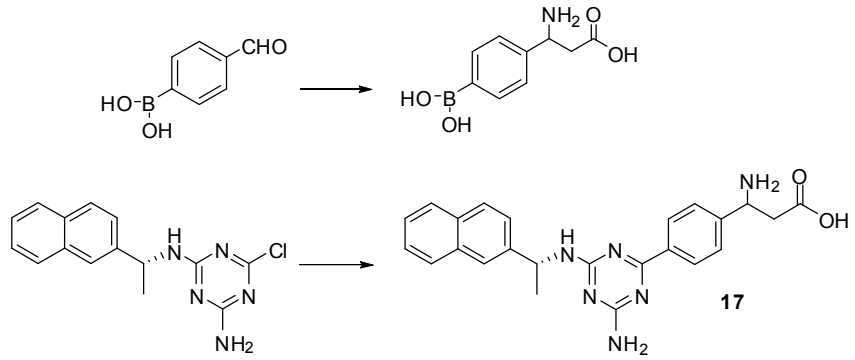


2-isocyano-2-methyl-3-(4-(4,4,5,5-tetramethyl-(1,3,2)dioxaborolan-2-yl)-phenyl)-propionic acid methyl ester. To a solution of 2-isocyano-propionic acid methyl ester (190 mg, 68 mmol) in THF (25 mL) was added a solution of LDA (0.93 mL, 1.8M in THF, 1.68 mmol) at -78^{0}C during 5 minutes. The resulting mixture was stirred for 30 min at the same temperature. A solution of 2-(4-bromomethyl-phenyl)-4,4,5,5-tetra methyl-(1,3,2) dioxa borolane (500 mg, 1.68 mmol) in THF (10 mL) was added drop wise to the reaction mixture over 5 min. The reaction was stirred for another 30 min at -78^{0}C and then brought to room temperature over 4h. The reaction was quenched with sat. NH_4Cl solution, water (30 mL) and extracted with EtOAc (2 x 40 mL). Combined organic layer was dried (Na_2SO_4), and concentrated at reduced pressure. Crude product was purified by silica gel column chromatography (hexanes: EtOAc) to afford the titled compound as semi-solid (278 mg, yield 50%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.72 (d, *J*=8.08 Hz, 2 H), 7.26 (d, *J*=8.08 Hz, 2 H), 3.77 (s, 3 H), 3.29 (d, *J*=13.64 Hz, 1 H), 3.12 (d, *J*=13.39 Hz, 1 H), 1.70 (s, 3 H), 1.36 (s, 9 H); MS (EI) m/z: 347 M+NH_4.

2-**Amino-3-(4-(4-amino-6-(R-1-(naphthalene-2-yl)ethylamino)-(1,3,5-trizin-2-yl)-pheny)-2-propanoic acid** (**16**). A microwave reaction vial (20 mL) was charged with (R)-6-chloro-N^2-(1-(naphthalene-2-yl)ethyl)-1,3,5-triazine-2,4-diamine (136 mg, 0.45 mmol), 2-isocyano-2-methyl-3-(4-(4,4,5,5-tetramethyl-(1,3,2)dioxaborolan-2-yl)-phenyl)-propionicacid methyl ester (150 mg, 0.45 mmol), acetonitrile (7 mL), water (7 mL), 1M sodium carbonate solution (0.9 mL, 0.9 mmol), and dichloro bis(triphenylphosphine) palladium (10 mol %). The reaction vessel was sealed and

irradiated at 190°C for 20 min on a microwave reactor. LCMS showed hydrolysis of isonitrile to formyl group. Reaction mixture was cooled to room temperature, added water (20 mL) and extracted with EtOAc (2 x 20 mL). Solvent was removed and the crude product was dissolved in MeOH and con. HCl (1:1, 10 mL) and refluxed for 12 h. Mixture was cooled to room temperature and solvent was removed. To the residue was added sat. $NaHCO_3$ solution (10 mL) and extracted with EtOAc (20 mL). Solvent was concentrated and the resulting methyl ester was hydrolyzed using LiOH monohydrate (38 mg, 0.9 mmol) in THF and water (4:1, 15 mL). Solvent was concentrated and the residue was dissolved in methanol (5 mL) and purified by preparative HPLC to afford the titled product 70 mg (35%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.20(m, 2H), 7.85(m, 4H), 7.56 (m, 1H), 7.36-7.51 (m, 3H), 7.32 (m, 1H), 5.48 (m, 1H), 3.40 (m, 1H), 3.12 (m, 1H), 1.66 (d, 3H, J = 7.26 Hz), 1.61 (s, 3H); MS (EI) m/z: 443 (M +H).

22, Synthesis of 3-amino-3-(4-(4-amino-6-((S)-1-naphthalen-2-yl)ethylamino)-1,3,5-triazin-2-yl)phenyl)propanoic acid (17).



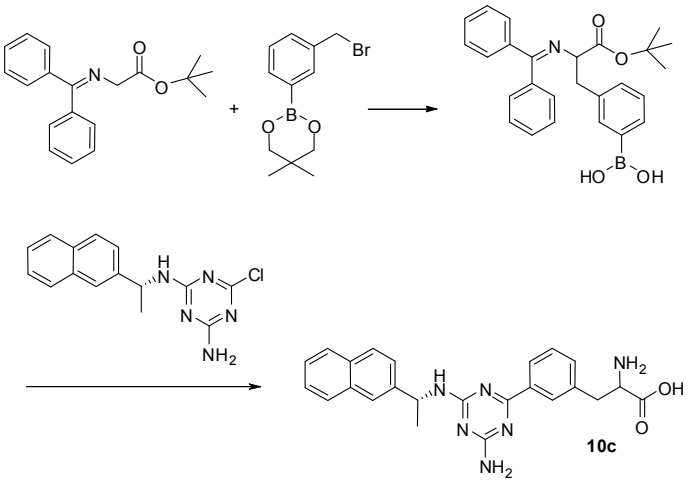
3-Amino-3-(4-bronophenyl)propanic acid. The mixture of 4-formylphenylbronic acid (200 mg, 1.33 mmol), malonic acid (139 mg, 1.33 mmol) and ammonium acetate (205 mg, 2.66 mmol) in anhydrous ethanol (20 mL) were refluxed for 15h. The solvent was removed under reduced pressure to give the titled crude product, which was used directly in the next step.

(*R*)**-6-Chloro-N^2-(1-naphthalen-2yl)ethyl)-1,3,5-triazine-2,4-diamine.** To a 250 mL flask, R-(+)-1-(2-naphthyl)ethylamine (400 mg, 2.424 mmol), 2-amino-4,6-dichloro triazine (373 mg, 2.181 mmol), anhydrous 1,4-dioxane (40 mL), N,N-diisopropylethyl amine (1 mL, 5.732 mmol) were added. The mixture was refluxed for 4h. The reaction

was monitored carefully in order to avoid the formation of the di-substituted product. (If the reaction is kept longer, more di-substituted product is formed). After 4h, reaction mixture was cooled to ambient temperature, and the solvent was removed under reduced pressure. To the residue was added water (100 mL) and the mixture was sonicated for 2-3 min. It was then filtered, washed with water and dried to give 540 mg of the crude titled compound, which was used directly in the next step.

3-Amino-3-(4-(4-amino-6-((S)-1-naphthalen-2-yl)ethylamino)-1,3,5-triazin-2-yl) phenyl)propanoic acid (17). Compound **17** was prepared using 3-amino-3-(4-brono phenyl)propanic acid (50 mg, 0.24 mmol), (*R*)-6-chloro-N^2-(1-naphthalen-2yl)ethyl)-1,3,5-triazine-2,4-diamine (72 mg, 0.24 mmol), Na_2CO_3 (50.9 mg, 0.48 mmol), dichloro bis(triphenylphosphine)palladium (8 mg, 0.012 mmol) by following similar procedure described for **1a. 17** (TFA salt, 3 mg, 3%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.28 (d, *J* = 8.40 Hz, 2 H), 7.86-7.90 (m, 4 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.53-7.63 (m, 2H), 7.42-7.56 (m, 2H), 5.49 (q, *J* = 8.0 Hz, 1 H), 4.74-4.86 (m, 1 H), 3.00 - 3.15 (m, 2 H), 1.69 (d, *J* = 6.94 Hz, 3 H); MS (EI) m/z: 429 (M +H).

23, Synthesis of 2-amino-3-(4(4-amino-6-(R)-1-(naphthalene-2-yl)ethylamino)-1,3,5-trizin-2-yl) phenyl)propanoic acid (10c).

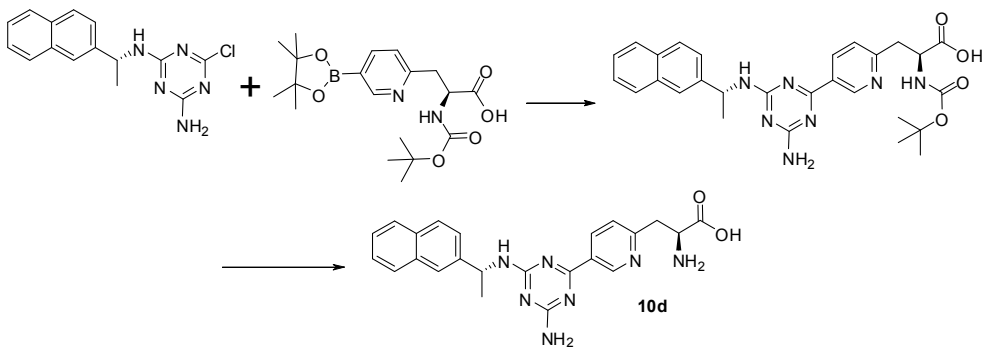


3-(3-tert-butoxy-2-(diphenylmethyleneamino)-3-oxopropyl)phenylboronic acid. To a solution of *tert*-butyl 2-(diphenylmethyleneamino)acetate (400 mg, 1.35 mmol) in THF (25 mL) was added a solution of LDA (1.5 mL, 1.8M in THF, 2.7 mmol)

at -78^{0}C over 5 minutes. The resulting mixture was stirred for 20 min at the same temperature. A solution of 2-(3-(bromomethyl)phenyl)-5,5-dimethyl-1,3,2-dioxa borinane (460 mg, 1.62 mmol) in THF (10 mL) was added drop wise to the reaction mixture over 5 min. The reaction mixture was stirred for 30 min at -78^{0}C and brought to room temperature over 3h. The reaction was quenched with sat. NH_4Cl solution, water (30 mL) and extracted with EtOAc (2 x 40 mL). Combined organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography to afford the titled compound as semi-solid (460 mg, 68 %). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.47 - 7.53 (m, 2 H), 7.28 - 7.45 (m, 6 H), 7.03 (t, *J*=7.83 Hz, 1 H), 6.58 - 6.71 (m, 3 H), 6.44 - 6.54 (m, 2 H), 4.12 (dd, *J*=9.60, 4.29 Hz, 1 H), 3.13 (d, *J*=4.29 Hz, 1 H), 3.03 (d, *J*=9.35 Hz, 1 H), 1.48 (s, 9 H); MS (EI) m/z: 402 (M+H)

2-Amino-3-(4(4-amino-6-(R)-1-(naphthalene-2-yl)ethylamino)-1,3,5-trizin-2-yl)phenyl)propanoic acid. A microwave reaction vial (20 mL) was charged with (R)-6-chloro-N^2-(1-(naphthalene-2-yl)ethyl)-1,3,5-triazine-2,4-diamine (100 mg, 0.33 mmol), *tert*-Butyl 3-(3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)-2-(diphenyl methy lleneamino)propanoate (248 mg, 0.5 mmol), acetonitrile (6 mL), aqueous sodium carbonate (6 mL, 1M), and dichloro bis(triphenylphosphine) palladium(II) (23 mg, 0.033 mmol). The reaction vessel was sealed and irradiated at 190°C for 10 min in a microwave reactor. After cooling to room temperature, solvents were removed. The residue was dissolved in THF (10 mL), added 5N HCl (5 mL) and refluxed for 2h. The mixture was concentrated, dissolved in methanol (8 mL) and purified by reverse phase preparative HPLC to give the titled compound **10c** (TFA salt, 15 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (m, 1H), 7.91(m, 4H), 7.42-7.78(m, 5H), 5.50 (m, 1H), 4.35 (m, 1H), 3.48(m, 1H), 3.27 (m, 1H), 1.7 (d, 3H, *J* = 6.97 Hz); MS (EI) m/z: 429 (M +H).

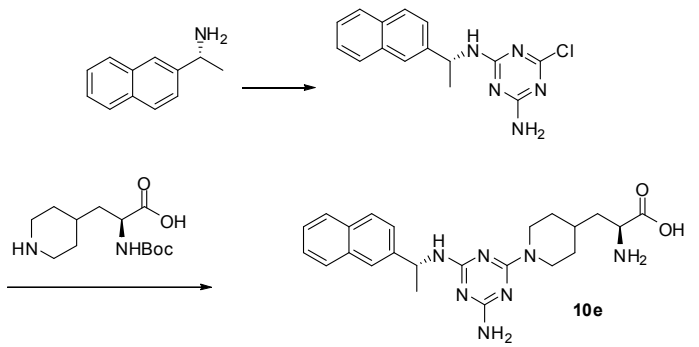
24, Synthesis of (S)-2-amino-3-(5-(4-amino-6-((R)-1-(naphthalen-1-yl)-ethylamino)-1,3, 5-triazin-2-yl)pyridin-2-yl)propanoic acid (10d).



(S)-3-(5-(4-amino-6-((R)-1-(naphthalen-1-yl)ethylamino)-1,3,5-triazin-2-yl)pyridin-2-yl)-2-(tert-butoxycarbonylamino)propanoic acid. This compound was prepared using (R)-6-chloro-N-(1-naphthalen-1-yl-ethyl)-1,3,5-triazine-2,4-diamine (30 mg, 0.1 mmol), (S)-2-(*tert*-butoxycarbonylamino)-3-{5-(4,4,5,5,-tetra methyl-1,3,2-dioxa borolan-2-yl)-pyridin2-yl-)-propanoic acid (50 mg, 0.15 mmol), aqueous sodium carbonate solution (0.3 mL, 1N) and dichlorobis(triphenylphosphine)-palladium (II) (5.3 mg, 0.0075 mmol) by following similar procedure described for **1a**. After purification, 7 mg of the titled product was obtained. ^{1}H NMR (300 MHz, CD_3OD) δ 9.35 (d, 1 H, J = 13.2 Hz), 8.56 (m, 1 H), 7.86 (m, 4H), 7.46-7.58 (m, 4 H), 6.94 (s, 1H), 5.47 (m, 1H), 4.52 (m, 1H), 3.46 – 3.55 (m, 2H), 2.23 (s, 2H), 1.66 (d, *J* = 7.1 Hz, 3H), 1.41 (s, 9H). MS (EI) m/z: 530 (M +H).

(S)-2-amino-3-(5-(4-amino-6-((R)-1-(naphthalen-1-yl)-ethylamino)-1,3,5-triazin-2-yl]pyridin-2-yl}propanonic acid (10d). 7.0 mg above product was dissolved in 0.1mL of 10%TFA/DCM solution and stirred for 2 h at room temperature. Solvents were removed and the crude residue was purified by preparative HPLC to provide (S)-2-amino-3-(5-(4-amino-6-((R)-1-(naphthalen-1-yl)-ethylamino)-1,3,5-triazin-2-yl]pyridin-2-yl}propanonic acid **10d** as TFA salt (1.1 mg). ^{1}H NMR (300 MHz, CD_3OD) δ 9.22 (m, 1 H), 8.43 (m, 1 H), 7.74 (m, 4H), 7.39 (m, 4 H), 5.38 (m, 1H), 4.41 (m, 2H), 3.42 (m, 1H), 1.56 (d, *J* = 6 Hz, 3H,). MS (EI) m/z: 430 (M +H).

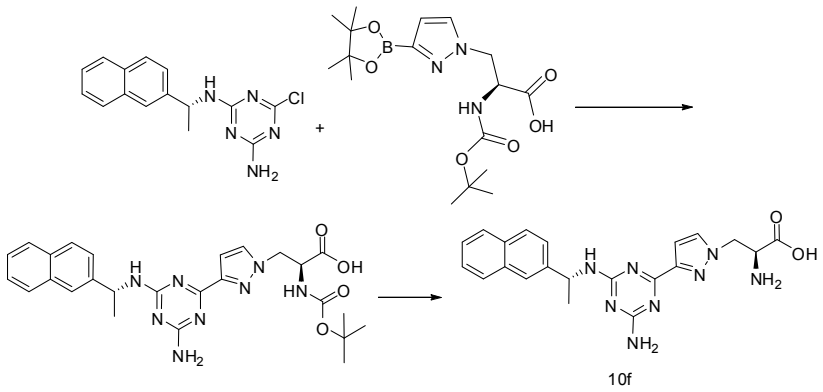
25, Synthesis of (S)-2-amino-3-(1-(4-amino-6-((R)-1-(naphthalen-2-yl)ethylamino)-1,3,5-triazin-2-yl)piperidin-4-yl)propanoic acid (10e).



(**R)-6-chloro-N2-(1-(naphthalen-2-yl)ethyl)-1,3,5-triazine-2,4-diamine. 2-**Amino-4,6-dichlorotriazine (5 g, 30.3 mmol) was dissolved in 1,4-dioxane (100 mL). To the mixture, was added (R)-1-(naphthalen-2-yl)ethanamine (5 g, 29.2 mmol) and N,N-diisopropyl ethylamine (7.4 mL, 42.6 mmol) and stirred at 100^{o}C for 15h. The dioxane was evaporated *in-vacuo*. The crude mixture was extracted with methylene chloride, washed with water twice and dried over sodium sulfate. Removal of solvent gave crude product which was purified by silica gel column chromatography to afford 2.7 g of the titled compound. ^{1}H NMR (400 MHz, d6-DMSO): δ 8.40 (d, 1H, *J* = 8.4 Hz), 7.88 (d, 3H, *J* = 7.8 Hz), 7.80 (s, 1H), 7.55-7.45 (m, 3H), 7.25 (m, 2H), 5.27 (m, 1H), 1.49 (d, 3H, *J* = 6.9Hz); M+1 = 300.

(**S)-2-amino-3-(1-(4-amino-6-((R)-1-(naphthalen-2-yl)ethylamino)-1,3,5-triazin-2-yl)piperidin-4-yl)propanoic acid (10e).** To a microwave reactoin vial, (R)-6-chloro-N2-(1-(naphthalen-2-yl)ethyl)-1,3,5-triazine-2,4-diamine (60 mg, 0.2 mmol), N-boc-(S)-2-amino-3-(piperidin-4-yl)propanoic acid (65 mg, 0.24 mmol), cesium carbonate (130 mg, 0.4 mmol) and 1,4-dioxane (4 mL) were added. The vial was sealed and irradiated under microwave at 150^{o}C for 6 minutes. The mixture was cooled to room temperature, and then transferred to a round bottom flask. Hydrochloric acid (1M aqueous) was added to adjust pH to 1-2. The mixture was stirred at room temperature until the complete deprotection of Boc which was monitored by LCMS. The crude mixture was purified by preparative HPLC to give the titled compound **10e (**11 mg**)** as TFA salt. ^{1}H NMR (300 MHz , CD_3OD): δ 7.85 (m, 4H), 7.48 (m, 3H), 5.26 (m, 1H), 4.67 (m, 2H), 3.84 (m, 1H), 2.86 (m, 2H), 1.74 (m, 4H), 1.65 (d, *J* = 6 Hz, 3H), 1.52 (m, 1H), 1.22 (m, 2H); MS (EI) m/z: 436 (M+H).

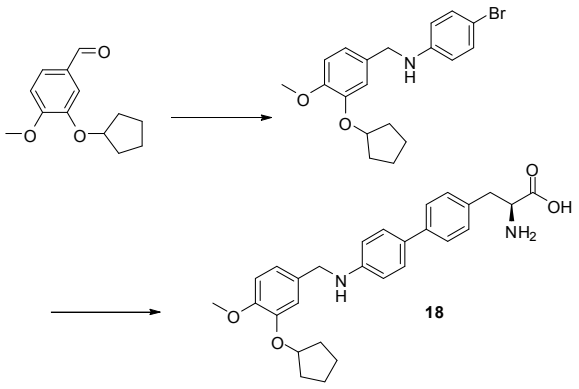
26, Synthesis of (S)-2-amino-3-(3-(4-amino-6-((R)-1-(naphthalen-1-yl)ethylamino)-1,3,5 -triazin-2-yl)-1H-pyrazol-1-yl)propanoic acid (10f).



(S)-3-(3-(4-amino-6-((R)1-naphthalen-1-yl)ethylamino)-1,3,5-triazin-2-yl)-pyrazol-1-yl)-2-(tert-butoxycarbonylamino)propanoic acid. This compound was prepared using (R)-6-chloro-N-(1-naphthalen-1-yl-ethyl)-1,3,5-triazine-2,4-diamine (30 mg, 0.1 mmol), (S)-2-(*tert*-butoxycarbonylamino)-3-(3-(4,4,5,5,-tetramethyl-1,3,2dioxa borolan-2-yl)-1*H* -pyrazol-1-yl)propanoic acid (50 mg, 0.15 mmol), aqueous sodium carbonate (0.3 mL, 1N) and dichlorobis(triphenylphosphine)-palladium(II) (5 mol %) by following similar procedure described for **1a**. 6.8 mg of titled compound was obtained as TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 8.20 (m, 1 H), 8.06 (m, 1 H), 7.83 (m, 4 H), 7.56 (m, 1H), 7.45 (m, 2H), 5.45 (m, 1H), 4.64(m, 1H), 4.48 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3 H), 1.38 (s, 9H) MS (EI) m/z: 519 (M+H)

(**S)-2-amino-3-(3-(4-amino-6-((R)-1-(naphthalen-1-yl)ethylamino)-1,3,5-triazin-2-yl)-1H-pyrazol-1-yl)propanoic acid (10f)**. 6.8 mg above product was stirred in 10%TFA/DCM (0.1 mL) solution for 2 h, and purified by reverse phase preparative HPLC to afford 3 mg of the titled compound **10f** as TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 8.73 (m, 1 H), 8.35 (m, 1 H), 7.95 (m, 4 H), 7.62 (m, 3H), 5.63 (m, 1H), 4.84(m, 2H), 4.47 (m, 1H), 1.78 (d, *J* = 6 Hz, 3 H). MS (EI) m/z: 419 (M+H)

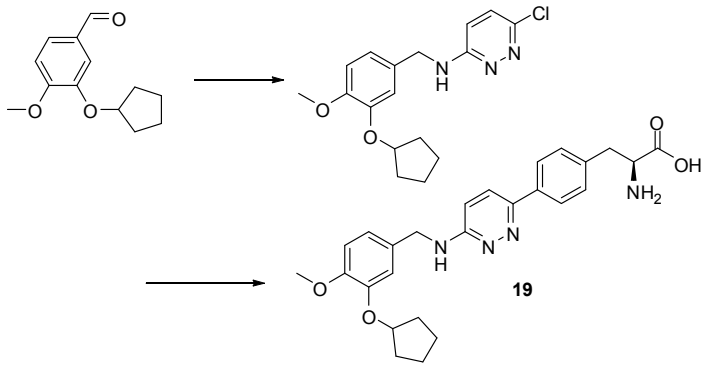
27, Synthesis of (S)-2-amino-3-(4'-(3-(cyclopentyloxy)-4-methoxy benzy lamino)bi phenyl-4-yl)propanoic acid (18).



4-**bromo-N-(3-(cyclopentyloxy)-4-methoxybenzyl)aniline.** This compound was prepared using sodium triacetoxyborohydride (470 mg, 2.21 mmol), 4-bromoaniline (252 mg, 1.47 mmol) and 3-(cyclopentyloxy)-4-methoxybenzaldehyde (324 mg, 1.47 mmol) and HOAc (0.5 mL) by following similar procedure described for 9**c**. 656 mg of titled crude product was obtained and partially used in the next step.

2-Amino-3-[4'-(3-cyclophentyloxy-4-methoxy-benzylamino)-biphenyl-4-yl]-propionic acid (18). Compound **18** was prepared using 4-bromo-N-(3-(cyclo pentyloxy)-4-methoxybenzyl)aniline (84 mg, 0.22 mmol), (S)-2-amino-3-(4-boronophenyl)propa noic acid (46 mg, 0.22 mmol), aqueous sodium carbonate (2 mL, 1M), and dichloro bis (triphenylphosphine)palladium(II) (7.7 mg, 0.011 mmol) by following similar procedure described for **1a**. **18** (TFA salt, 5 mg). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.18 (bs, 2 H), 7.59 (dd, J = 8.01, 1.72 Hz, 1 H), 7.43 (d, J = 8.20 Hz, 2 H), 7.31 (d, J = 8.58 Hz, 2 H), 7.18 (d, J = 8.39 Hz, 1 H) 6.88 (s, 1 H), 6.81 (s, 1 H), 6.59 (d, J = 8.77 Hz, 1 H), 4.65 (m, 1 H), 4.14 (s, 3 H), 3.63 (s, 2 H), 3.01 (d, J = 6.29 Hz, 2 H), 1.75 (m, 2 H), 1.62 (m, 4 H), 1.47 (bs, 2 H); MS (EI) m/z: 461(M+H). Analysis calculated for $C_{28}H_{32}N_2O_4$. $2C_2HF_3O2.0.5H2O$: C 55.09 H 5.06 N 4.02 Found: C 54.94 H 4.89 N 3.97.

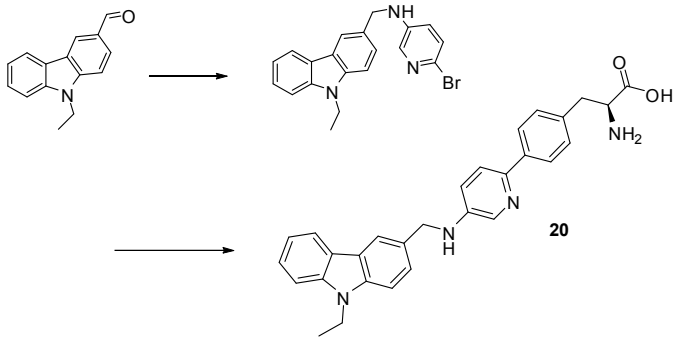
28, Synthesis of (S)-2-amino-3-(4-(6-(3-(cyclopentyloxy)-4-methoxybenzylamino)pyridazin-3-yl)phenyl)propanoic acid (19).



6-chloro-N-(3-(cyclopentyloxy)-4-methoxybenzyl)pyridazin-3-amine. This compound was prepared using sodium triacetoxyborohydride (718 mg, 3.39 mmol), 6-chloro pyridazin-3-amine (292 mg, 2.26 mmol), 3-(cyclopentyloxy)-4-methoxy benzaldehyde (500 mg, 2.26 mmol) and HOAc (0.5 mL), following similar procedure described for **9c**. The crude product was purified by recrystallization using dichloromethane/ hexane (7 mL) to give the titled product (78 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J*=9.35 Hz, 1 H), 6.84 - 6.91 (m, 2 H), 6.77 - 6.83 (m, 1 H), 6.70 (d, *J*=9.35 Hz, 1 H), 5.57 (br. s., 1 H), 4.66 - 4.78 (m, 1 H), 4.50 (d, *J*=5.05 Hz, 2 H), 3.81 (s, 3 H), 1.71 - 1.95 (m, 6 H), 1.48 - 1.67 (m, 2 H); MS (EI) m/z: 333 (M +H)

(S)-2-amino-3-(4-(6-(3-(cyclopentyloxy)-4-methoxybenzylamino)pyridazin-3-yl)phenyl)propanoic acid (19). Compound **19** was prepared using 6-chloro-N-(3-(cyclopentyloxy)-4-methoxybenzyl)pyridazin-3-amine (33 mg, 0.1 mmol), (S)-2-amino-3-(4-boronophenyl)propanoic acid (21 mg, 0.1 mmol), aqueous sodium carbonate (2 mL, 1M) and dichlorobis(triphenylphosphine)palladium(3.5 mg, 0.005 mmol) by following similar procedure used for **1a**. **19** (TFA salt) 5 mg . ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (br. s., 3 H), 7.88 (d, *J* = 8.40 Hz, 2 H), 7.33 (d, *J* = 8.21 Hz, 2 H), 6.93 (s, 1 H), 6.86 (s, 1 H), 4.76 - 4.59 (m, 1 H), 4.47 (d, *J* = 5.47 Hz, 2 H), 4.32 - 4.12 (m, 1 H), 3.65 (s, 3 H), 3.09 (d, 2 H), 1.71 - 1.90 (m, 2 H), 1.70 - 1.55 (m, 4 H), 1.48 (m., 2 H). MS (EI) m/z: 463 (M+H).

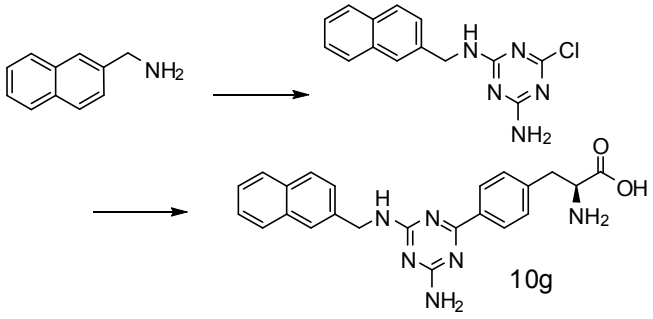
29, Synthesis of (S)-2-amino-3-(4-(5-((9-ethyl-9H-carbazol-3-yl)methylamino)pyridin-2-yl)phenyl)propanoic acid (20).



6-Bromo-N-((9-ethyl-9H-carbazol-3-yl)methyl)pyridin-3-amine. This compound was prepared using sodium triacetoxyborohydride (1.19 g, 5.61 mmol), 6-bromopyridin-3-amine (775 mg, 4.48 mmol), 9-ethyl-9H-carbazole-3-carbaldehyde (1g, 4.48 mmol), HOAc (0.5 mL) following the similar procedure described for 9**c**. 1.7g of the crude titled product was obtained and small amount was used in the following step.

(**S)-2-amino-3-(4-(5-((9-ethyl-9H-carbazol-3-yl)methylamino)pyridin-2-yl)phenyl) propanoic acid (20).** Compound **20** was prepared using (6-bromo-N-((9-ethyl-9H-carbazol-3-yl)methyl)pyridin-3-amine (56 mg, 0.15 mmol), (S)-2-amino-3-(4-borono phenyl)propanoic acid (31 mg, 0.15 mmol), aqueous sodium carbonate (2 mL, 1M) and dichlorobis(triphenylphosphine)-palladium(II) (5.3 mg, 0.0075 mmol), by following the similar procedure described for **1a**. **20** (TFA salt, 5 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (s, 1 H), 8.07 (d, *J* = 7.62 Hz, 1 H), 7.90 (m, 2 H), 7.74 (m, 2 H), 7.52 (s, 1 H), 7.50 (m, 4 H), 7.23 (m, 1 H), 4.65 (s, 2 H), 4.43 (d, 2 H), 3.27 (m, 2 H), 2.19 (d, *J* = 8.40 Hz, 2 H), 1.38 (t, *J* = 7.13 Hz, 3 H). MS (EI) m/z: 465 (M+H)

30, Synthesis of (S)-2-Amino-3-(4-(4-amino-6-((naphthalene-2-ylmethyl)-amino)-(1,3,5)triazin-2-yl)-phenyl)-propionic acid (10g)

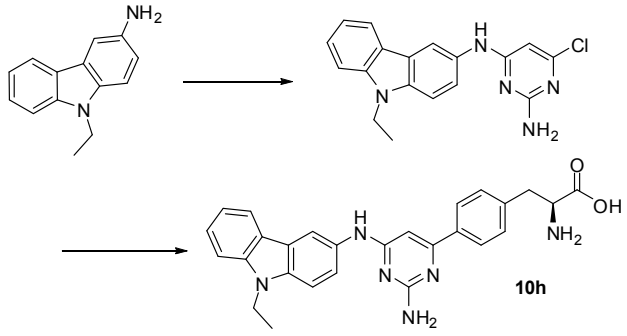


6-Chloro-N-naphthalen-2-ylmethyl-(1,3,5) triazine-2,4-diamine: To a solution of C-naphthalen-2-yl-methylamine(1g, 6.06 mmol) and 4,6-dichloro-(1,3,5)triazin-2-

ylamine (1.17 g, 6.06 mmol) in dry EtOAc(50 mL) was added drop wise N,N-diisopropyl ethylamine (2.78 mL, 18.18 mmol). Progress of reaction was monitored by LCMS. After completion of reaction, EtOAc was removed. DCM (2x20 mL) was added to the residue and the mixture was filtered. The filtrate was concentrated to give the crude product (400 mg, 20%), which was used in the next step without further purification.

(S)-2-Amino-3-(4-(4-amino-6-((naphthalene-2-ylmethyl)-amino)-(1,3,5)triazin-2-yl)-phenyl)-propionic acid(10g): A microwave reaction vial (20 mL) was charged with 6-chloro-N-naphthalen-2-ylmethyl-(1,3,5) triazine-2,4-diamine (200 mg, 0.7 mmol,), 4-borono-L-phenylalanine (146 mg, 0.7 mmol), sodium carbonate (148 mg, 1.4 mmol,) 10 mol % of dichloro bis(triphenylphosphine)-palladium(II), acetonitrile (8 mL) and water (8 mL). The reaction vessel was sealed and irradiated in a microwave reactor at 180°C for 10 min. After cooling to room temperature, the reaction mixture was evaporated to dryness. The residue was dissolved in MeOH and H_2O, and further purified by reverse phase preparative HPLC to give 168 mg (58%) of the titled compound as TFA salt (**28**). ^{1}H-NMR (400 MHz, CD_3OD): δ 3.3 (m, 1H), 3.42 (m, 1H), 4.32 (m, 1H), 5.05(s, 2H), 7.47 (m, 5H), 7.87(m, 4H), 8.2(m, 2H). MS (EI) m/z: 415 (M+H).

31, Synthesis of (S)-2-amino-3-(4-(2-amino-6-(9-ethyl-9H-carbazol-3-ylamino) pyrimidin-4-yl)phenyl)propanoic acid (10h).

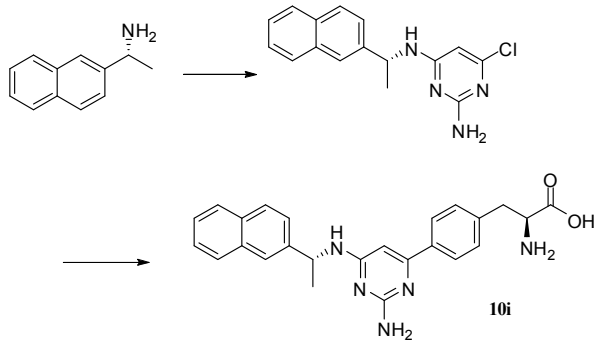


6-Chloro-N-4-(9-ethyl-9H-carbazol-3-yl)pyrimidine-2,4-diamine. To a seal tube, 2-amino-4,6-dichloropyrimidine (740 mg, 4.51 mmol), 9-ethyl-9H-carbazol-3-amine (0.95 g, 4.52 mmol), cesium carbonate (1.47 g, 4.51 mmol) and 1,4-dioxane (20 mL) were added. The tube was sealed and heated at 120^{o}C under stirring for 72 hrs. The mixture was cooled to room temperature, methylene chloride (100 mL) and water (50

mL) were added. The organic layer was separated, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give the crude titled product as brown solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 2 Hz, 1H), 7.52 (m, 1H), 7.44 (m, 2H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.25 (m, 1H), 6.86 (s, 1H), 5.97 (s, 1H), 4.93 (s, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H); MS (EI) m/z: 338 (M+H).

(S)-2-amino-3-(4-(2-amino-6-(9-ethyl-9H-carbazol-3-ylamino) pyrimidin-4-yl)phenyl)propanoic acid (10h). Compound **10h** was prepared using 6-chloro-N4-(9-ethyl-9H-carbazol-3-yl)pyrimidine-2,4-diamine (41 mg, 0.12 mmole), (S)-2-amino-3-(4-boronophenyl)propanoic acid (25 mg, 0.12 mmole), dichloro bis(triphenylphosphine) palladium(4.3 mg, 0.006 mmole), Na_2CO_3 (0.24 mL, 1M in water), by following similar procedure described for **1a. 10h**(TFA salt, 22 mg). ^{1}H NMR (300 MHz, CD_3OD): δ 8.58 (s, 1H), 8.15 (d, *J* = 6Hz, 2H), 7.81 (d, *J* = 6 Hz, 2H), 7.46-7.58 (m, 5H), 7.24 (m, 1H), 6.58 (s, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 4.28 (m, 1H), 3.31 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); MS (EI) m/z: 467 (M+H).

32, Synthesis of (S)-2-amino-3-(4-(2-amino-6-((R)-1-(naphthalen-2-yl)ethylamino) pyrimidin-4-yl)phenyl)propanoic acid (10i).

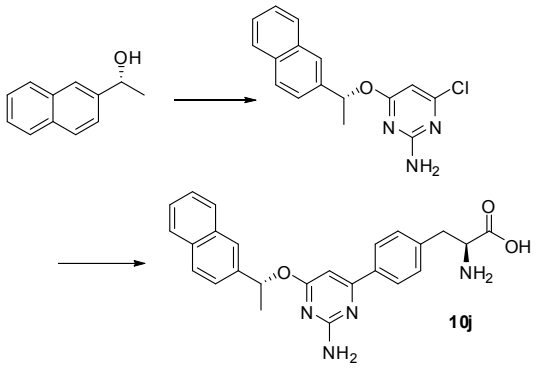


(R)-6-chloro-N4-(1-(naphthalen-2-yl)ethyl)pyrimidine-2,4-diamine. 4,6-dichloro pyrimidin-2-amine (0.327 g, 2 mmol), (R)-1-(naphthalen-2-yl)ethanamine (0.342 g, 2 mmol), cesium carbonate (0.717 g, 2.2 mmol) were added to a mixture of 1,4-dioxane (7.5 mL) and H_2O (7.5mL) in a 20 mL microwave vial. Vial was sealed and irradiated at 210 ^oC for 20 min in a microwave reactor. Mixture was cooled to room temperature and the solvent was removed. Residue was dissolved in 5 % methanol in

CH_2Cl_2 (50 mL), filtered and concentrated to get the crude titled product (0.70 g) which was used in the following step.

(S)-2-amino-3-(4-(2-amino-6-((R)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)phenyl)propanoic acid (10i). Compound **10i** was prepared using (R)-6-chloro-N4-(1-(naphthalen-2-yl)ethyl)pyrimidine-2,4-diamine (0.70 g), (S)-2-amino-3-(4-borono phenyl)propanoic acid (0.420 g, 2 mmol), sodium carbonate (0.42 g, 4 mmol), dichlorobis(triphenylphosphine)-palladium(II) (50 mg, 0.072 mmol) by following the similar procedure described for **1a**. **10i** (TFA salt, 370 mg, 29 %). ^{1}H NMR (400 MHz, CD_3OD): δ 7.87-7.81 (m, 4H), 7.73 (d, 2H, *J* = 8.4 Hz), 7.55-7.40 (m, 5H), 6.41 (s, 1H), 5.59 (q, 1H, 6.9 Hz), 4.31 (t, 1H, *J* = 6.2 Hz), 3.41-3.34 (m, 1H), 3.29-3.20 (m, 1H), 1.66 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (400 MHz, CD_3OD): δ 171.25, 164.19, 157.94, 152.15, 141.63, 140.28, 134.86, 134.23, 131.67, 129.48, 128.89, 128.64, 128.38, 127.30, 126.98, 125.78, 125.68, 96.47, 54.98, 51.74, 37.12, 22.10; MS (EI) m/z: 428 (M +H). HRMS (ES+) calculated for $C_{25}H_{26}N_5O_2^+$ $(M + H)^+$ 428.2087, found 428.2087.

33, Synthesis of (S)-2-amino-3-(4-(2-amino-6-((R)-1-(naphthalen-2-yl)ethoxy)pyrimidin-4-yl)phenyl)propanoic acid (10j).

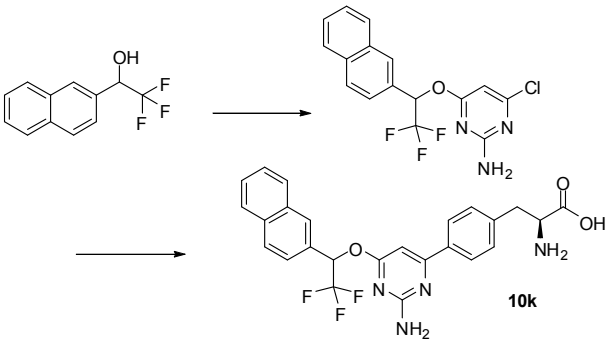


(R)-4-chloro-6-(1-(naphthalen-2-yl)ethoxy)pyrimidin-2-amine. 4,6-Dichloro pyrimidin-2-amine (0.361 g, 2.2 mmol), (R)-1-(naphthalen-2-yl)ethanol (0.344 g, 2.0 mmol), NaH (80 mg, 2.0 mmol) were added to anhydrous 1,4-dioxane (20 mL) under nitrogen atmosphere. The reaction was stirred at 100 ^{o}C for 6h. The mixture was then cooled to room temperature, quenched with water (0.2 mL). The solvent were removed under reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (50 mL),

washed with water (20 mL), brine (20 mL) dried (Na_2SO_4) and concentrated to get the crude titled product (0.60 g) which was directly used in the following step.

(S)-2-amino-3-(4-(2-amino-6-((R)-1-(naphthalen-2-yl)ethoxy)pyrimidin-4-yl)phenyl) propanoic acid (10j). Compound **10j** was prepared using (R)-4-chloro-6-(1-(naphthalen-2-yl)ethoxy)pyrimidin-2-amine (0.30 g), (S)-2-amino-3-(4-boronophenyl)propanoic acid (0.30 g, 1.4 mmol), sodium carbonate (0.30 g, 2.8 mmol), dichlorobis(triphenyl phosphine)palladium(II) (40 mg, 0.057 mmol) by following the similar procedure described for **1a**. Small amount of crude product was purified by preparative HPLC to afford **10j** (TFA salt, 11 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.78-7.73 (m, 2H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.61-7.65 (m, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.45-7.29 (m, 5H), 4.28-4.22 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 1H) 3.39 -3.32 (m, 1H), 3.23-3.15 (m, 1H), 1.76 (d, *J* = 7.1 Hz, 3H); (EI) m/z: 429 (M +H).

34, Synthesis of (2S)-2-amino-3-(4-(2-amino-6-(2,2,2-trifluoro-1-(naphthalen-2-yl) ethoxy)pyrimidin-4-yl)phenyl)propanoic acid (10k).

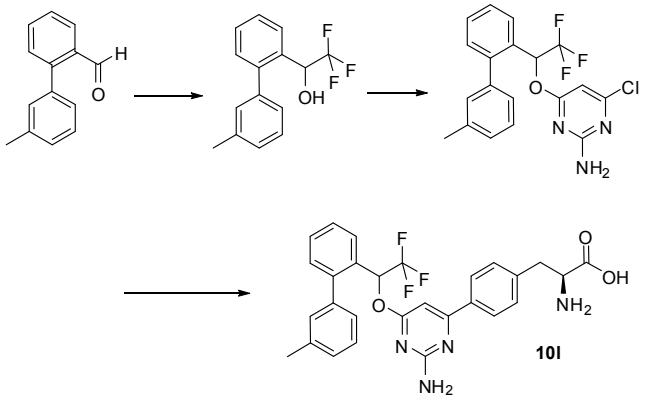


4-chloro-6-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethoxy)pyrimidin-2- amine. This compound was prepared using 4,6-dichloropyrimidin-2-amine (0.114 g, 0.7 mmol), 2,2,2-trifluoro-1-(naphthalen-2-yl)ethanol (0.156 g, 0.7 mmol) and Cs_2CO_3 (0.25 g, 1.1 mmol) by following the similar procedure used for **16**. Crude titled product (213 mg) obtained was directly used in the following step.

(2S)-2-amino-3-(4-(2-amino-6-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethoxy) pyrimidin-4-yl)phenyl)propanoic acid (10k). Compound **10k** was prepared using 4-chloro-6-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethoxy)pyrimidin-2- amine (0.213 g, 0.6 mmol), (S)-2-amino-3-(4-boronophenyl)propanoic acid (0.125 g, 0.6 mmol), sodium

carbonate (0.125g, 1.2 mmol), dichlorobis(triphenylphosphine)palladium(II) (8 mg, 0.012 mmol) by following the similar procedure used for **1a**. Small amount of crude product was purified by preparative HPLC to afford **10k**(TFA salt, 1.5 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.02 (s, 1H), 7.87-7.79 (m, 5H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.48-7.42 (m, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.86 (q, *J* = 6.8 Hz, 1H), 6.78 (s, 1H), 3.32 -3.24 (m, 1H), 3.22-3.20 (m, 1H), 3.17-3.10 (m, 1H); MS (EI) m/z: 483 (M +H).

35, Synthesis of (S)-2-Amino-3-(4-{2-amino-6-[2,2,2-trifluoro-1-(3'-methyl-biphenyl-2-yl)-ethoxy]-pyrimidin-4-yl}-phenyl)propionic acid (10l).



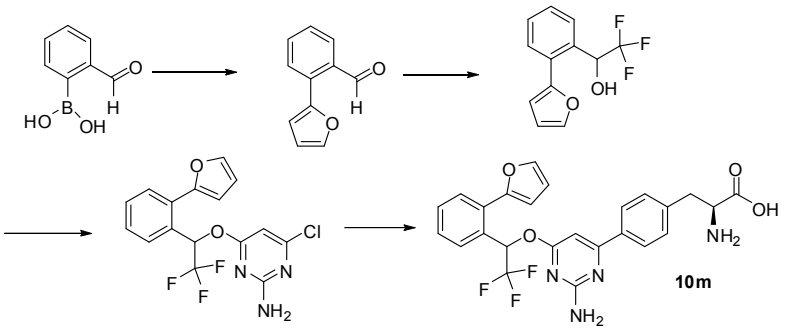
2,2,2-Trifluoro-1-(3'-methyl-biphenyl-2-yl)-ethanol. Tetrabutylammonium fluoride (13 µl, 1.0M in THF) was added to a reaction mixture containing 3'-methyl-biphenyl-2-carbaldehyde (0.25g, 1.274 mmol) and trifluoromethyltrimethylsilane (0.25g, 1.526 mmol) in THF (10 mL) at 0^o C. The reaction was warmed to room temperature and stirred for 4 hours. 2.0 M HCl (2.0 mL) was added and the mixture was further stirred for 3 hours. The mixture was concentrated and the residue was dissolved in dichloromethane, filtered through a plug of silica gel and concentrated to give 0.15 g of the crude titled compound.

4-Chloro-6-[2,2,2-trifluoro-1-(3'-methyl-biphenyl-2-yl)-ethoxy]-pyrimidin-2-ylamine. 2,2,2-Trifluoro-1-(3'-methyl-biphenyl-2-yl)-ethanol (0.15g, 0.5633 mmol) was treated with sodium hydride (45 mg, 1.127 mmol) in THF (5 mL) for 30 minutes. 2-amino-4,6-dichloropyrimidine (92 mg, 0.5633 mmol) was added and the reaction was stirred for 18 hours at room temperature. The reaction was quenched with water and concentrated. The crude product was purified by silica gel column chromatography using

methanol (2%) in dichloromethane to give 0.16 g of the titled product. ^{1}H NMR (400 MHz , DMSO-d6): δ 7.67 (d, J=7.45 Hz, 1H), 7.54-7.50 (m, 2H), 7.45 (t, J=7.52 Hz, 1H), 7.32-7.22 (m, 3H), 7.18 (s, 1H), 7.13-7.05 (m, 1H), 6.83-6.76 (m, 1H), 6.36 (s, 1H), 2.38 (s, 3H) ; MS (EI) m/z: 394 (M+H).

(S)-2-Amino-3-(4-{2-amino-6-[2,2,2-trifluoro-1-(3'-methyl-biphenyl-2-yl)-ethoxy]-pyrimidin-4-yl}-phenyl)-propionic acid (10l). Compound **10l** was prepared using 4-chloro-6-[2,2,2-trifluoro-1-(3'-methyl-biphenyl-2-yl)-ethoxy]-pyrimidin-2-ylamine (0.16 g, 0.406 mmol), 4-borono-L-phenylalanine (0.10 g, 0.487 mmol), dicholoro bis(triphenylphosphin palladium (17 mg, 0.024 mmol), sodium carbonate (95 mg, 0.894 mmol), by following a similar procedure described for **1a**. **10l** (TFA salt, 105 mg). Compound **32** was suspended in 1 N HCl (2 mL), diluted with water (3 mL), frozen and lyophilized to get the dihydrochloride salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.85 (d, 2H, *J* = 7.4 Hz), 7.7 (d, 1H, *J* = 7.4 Hz), 7.49-7.37 (m, 3H), 7.31 (t, 1H, *J* = 8.2 Hz), 7.24-7.17 (m, 2H), 7.13-7.06 (m, 2H), 6.91-6.82 (m, 2H), 4.25 (t, 1H, *J* = 7.9 Hz), 3.35-3.16 (m, 3H), 2.31 (s, 3H); MS (EI) m/z: 523 (M +H). Analysis calculated for $C_{28}H_{25}F_3N_4O_3.2HCl.2H_2O$: C 53.26 H 4.95 N 8.87 Found : C 52.73 H 4.66 N 8.75. HRMS (ES+) calculated for $C_{28}H_{26}F_3N_4O_3^+$ $(M + H)^+$ 523.1957, found 523.1962. ^{13}C NMR (400 MHz, CD_3OD): δ 172.58, 171.29, 159.95, 159.56, 145.45, 141.78, 141.50, 140.04, 132.25, 132.22, 131.64, 131.52, 131.37, 130.14, 130.01, 129.71, 129.67, 129.63, 129.49, 127.81, 97.72, 73.95, 73.63, 73.30, 72.97, 55.15, 37.53, 21.99.

36, Synthesis of (2S)-2-amino-3-(4-(2-amino-6-(2,2,2-trifluoro-1-(2-(furan-2-yl)phenyl)ethoxy)pyrimidin-4-yl)phenyl)propanoic acid (10m).



2-(Furan-2-yl)benzaldehyde. To a microwave vial 2-bromofuran (295 mg, 2.01 mmol), 2-formylphenylboronic acid (300 mg, 2.01 mmol), actonitrile (4 mL), aqueous

sodium carbonate solution (4 mL, 1N), dichlorobis(triphenylphosphine)palladium(II) (70 mg, 0.101 mmol) were added. The reaction vessel was sealed and heated at 150°C for 7 minutes with microwave irradiation. After cooling to ambient temperature, ethyl acetate (50 mL) was added. Organic layer was separated, washed with water, dried (sodium sulfate) and concentrated. The residue was purified by silica gel column chromatography to give the titled compound (270 mg, 78%). ^{1}H NMR (400 MHz, CHLOROFORM-*d*): δ 10.41 (s, 1 H), 8.00 (dd, *J*=7.83, 1.26 Hz, 1 H), 7.68 - 7.77 (m, 1 H), 7.60 - 7.68 (m, 2 H), 7.47 (t, *J*=7.45 Hz, 1 H), 6.66 (d, *J*=3.54 Hz, 1 H), 6.59 (dd, *J*=3.41, 1.89 Hz, 1 H); MS (EI) m/z: 172 (M +H)

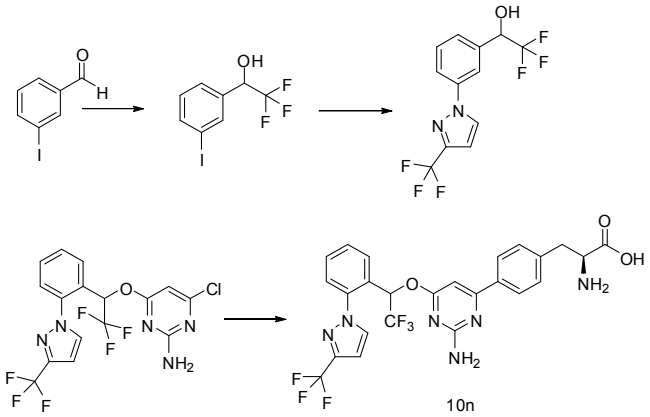
2,2,2-trifluoro-1-(2-(furan-2-yl)phenyl)ethanol. Tetrabutylammonium fluoride (0.024 mL, 1.0 M in tetrahydrofuran) was added to a solution of 2-(furan-2-yl)benzaldehyde (270 mg, 1.57 mmol) and trifluoromethyltrimethylsilane ($TMSCF_3$) (278 uL, 1.88 mmol) in THF (5 mL) at 0°C. The formed mixture was warmed up to room temperature and stirred for 4 hours. The reaction mixture was then treated with 5 mL of 1N HCl and stirred overnight. The product was extracted with ethyl acetate (3 x 50 mL). The organic layer was separated and dried over sodium sulfate. The organic solvent was evaporated to give the crude titled compound (432 mg, 81%).

4-chloro-6-(2,2,2-trifluoro-1-(2-(furan-2-yl)phenyl)ethoxy)pyrimidin-2-amine. A mixture of 2,2,2-trifluoro-1-(2-(furan-2-yl)phenyl)ethanol (97 mg, 0.4 mmol), 4,6-dichloro-pyrimidin-2-ylamine (60 mg, 0.36 mmol), and cesium carbonate (468 mg, 1.44 mmol) was dissolved in 1,4-dioxane (1 mL) and heated at 110 ^{o}C overnight. The reaction mixture was cooled to room temperature, ethyl acetate (10 mL) was added and then filtered through celite, and the filtrate was concentrated to give the crude titled compound (120 mg, 88 %)

(2S)-2-amino-3-(4-(2-amino-6-(2,2,2-trifluoro-1-(2-(furan-2-yl)phenyl)ethoxy) pyrimidin-4-yl)phenyl)propanoic acid (10m). Compound **10m** was prepared using 4-chloro-6-(2,2,2-trifluoro-1-(2-(furan-2-yl)phenyl)ethoxy)pyrimidin-2-amine (30 mg, 0.081 mmol), (S)-2-amino-3-(4-borono phenyl)propanoic acid (20 mg, 0.098 mmol), 1N aqueous sodium carbonate (0.3 mL) and dichlorobis(triphenylphosphine)palladium(II) (2.8 mg, 0.004 mmol) by following a similar procedure used for **1a**. **10m** (TFA salt, 7.7 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.83 (d, *J* = 8.34 Hz, 2 H), 7.66 - 7.73 (m, 2 H),

7.61 (dd, *J* = 7.83, 1.26 Hz, 1 H), 7.51 (d, *J* = 6.32 Hz, 1 H), 7.39 - 7.47 (m, 2 H), 7.31 - 7.39 (m, 1 H), 6.87 (s, 1 H), 6.74 (d, *J* = 3.28 Hz, 1 H), 6.56 (dd, *J* = 3.28, 1.77 Hz, 1 H), 4.24 (t, *J* = 6.69 Hz, 1 H), 3.25 - 3.34 (m, 1 H), 3.14 - 3.20 (m, 1 H). MS (EI) m/z: 499 (M +H)

37, Synthesis of (S) -2-amino-3-[4-(2-amino-6-[2,2,2-trifluoro-1-(2-(3-trifluoromethyl-pyrazol-1-yl-phenyl)-ethoxy]-pyrimidin-4-yl]-phenyl-propionic acid (10n).



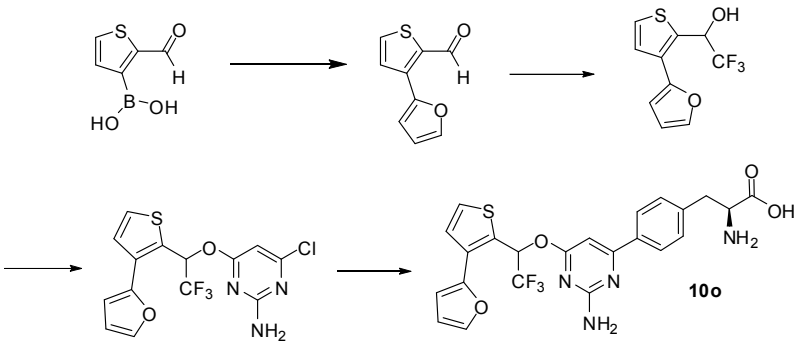
(2,2,2-Trifluoro-1-(2-iodo-phenyl)-ethanol. This compound was prepared using 3-iodo-benzaldehyde (1.85 g, 8 mmol), trifluoro trimethyl silane (0.96 g, 10 mmol), tetrabutyl ammonium fluoride (0.2 ml, 0.2 mmol, 1M in THF) by using a similar procedure described for **10m**. The crude product (2.3 g, 95 %) was directly used in the following step.

2,2,2-trifluoro-1-[2-(3-trifluoro methyl-pyrazol-1-yl)-phenyl]-ethanol. 2,2,2-Trifluoro-1-(2-iodo-phenyl)-ethanol (0.331 g, 1.1 mmol) , 3-trifluoromethyl pyrazole (0.136 g, 1.0 mmol), CuI (0.019 g, 0.1 mmol), K_2CO_3 (0.290 g, 2.1 mmol), (1R,2R)-N,N'-dimethyl-cyclohexane-1,2-diamine (0.028 g, 0.2 mmol) and toluene (10 mL) were taken in a 20 mL pressure tube and heated at 130 ^oC for 12 h. The reaction mixture was diluted with ethyl acetate, washed with H_2O (2 x 20 mL), brine, dried and concentrated. The crude product was separated by silica gel column chromatography using 5-10 % ethyl acetate in hexane as solvent to get the titled compound (140 mg, 45 %). MS (EI) m/z: 311 (M +H).

4-chloro-6-[2, 2, 2-trifluoro-1-[2-(3-trifluoromethyl-pyrazol-1-yl)phenyl]-ethoxy]-pyrimidine-2-ylamine. 4, 6-Dichloro pyrimidine (0.074 g, 0.45 mmol), 2,2,2-trifluoro-1-[2-(3-trifluoro methyl-pyrazol-1-yl)-phenyl]-ethanol (0.140 g, 0.45 mmol), NaH (0.022 g, 0.59 mmol) were added to anhydrous THF (10 mL) under nitrogen atmosphere. The reaction was stirred at 40-45 ^{o}C for 6 h, then cooled to room temperature, quenched with water (0.2 ml) and concentrated to afford the crude titled compound (0.21 g), which was directly used in the following step. MS (EI) m/z: 438 (M +H)

(S) -2-amino-3-[4-(2-amino-6-[2,2,2-trifluoro-1-(2-(3-trifluoromethyl-pyrazol-1-yl-phenyl)-ethoxy]-pyrimidin-4-yl]-phenyl-propionic acid (10n). Compound **10n** was prepared using crude 4-chloro-6-[2, 2, 2-trifluoro-1-[2-(3-trifluoromethyl-pyrazol-1-yl)phenyl]-ethoxy]-pyrimidine-2-ylamine (0.21 g), L-p-borono-phenylalanine (0.1 g, 0.48 mmol), sodium carbonate (0.1 g, 0.94 mmol), and dichloro bis(triphenylphosphine)-palladium(II) (15 mg, 0.021 mmol) by following a similar procedure described for **1a** to give **10n** (12 mg) as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 8.20 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.88-7.84 (m, 1H), 7.68-7.62 (m, 2H), 7.59-7.55 (m, 1H), 7.42 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 6.85-6.78 (m, 2H), 4.32-4.27 (m, 1H), 3.41-3.34 (m, 1H), 3.26-3.17 (m, 1H)); MS (EI) m/z: 567 (M +H).

38, Synthesis of (2S)-2-amino-3-(4-(2-amino-6-(2,2,2-trifluoro-1-(3-(furan-2-yl)thiophen-2-yl)ethoxy)pyrimidin-4-yl) phenyl)propanoic acid (10o).



3-(furan-2-yl)thiophene-2-carbaldehyde. This compound was prepared using 2-formyl thiophen-3-yl boronic acid (156 mg, 1.0 mmol), 2-bromo-furan (145 mg, 1.0 mmol), aqueous sodium carbonate (1M, 2 mL), and dichlorobis(triphenylphosphine) palladium(II) (50 mg, 0.071 mmol) by following a similar procedure described for **1a** to

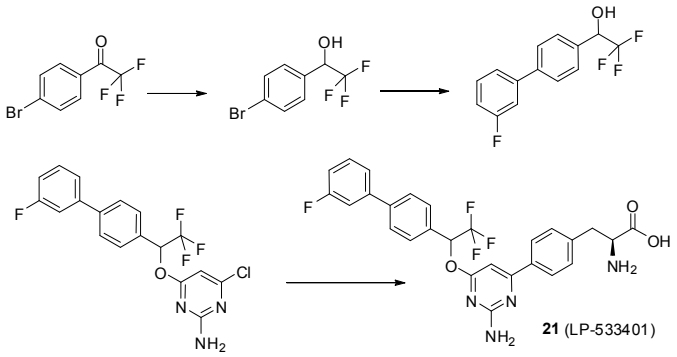
provide the crude material which was purified by silica gel column chromatography to afford the titled compound (162 mg, 95%) for immediate use in next step. MS (EI) m/z: 179

2,2,2-trifluoro-1-(3-(furan-2-yl)thiophen-2-yl)-ethanol. This compound was prepared using tetrabutylammonium fluoride (0.1 mL, 1M in THF), 3-(furan-2-yl)thiophene-2-carbaldehyde (178 mg, 1 mmol) and trifluoromethyl trimethylsilane (0.2 mL, 1.2 mmol), by following a similar procedure described for **10m** to give 0.180 g (90 %) of the crude titled compound which was directly used in next step.

4-Chloro-6-[2,2,2-trifluoro-1-(3-(furan-2-yl)thiophen-2-yl)ethoxy]-pyrimidin-2-yl amine. Cs_2CO_3 (325 mg, 1.0 mmol) was added to a solution of 2,2,2-trifluoro-1-(3-(furan-2-yl)thiophen-2-yl)-ethanol (50 mg, 0.2 mmol) in anhydrous 1,4-dioxane (10 mL). The mixture was stirred for 20 min, 2-amino-4,6-dichloro-pyrimidine (30 mg, 0.22 mmol) was added and then the reaction mixture was heated at 110^0C until the reaction was completed. After cooling to room temperature, water (5 mL) was added and ethyl acetate (20 mL) was used to extract the product. The organic layer was dried over sodium sulfate. The solvent was removed by rotovap to give 71 mg (78 %) of the crude product.

(2S)-2-amino-3-(4-(2-amino-6-(2,2,2-trifluoro-1-(3-(furan-2-yl)thiophen-2-yl) ethoxy)pyrimidin-4-yl)phenyl)propanoic acid (10o). Compound **10o** was prepared using 4-chloro-6-[2,2,2-trifluoro-1-(3-(furan-2-yl)thiophen-2-yl)ethoxy]-pyrimidin-2-ylamine (38 mg, 0.1 mmol), 4-borono-L-phenylalanine (31 mg, 0.15 mmol), aqueous sodium carbonate (0.3 mL, 1M) and dichlorobis(triphenylphosphine)-palladium(II) (3.5 mg, 0.005 mmol) by following a similar procedure described for **1a**. **10o** (TFA salt, 5.0 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (d, J = 8.3Hz, 2H), 7.82 (m, 1 H), 7.73 (s, 1H), 7.57 (d, J = 1.0 Hz, 1H), 7.43 (d, J = 8.34 Hz, 2H), 7.34 (d, J = 5.3Hz, 1H), 6.80 (d, J = 3.5Hz, 1H), 6.65 (m, 2H), 3.85 (m, 1 H), 3.33-3.09 (m, 2H). MS (EI) m/z: 505 (M +H).

39, Synthesis of (S)-2-amino-3-(4-{2-amino-6-[2,2,2-trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethoxy]-pyrimidin-4-yl}-phenyl)-propionic acid (compound 21).



1-(4-Bromo-phenyl)-2,2,2-trifluoro-ethanol. 1-(4-bromo-phenyl)-2,2,2-trifluoro-ethanone (5.0 g, 19.76 mmol) was dissolved in THF (50 mL) and treated with sodium borohydride (0.82 g, 21.74 mmol). The mixture was stirred at room temperature for 1 hour then quenched with water. Most of the THF was removed under reduced pressure and the residue was extracted twice with dichloromethane. Organic layer was combined, washed with brine, dried ($MgSO_4$), filtered through a plug of silica gel, and concentrated to give 4.65g (92%) of the titled compound, which was directly used in the following step.

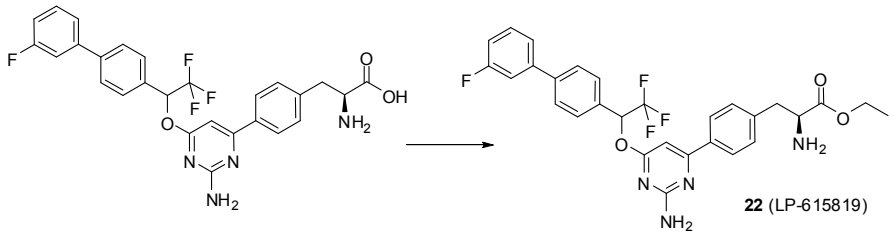
2,2,2-Trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethanol. 3-Fluorophenylmagnesium bromide (1.0 M in THF, 55 ml, 55.0 mmol) was added to solid tetrakis triphenyl phosphine palladium (2.1g, 1.823 mmol) at 0^o C over 15 min. The mixture was stirred for 30 min at 0^oC and allowed to warm to room temperature. 1-(4-bromo-phenyl)-2,2,2-trifluoro-ethanol (4.65g, 18.23 mmol) in THF (50 mL) was added over 10 minutes. The mixture was heated to reflux for 3 hours, then cooled and quenched with water. Most of the THF was removed in vacuo and the mixture was extracted 3 times with dichloromethane. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography using dichloromethane to give 4.64g of the titled compound (94 %). ^{1}H NMR (400 MHz, DMSO-d6): δ 7.75 (d, 2H, J = 8.4 Hz), 7.60 – 7.52 (m, 5H), 7.20 (m, 1H), 6.90 (d, 1H, J = 5.6 Hz), 5.25 (m, 1H); MS (EI) m/z: M+1 = 271.

4-Chloro-6-[2,2,2-trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethoxy]-pyrimidin-2-ylamine. 2,2,2-Trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethanol (1.4 g, 5.181 mmol) was treated with NaH (60% in mineral oil, 0.31g, 7.772 mmol) in THF (50 mL) at 0^o C. The mixture was stirred for 30 min at 0^oC and then allowed to warm to room temperature. 2-

amino-4,6-dicloro pyrimidine (0.85 g, 5.18 mmol) in THF (25 mL) was added. The mixture was heated at 50°C for 5 hours. The mixture was cooled, quenched with sat. NaCl solution and extracted with dichloromethane (3x). The organic alyers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography using dichloromethane/methanol to give 1.48 g (73%) of the titled compound. ^{1}H NMR (400 MHz , DMSO-d6): δ 7.65-7.57 (m, 4H), 7.48-7.35 (m, 3H), 7.32-7.26 (m, 2H), 7.12-7.06 (m, 1H), 6.58 (q, J=6.96, 1H), 6.36 (s, 1H); MS (EI) m/z: 398 (M-H).

(S)-2-Amino-3-(4-{2-amino-6-[2,2,2-trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethoxy]-pyrimidin-4-yl}-phenyl)-propionic acid. 4-Chloro-6-[2,2,2-trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethoxy]-pyrimidin-2-ylamine (0.75 g, 1.89 mmol), 4-borono-L-phenylalanine(0.47 g, 2.26 mmol), dichloro bis(triphenylphosphine) palladium (79 mg, 0.113 mmol), sodium carbonate (0.44 g, 4.15 mmol), acetonitrile (10 mL), and water (10 mL) were charged to a vial. Vial was sealed and irradiated at 150 °C for 7 min in a microwave reactor. The mixture was cooled, filtered, concentrated. The residue was taken up in water (10 mL) and 1.0N NaOH (10 mL) was added. The basic solution was acidified to pH = 6.5 with 1.0 N HCl in an ice bath. The mixture was stirred at 0° C for 30 minutes and the precipitated product was filtered, washed with water, dried, and then triturated with dichloromethane to give 1.12 g of the titled compound as HCl salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.86 (d, 2H, *J* = 7.3 Hz), 7.64 (s, 3H), 7.49 (d, 2H, *J* = 8.3 Hz), 7.36 (m, 2H), 7.28 (m, 1H), 7.01 (m, 1H), 6.95 (s, 1H), 6.75 (q, 1H, *J* = 6.4 Hz), 4.26 (t, 1H, *J* = 6.8 Hz), 3.34-3.18 (m, 3H); M+1 = 527. ^{13}C NMR (400 MHz, CD_3OD) δ 172.15, 170.90, 166.30, 163.05, 159.02, 158.82, 143.75, 143.64, 143.14, 141.58, 131.88, 131.79, 131.39, 130.47, 130.11, 129.29, 128.56., 124.02, 123.98, 115.76, 115.47, 114.93, 114.63, 97.36, 76.87, 76.42, 75.97, 75.53, 54.70, 37.09. MS (EI) m/z: 527 (M +H).

40, Synthesis of (S)-2-amino-3-(4-{2-amino-6-[2,2,2-trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethoxy]-pyrimidin-4-yl}-phenyl)-propionic acid ethyl ester (compound 22)

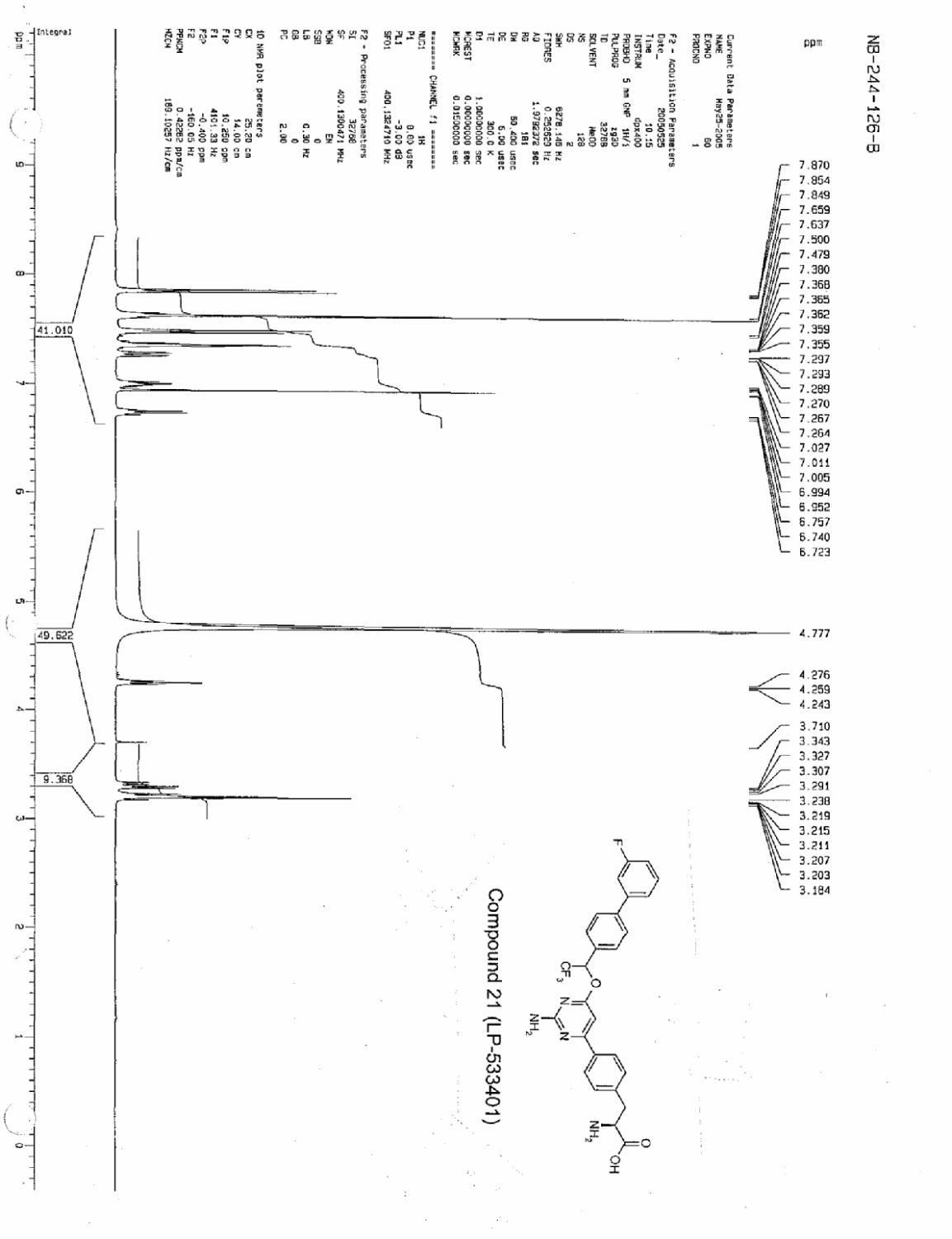


(S)-2-Amino-3-(4-{2-amino-6-[2,2,2-trifluoro-1-(3'-fluoro-biphenyl-4-yl)-ethoxy]-pyrimidin-4-yl}-phenyl)-propionic acid hydrochloride (1.1 g, 2.1 mmol) was treated with thionyl chloride (0.72 g, 6.077 mmol) in ethanol (50 mL) at 0° C. The mixture was heated at 75°C for 16 hours, then cooled and concentrated. Residue was slurried in dichloromethane and treated with an excess of triethylamine to liberate the free base. The mixture was concentrated and purified by silica gel column chromatography with methanol (2%) in dichloromethane to give 710 mgs (61%) of the titled free base. The free base was treated with excess of 2N HCl in ether, then concentrated to give the titled compound as HCl salt. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, 2H, *J* = 8.9 Hz), 7.63 (m, 3H), 7.45-7.28 (m, 3H), 7.08 (m, 1H), 6.69 (m, 2H), 5.02 (s, 2H), 4.19 (q, 2H, *J* = 7.5 Hz), 3.81 (t, 1H, *J* = 6.7 Hz), 3.2-2.95 (m, 4H), 2.02 (s, 3H), 1.26 (t, 3H, *J* = 6.9 Hz); M+1 = 555. ^{13}C NMR (400 MHz, CD_3OD): δ 172.45, 170.12, 166.32, 163.89, 160.21, 159.81, 144.19, 144.11, 143.51, 141.44, 132.27, 132.21, 131.93, 131.65, 130.49, 129.67, 128.96, 124.42, 124.40, 116.10, 115.89, 115.31, 115.09, 97.51, 76.94, 76.60, 76.27, 75.94, 64.24, 55.25, 37.62, 14.75. Analysis calculated for $C_{29}H_{26}F_4N_4O_3$(free base): C 62.81 H 4.73 N 10.1 Found C 62.80 H 4.59 N 9.98. HRMS (ES^+) calculated for $C_{29}H_{27}F_4N_4O_3^+$ $(M+H)^+$ 555.2019, Found 555.2021.

Table of compound purity.

Compound	Purity (%)	Analytical method
1a	100	HPLC; LCMS; 1H/13C NMR; elemental
9a	94	HPLC; LCMS; 1H NMR;
9b	93	HPLC; LCMS; 1H NMR;
9c	94	HPLC; LCMS; 1H NMR;
9d	98	HPLC; LCMS; 1H NMR;
9e	96	HPLC; LCMS; 1H NMR;
9f	96	HPLC; LCMS; 1H NMR;
9g	98	HPLC; LCMS; 1H/13C NMR; elemental
9h	96	HPLC; LCMS; 1H NMR;
9i	93	HPLC; LCMS; 1H NMR;
9j	98	HPLC; LCMS; 1H NMR; elemental
9k	98	HPLC; LCMS; 1H NMR;
9l	98	HPLC; LCMS; 1H NMR;
11	91	HPLC; LCMS; 1H NMR;
12	100	HPLC; LCMS; 1H NMR;
13	100	HPLC; LCMS; 1H NMR;
14	98	HPLC; LCMS; 1H NMR;
15	98	HPLC; LCMS; 1H NMR;
10a	100	HPLC; LCMS; 1H/13C NMR; elemental
10b	100	HPLC; LCMS; 1H NMR
16	98	HPLC; LCMS; 1H NMR
17	98	HPLC; LCMS; 1H NMR
10c	99	HPLC; LCMS; 1H NMR
10d	98	HPLC; LCMS; 1H NMR

10e	96	HPLC; LCMS; 1H NMR
10f	96	HPLC; LCMS; 1H NMR
18	98	HPLC; LCMS; 1H NMR; elemental
19	97	HPLC; LCMS; 1H NMR
20	97	HPLC; LCMS; 1H NMR
10g	99	HPLC; LCMS; 1H NMR
10h	96	HPLC; LCMS; 1H NMR
10i	98	HPLC; LCMS; 1H NMR; HRMS
10j	100	HPLC; LCMS; 1H NMR
10k	99	HPLC; LCMS; 1H NMR
10l	98	HPLC; LCMS; 1H/13C NMR; elemental; HRMS
10m	98	HPLC; LCMS; 1HNMR
10n	96	HPLC; LCMS; 1HNMR
10o	100	HPLC, LCMS; 1H NMR
21	98	HPLC; LCMS; 1H/13C NMR
22	100	HPLC; elemental; LCMS; 1H/13C NMR


NB-244-126-B
Compound 21 (LP-533401)
41.010
49.622
9.368
7.870
7.854
7.849
7.659
7.637
7.500
7.479
7.380
7.368
7.365
7.362
7.359
7.355
7.297
7.293
7.289
7.270
7.267
7.264
7.027
7.011
7.005
6.994
6.952
6.757
6.740
6.723
4.777
4.276
4.259
4.243
3.710
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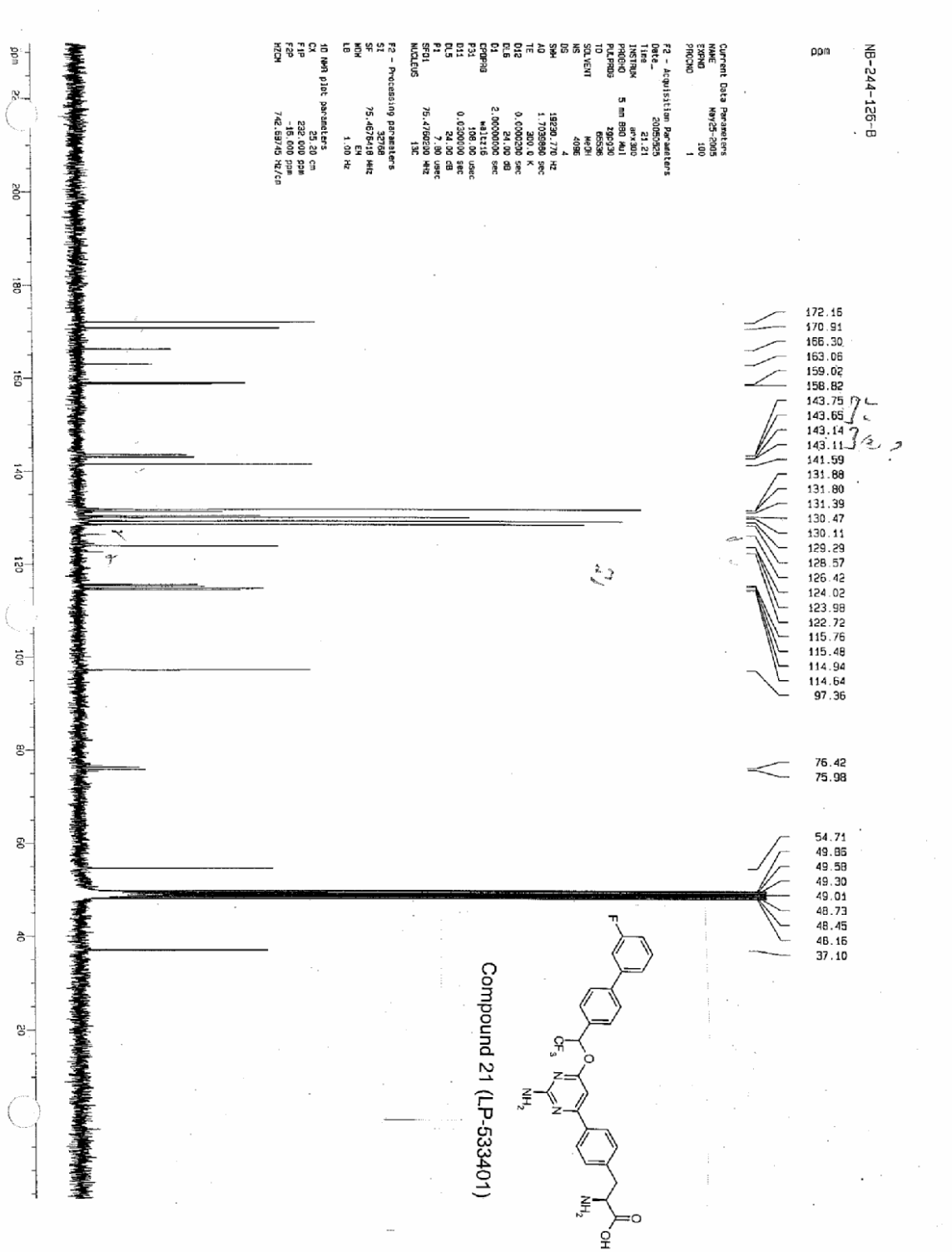
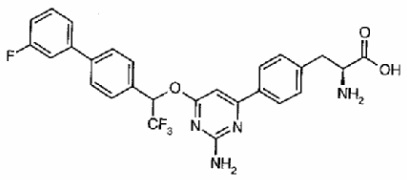
3.219
3.215
3.211
3.207
3.203
3.184

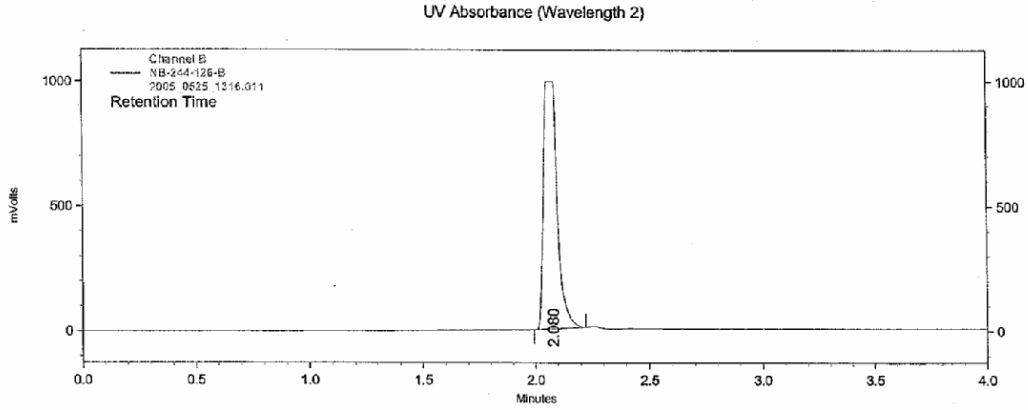

NB-244-126-B
ppm
172.16
170.91
166.30
163.06
159.02
156.82
143.75
143.65
143.14
143.11
141.59
131.88
131.80
131.39
130.47
130.11
129.29
128.57
126.42
124.02
123.98
122.72
115.76
115.48
114.94
114.64
97.36
76.42
75.98
54.71
49.85
49.58
49.30
49.01
48.73
48.45
48.16
37.10
Compound 21 (LP-533401)

Discovery VP HPLC Report (p 2)

File : c:\shimadzu\sumdata\BMarinelli\20050525\2005_0525_1316.011
Sample ID : NB-244-126-B
Acquired : 5/25/2005 1:24:24 PM
File Desc. : File = 2005_0525_1316.011
User = BMarinelli
Instrument = SZ-LC4
Vial = 71 Inj. Vol. = 10 uL
Start % B = 0
Final % B = 100
Gradient Time = 2 min
Flow Rate = 3.5 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = Standard Solvents
Solvent A = 90% Water/10% MeOH/.1% TFA
Solvent B = 10% Water/90% MeOH/.1% TFA
Column 3 : Shim-pack VP ODS 4.6 x 50 mm
NB-244-126-B



Compound 21 (LP-533401)

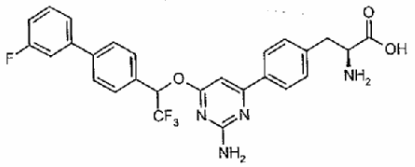


Channel B Results

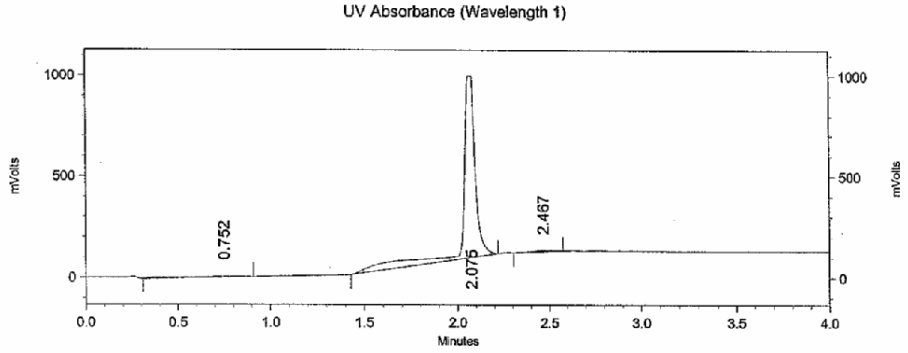
Pk #	Retention Time	Area	Area Percent
1	2.080	4202347	100.000
Totals		4202347	100.000

Discovery VP HPLC Report

File : c:\shimadzu\sumdata\BMarinelli\20050525\2005_0525_1316.011
Sample ID : NB-244-126-B
Acquired : 5/25/2005 1:24:24 PM
File Desc. : File = 2005_0525_1316.011
User = BMarinelli
Instrument = SZ-LC4
Vial = 71 Inj. Vol. = 10 uL
Start % B = 0
Final % B = 100
Gradient Time = 2 min
Flow Rate = 3.5 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = Standard Solvents
Solvent A = 90% Water/10% MeOH/.1% TFA
Solvent B = 10% Water/90% MeOH/.1% TFA
Column 3 : Shim-pack VP ODS 4.6 x 50 mm
NB-244-126-B

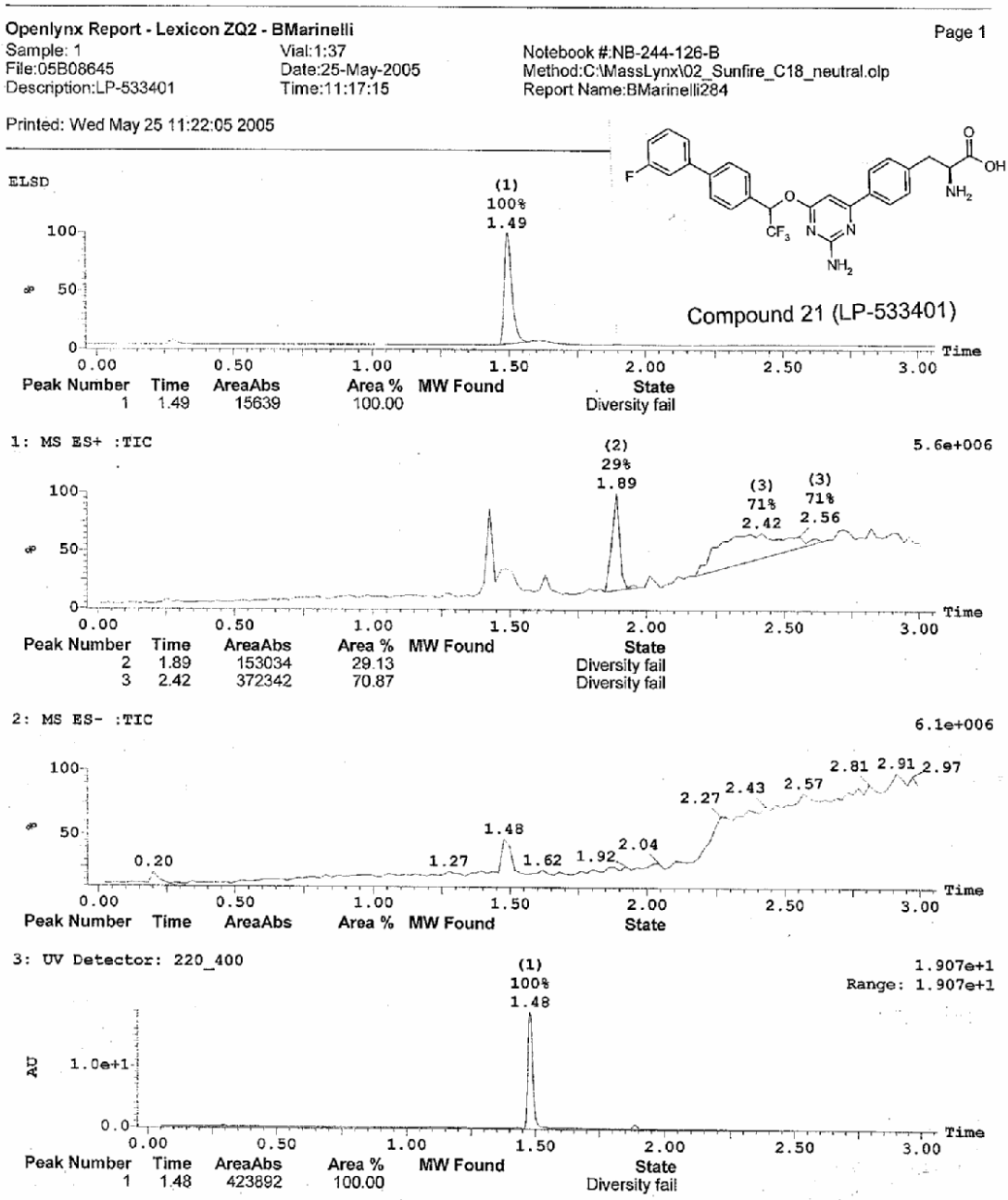


Compound 21 (LP-533401)



Channel A Results

Pk #	Retention Time	Area	Area Percent
1	0.752	119325	2.719
2	2.075	4217881	96.099
3	2.467	51908	1.183
Totals		4389114	100.000


Openlynx Report - Lexicon ZQ2 - BMarinelli
Page 1
Sample: 1
Vial:1:37
Notebook #:NB-244-126-B
File:05B08645
Date:25-May-2005
Method:C:\MassLynx\02_Sunfire_C18_neutral.olp
Description:LP-533401
Time:11:17:15
Report Name:BMarinelli284
Printed: Wed May 25 11:22:05 2005
ELSD
(1)
100%
1.49
Compound 21 (LP-533401)
Peak Number Time AreaAbs Area % MW Found State
1 1.49 15639 100.00 Diversity fail
1: MS ES+ :TIC
5.6e+006
(2)
29%
1.89
(3)
71%
2.42
(3)
71%
2.56
Peak Number Time AreaAbs Area % MW Found State
2 1.89 153034 29.13 Diversity fail
3 2.42 372342 70.87 Diversity fail
2: MS ES- :TIC
6.1e+006
0.20
1.27
1.48
1.62
1.92
2.04
2.27
2.43
2.57
2.81
2.91
2.97
Peak Number Time AreaAbs Area % MW Found State
3: UV Detector: 220_400
1.907e+1
Range: 1.907e+1
(1)
100%
1.48
AU
1.0e+1
0.0
Peak Number Time AreaAbs Area % MW Found State
1 1.48 423892 100.00 Diversity fail
Time

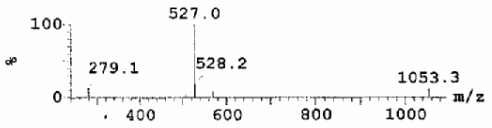
Openlynx Report - Lexicon ZQ2 - BMarinelli

Sample: 1 | Vial:1:37 | Notebook #:NB-244-126-B
File:05B08645 | Date:25-May-2005 | Method:C:\MassLynx\02_Sunfire_C18_neutral.olp
Description:LP-533401 | Time:11:17:15 | Report Name:BMarinelli284

Printed: Wed May 25 11:22:05 2005

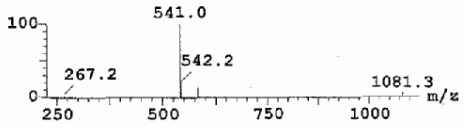
Peak ID	Time	MW Found	Compound	State
1	1.48			Diversity fail

1:(Time: 1.48) Combine (72:75-62:65) 1:MS ES+ 7.4e+005



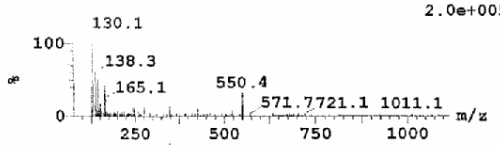
Peak ID	Time	MW Found	Compound	State
2	1.89			Diversity fail

2:(Time: 1.89) Combine (93:95-82:85) 1:MS ES+ 1.7e+006



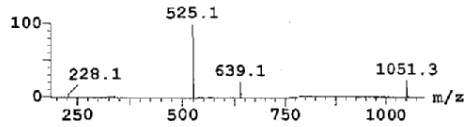
Peak ID	Time	MW Found	Compound	State
3	2.42			Diversity fail

3:(Time: 2.42) Combine (119:121-98:101) 1:MS ES+ 2.0e+005



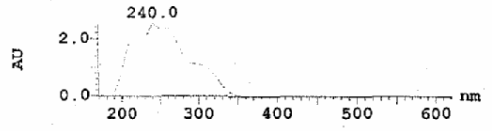
Peak ID	Time	MW Found	Compound	State
1	1.48			Diversity fail

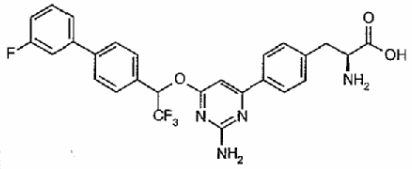
1:(Time: 1.48) Combine (72:74-62:64) 2:MS ES- 7.3e+005



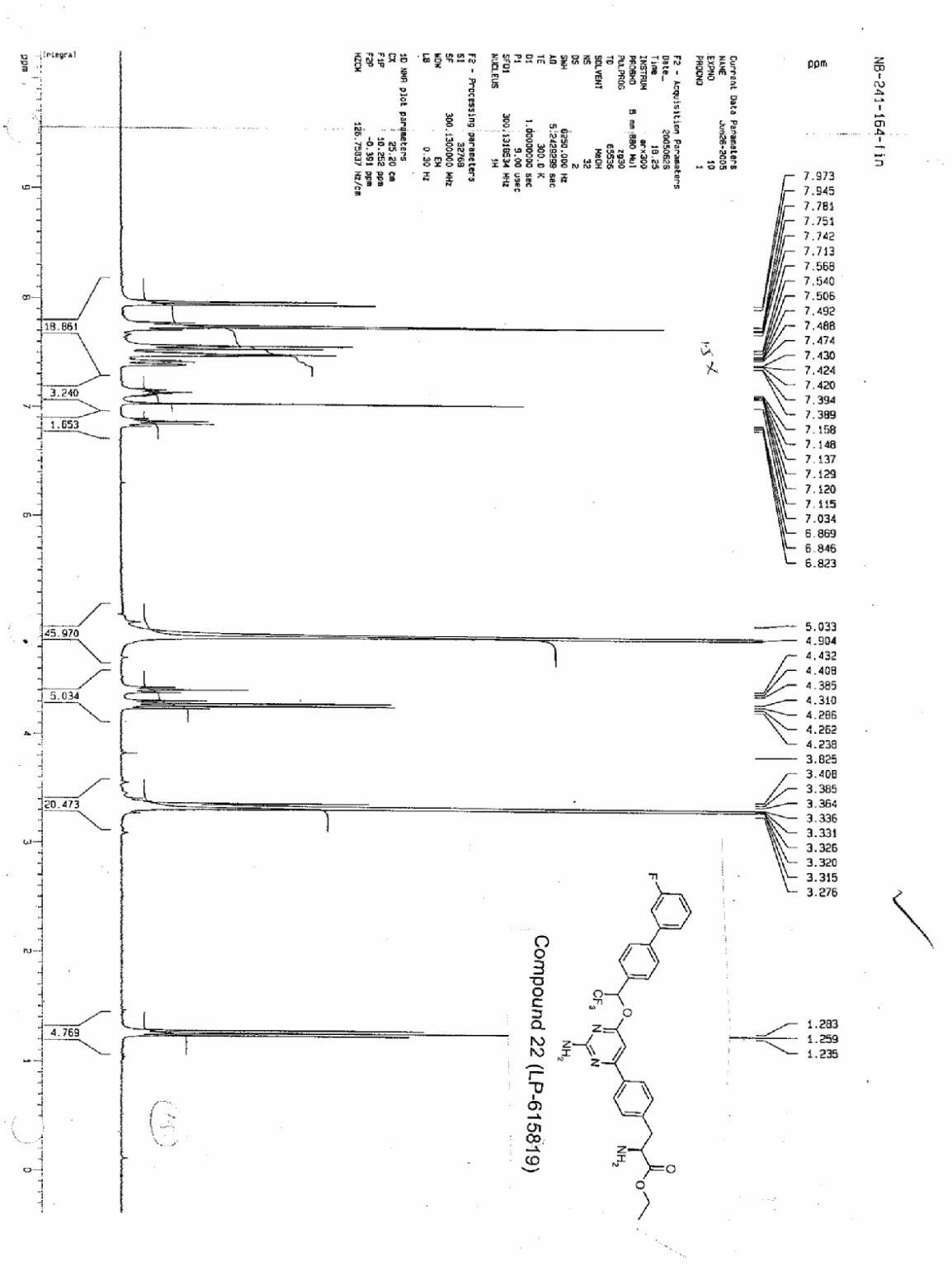
Peak ID	Time	MW Found	Compound	State
1	1.48			Noisy Diversity fail

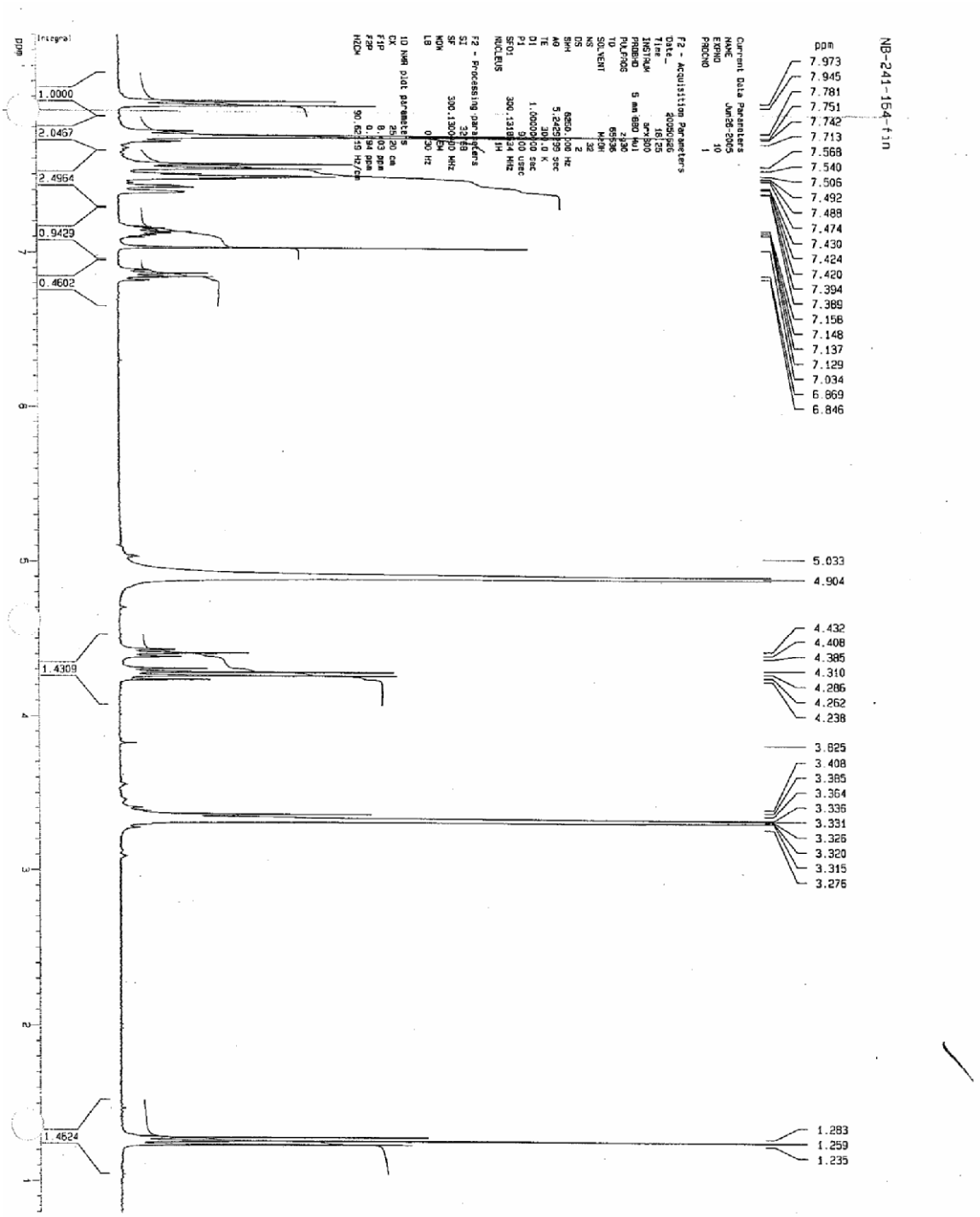
1:(Time: 1.48) Combine (938) 3:UV Detector 2.6e+006 mAU

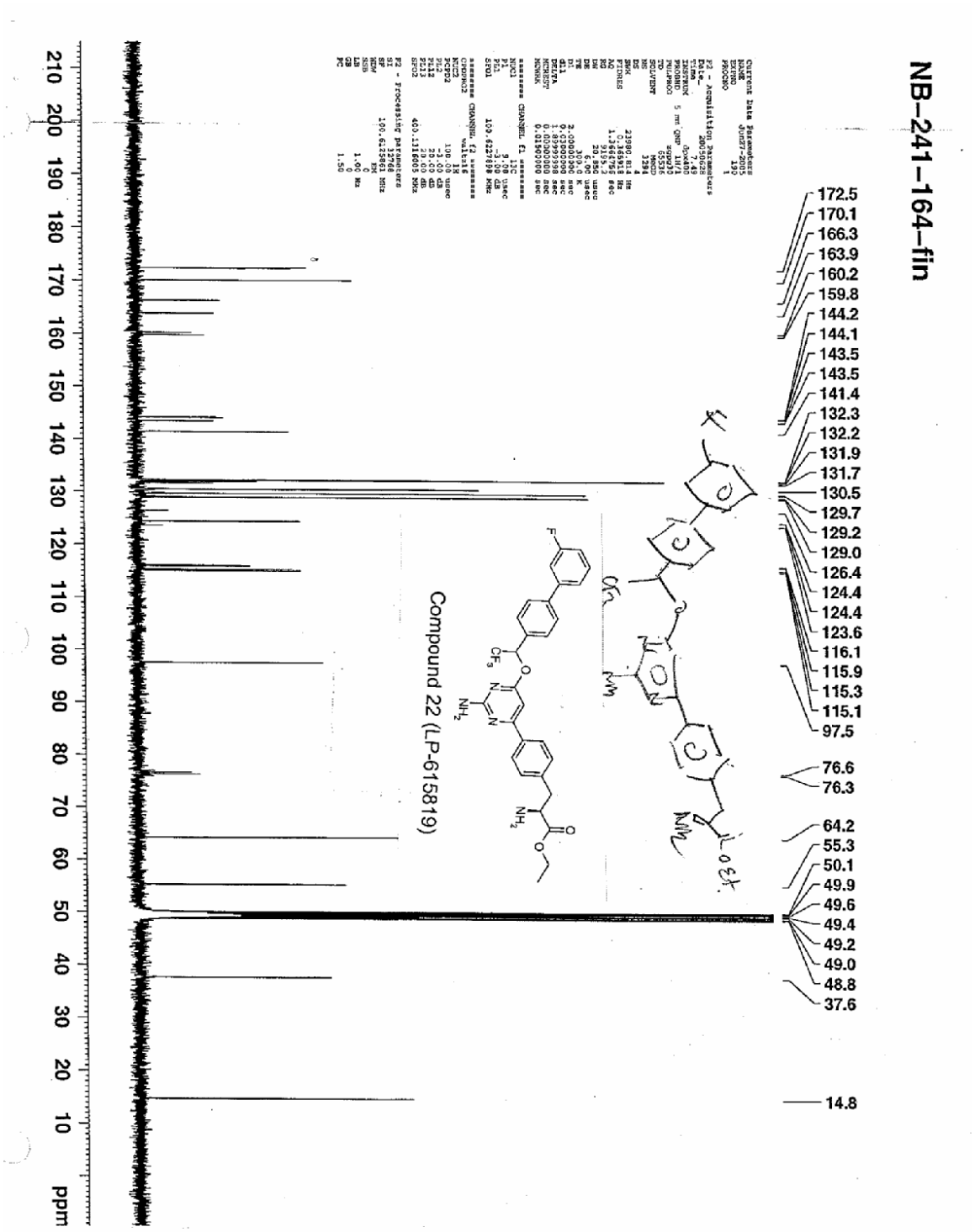




Compound 21 (LP-533401)


NB-241-164-fin
ppm
Integral
18.861
3.240
1.653
45.970
5.034
20.473
4.769
7.973
7.945
7.781
7.751
7.742
7.713
7.568
7.540
7.506
7.492
7.488
7.474
7.430
7.424
7.420
7.394
7.389
7.158
7.148
7.137
7.129
7.120
7.115
7.034
6.869
6.846
6.823
5.033
4.904
4.432
4.408
4.385
4.310
4.286
4.262
4.238
3.825
3.408
3.385
3.364
3.336
3.331
3.326
3.320
3.315
3.276
1.283
1.259
1.235
Compound 22 (LP-615819)


NB-241-154-fin
ppm
7.973
7.945
7.781
7.751
7.742
7.713
7.568
7.540
7.506
7.492
7.488
7.474
7.430
7.424
7.420
7.394
7.389
7.158
7.148
7.137
7.129
7.034
6.869
6.846
5.033
4.904
4.432
4.408
4.385
4.310
4.286
4.262
4.238
3.825
3.408
3.385
3.364
3.336
3.331
3.326
3.320
3.315
3.276
1.283
1.259
1.235
1.0000
2.0467
2.4964
0.9429
0.4602
1.4309
1.4624


NB-241-164-fin
172.5
170.1
166.3
163.9
160.2
159.8
144.2
144.1
143.5
143.5
141.4
132.3
132.2
131.9
131.7
130.5
129.7
129.2
129.0
126.4
124.4
124.4
123.6
116.1
115.9
115.3
115.1
97.5
76.6
76.3
64.2
55.3
50.1
49.9
49.6
49.4
49.2
49.0
48.8
37.6
14.8
Compound 22 (LP-615819)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Discovery VP HPLC Report

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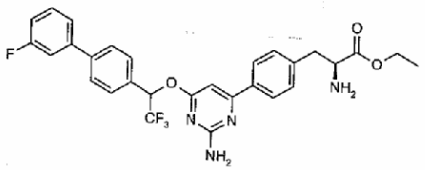
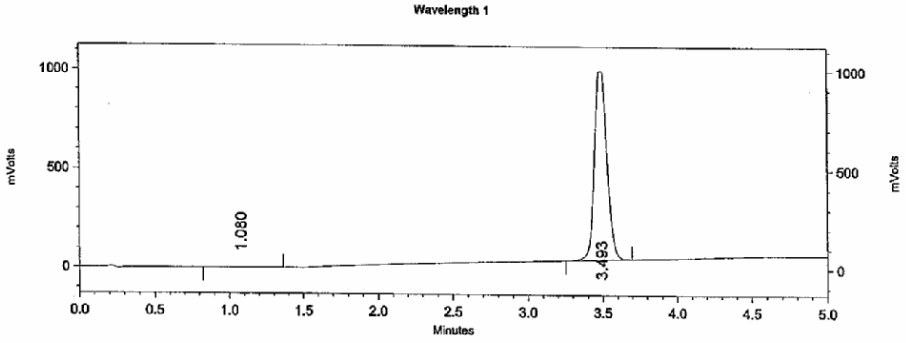
Acquired : 6/23/2005 12:35:02 PM
File Desc. : File = 2005_0623_1225.055
User = ADevasag
Instrument = SZ-LC1
Vial = 31 Inj. Vol. = 10 uL
Start % B = 0
Final % B = 100
Gradient Time = 4 min
Flow Rate = 2 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = Standard solvents
Solvent A = 90:10 Water : MeOH w/ 0.1% TFA
Solvent B = 90:10 MeOH : Water w/ 0.1% TFA
Column 1 : YMC Pack ODS-A 3.0 x 50 mm
NB-241-164-final



Compound 22 (LP-615819)



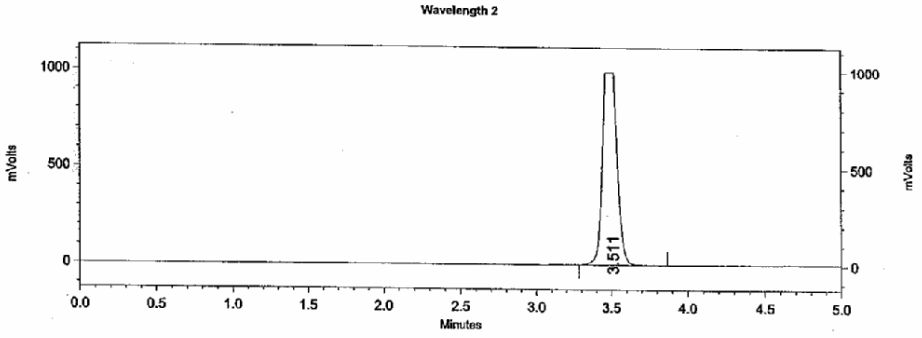
Channel A Results

Pk #	Retention Time	Area	Area Percent
1	1.080	21291	0.380
2	3.493	5588911	99.620
Totals		5610202	100.000

Page 1 of 2

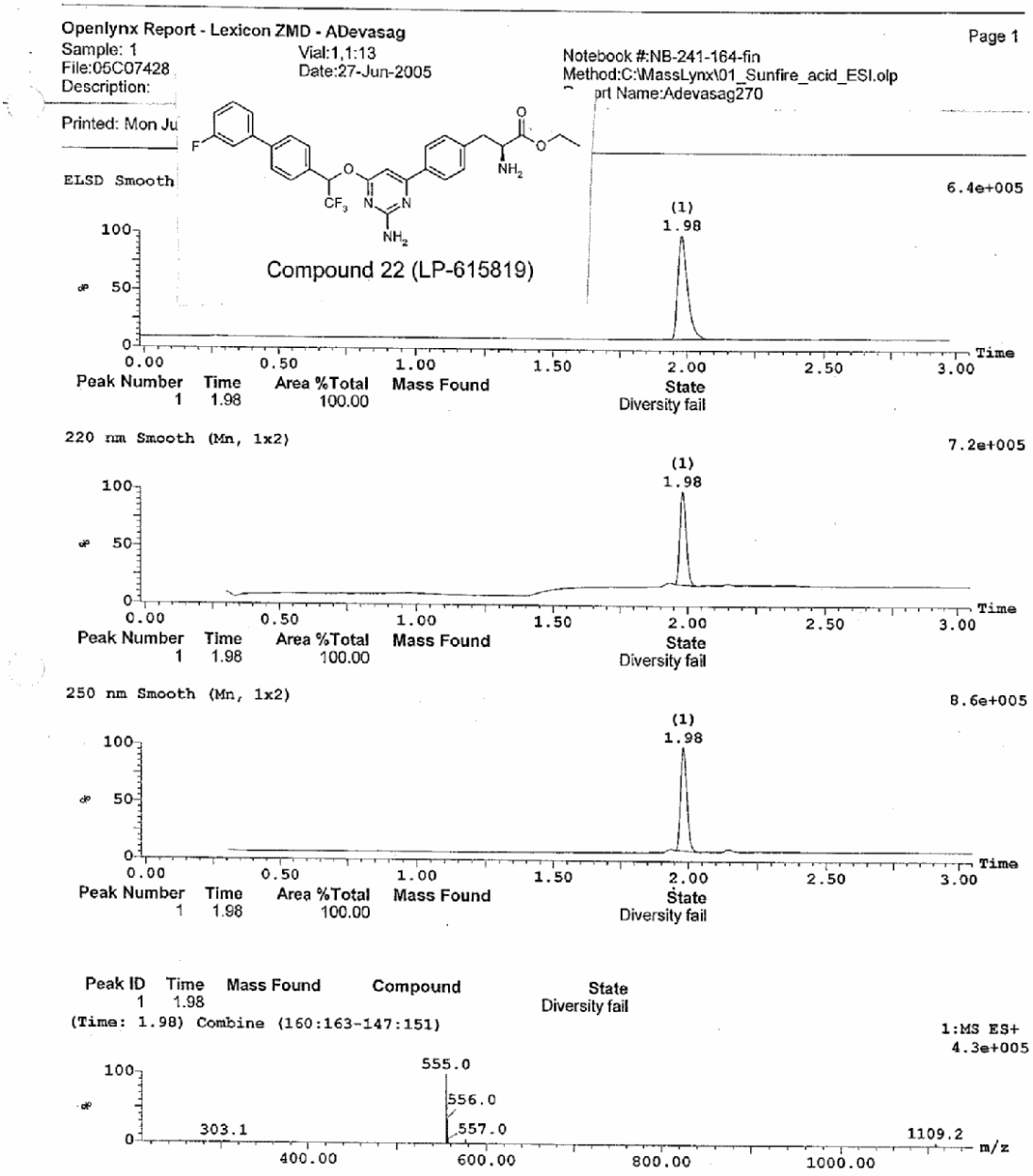
Discovery VP HPLC Report (p2)

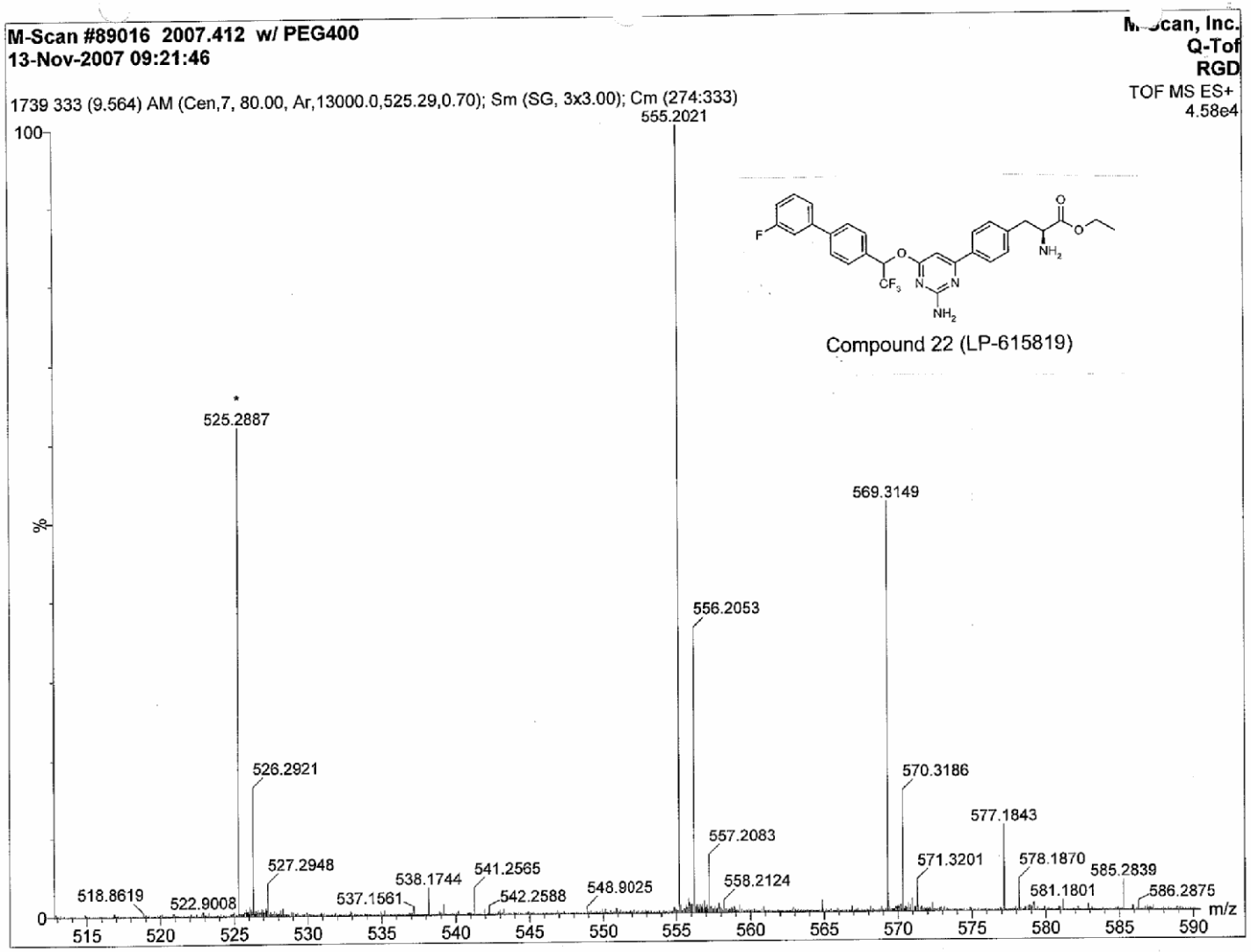
File : c:\shimadzu\sumdata\ADevasag\20050623\2005_0623_1225-055.dat
Sample ID : NB-241-164-final
Acquired : 6/23/2005 12:35:02 PM
File Desc. : File = 2005_0623_1225.055
User = ADevasag
Instrument = SZ-LC1
Vial = 31 Inj. Vol. = 10 uL
Start % B = 0
Final % B = 100
Gradient Time = 4 min
Flow Rate = 2 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = Standard solvents
Solvent A = 90:10 Water : MeOH w/ 0.1% TFA
Solvent B = 90:10 MeOH : Water w/ 0.1% TFA
Column 1 : YMC Pack ODS-A 3.0 x 50 mm
NB-241-164-final



Channel B Results

Pk #	Retention Time	Area	Area Percent
1	3.511	6765242	100.000
Totals		6765242	100.000


Openlynx Report - Lexicon ZMD - ADevasag
Page 1
Sample: 1
Vial:1,1:13
Notebook #:NB-241-164-fin
File:05C07428
Date:27-Jun-2005
Method:C:\MassLynx\01_Sunfire_acid_ESI.olp
Description:
Printed: Mon Ju
Compound 22 (LP-615819)
ELSD Smooth
6.4e+005
(1)
1.98
Time
Peak Number Time Area %Total Mass Found State
1 1.98 100.00 Diversity fail
220 nm Smooth (Mn, 1x2)
7.2e+005
(1)
1.98
Time
Peak Number Time Area %Total Mass Found State
1 1.98 100.00 Diversity fail
250 nm Smooth (Mn, 1x2)
8.6e+005
(1)
1.98
Time
Peak Number Time Area %Total Mass Found State
1 1.98 100.00 Diversity fail
Peak ID Time Mass Found Compound State
1 1.98 Diversity fail
(Time: 1.98) Combine (160:163-147:151)
1:MS ES+
4.3e+005
555.0
556.0
557.0
303.1
1109.2
m/z


M-Scan #89016 2007.412 w/ PEG400
13-Nov-2007 09:21:46
M-Scan, Inc.
Q-Tof
RGD
TOF MS ES+
4.58e4
1739 333 (9.564) AM (Cen,7, 80.00, Ar,13000.0,525.29,0.70); Sm (SG, 3x3.00); Cm (274:333)
Compound 22 (LP-615819)
555.2021
525.2887
569.3149
556.2053
526.2921
570.3186
577.1843
557.2083
571.3201
578.1870
585.2839
527.2948
538.1744
541.2565
558.2124
581.1801
586.2875
518.8619
522.9008
537.1561
542.2588
548.9025
%
m/z

$C_{29}H_{26}F_4N_4O_3$

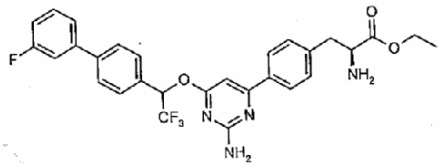
Mass: 554.54

Mass %:

	calc'd	found	|diff|
C	62.81	62.8	0.01
H	4.73	4.59	0.14
F	13.7	0	13.7
N	10.1	9.98	0.12
O	8.66	0	8.66
total	100%	77.37	22.63

elements of unsaturation: 17

Close Window



Compound 22 (LP-615819)