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Application of cultured human mast cells (CHMC) for the design and structure–activity relationship of IgE-mediated mast cell activation inhibitors

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ABSTRACT

Here we report the optimization of small molecule inhibitors of human mast cell degranulation via anti-IgE-mediated tryptase release following cross-linking and activation of IgE-loaded FcεR1 receptors. The compounds are selective upstream inhibitors of FcεR1-dependent human mast cell degranulation and proved to be devoid of activity in downstream ionomycin mediated degranulation. Structure–activity relationship (SAR) leading to compound **26** is outlined.

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The activation of IgE receptor, FcεR1, follows extracellular allergen cross-linking and this upstream event ultimately results in mast cell degranulation.^{1,2} Small molecule inhibitors, downstream from the activation of IgE receptor, FcεR1, in mast cells (and basophils) could therefore lead to novel therapeutic application for the treatment of allergic rhinitis, asthma and other allergic disorders.^{1,2} Targeting these initial signal transduction events the various pro-inflammatory factors released upon mast cell degranulation could be inhibited. Potentially presenting an opportunity to greatly enhance the impact of therapeutics for allergic diseases by alleviating multiple causative agents. Following allergen cross linking and activation of IgE-loaded FcεR1 on the extracellular surface of mast cells, a number of granule containing neutral proteases (chymases, tryptases), proteoglycans (heparin, chondroitin sulfate), and histamine are unleashed. Subsequently, arachidonic acid end products such as leukotriene (LT) B₄, LTC₄ and prostaglandin (PDG) 2 are generated to start the initial symptoms of inflammation.^{1,2}

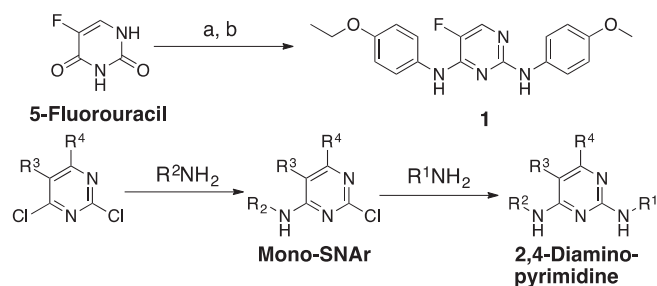
Other factors termed chemokines and cytokines such TNFα, IL-4, IL-5, IL-6, IL-8, IL-13 and IL-16 are consequently generated, and released. The consequence of the activation, synthesis, and release of chemokines and cytokines leads to the trademark inflammation symptoms typical of diseases such as allergic rhinitis.³

We instigated an effort to discover mast cell degranulation inhibitors via the generation of large populations of primary cultured human mast cells (CHMC) derived from umbilical cord blood and employ these in a high throughput screening (HTS) campaign. Our group has improved the reliability of previously described methods for the production of CHMC populations, and we complemented the phenotypic CHMC screens with a range of biochemical assays for target elucidation.² As we wanted to identify small molecules that inhibited upstream IgE receptor activation of CHMC degranulation as measured by tryptase release, methodology to determine pathway selectivity was essential. An important assay that allows the elimination of molecules targeting downstream pathways in mast cells is the use of ionomycin-induced degranulation via calcium mobilization.^{2c}

Upon HTS screening of our compound library in parallel assays measuring both anti-IgE activation and ionomycin-induced

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Scheme 1. Synthesis of **1** and general route. Reagents and conditions: (a) POCl₃, dimethylaniline (DMA), heat; (b) 4-ethoxyaniline, MeOH, heat.

degranulation diaminopyrimidine **1** emerged as a promising hit. Compound **1** inhibits anti-IgE-mediated CHMC degranulation with EC₅₀ = 1.67 μM, and satisfied the prerequisite criteria of no ionomycin-activated degranulation. Following thorough evaluation of kinase targets activated after allergen cross linking of IgE receptor, FcεR1, we determined that compound **1** inhibited spleen tyrosine kinase (Syk).^{2c,d} Although, here we disclose the structure–activity relationship (SAR) optimization of compound **1** exclusively through the use of CHMC assay. Our rationale for this approach was based on the premise that SAR derived through screening in a CHMC cell line could provide functional phenotypic screening data, which may be more relevant to a disease setting, and in parallel measure selectivity via differential means of activating mast cells, accompanied with biochemical on- and off-target assays.^{2c,d}

The structure and synthesis of HTS hit **1** is depicted in Scheme 1. Reaction of 5-fluorouracil with phosphorus oxychloride produced 2,4-dichloro-5-fluoropyrimidine, sequential S_NAr reaction with 4-ethoxyaniline in methanol in a sealed tube at 100 °C produced bis-S_NAr compound **1**, in 90% yield over 2 steps.⁴

We employed chemistry outlined in Scheme 1 to investigate SAR with the synthesis of pseudo-symmetrical (bis-S_NAr) substituted 2,4-diaminopyrimidines, further the mono-S_NAr products can be readily isolated for subsequent reaction with diverse set of amines. Key to the isolation of the mono-S_NAr product is the use of methanol/water, where the mono-S_NAr product precipitates out and hence not involved in further reaction as long as the temperature is maintained below or at 70 °C, with the use of stoichiometric equivalent amine.

Preliminary SAR of pseudo-symmetrical analogs is shown in Table 1. By moving the ethoxy groups on the phenyl rings from the 4-position to the 3-position the anti-IgE tryptase release was reduced approximately 2-fold with analog **2** showing on-target EC₅₀ = 3.10 μM. Fortunately complete selectivity over ionomycin is maintained as with other closely related compounds **3–4**, and amino analog **5**. The 3-aminophenyl **6** was initially the most potent compound however, with minor loss in selectivity over ionomycin. Incorporation of electron withdrawing group at the 4-position of the aryl ring, as exemplified by the 4-trifluoromethyl in **7** loses activity completely. Removal of the electronegative 5-fluorine atom on the central pyrimidine core in **1** led to compound **8** with diminished activity and supports the significant role of electronic influence at this position. Replacement of the 5-fluorine with hydrogen and chlorine at the 6-position of the pyrimidine, to maintain an electronic influence, led to a completely inactive compound **9**. The contribution of electronic influence at the 5-position of the pyrimidine was further verified with the 5-methyl derivative, **10** showing complete loss in activity.

In contrast to the more potent analog **6** introduction of a larger hydrophobic 4-morpholinophenyl group, as shown by analog **11**, led to 9-fold decrease in activity. The 3-cyanophenyl analog **13** is significantly more potent than the corresponding 4-cyanophenyl

Table 1
Exploratory SAR on initial hit compound **1**

ID	R ¹ , R ²	R ³	R ⁴	Tryptase, EC ₅₀ (μM)	
				Anti-IgE	Iono
1	4-EtOC ₆ H ₄	F	H	1.67	IA
2	3-EtOC ₆ H ₄	F	H	3.10	IA
3	4-MeOC ₆ H ₄	F	H	1.43	IA
4	3-MeOC ₆ H ₄	F	H	1.73	IA
5	4-H ₂ NC ₆ H ₄	F	H	4.25	IA
6	3-H ₂ NC ₆ H ₄	F	H	0.46	10
7	4-CF ₃ C ₆ H ₄	F	H	IA	IA
8	4-EtOC ₆ H ₄	H	H	3.38	IA
9	4-EtOC ₆ H ₄	H	Cl	IA	IA
10	4-EtOC ₆ H ₄	Me	H	IA	IA
11	4-MorpholinoC ₆ H ₄	F	H	4.14	IA
12	4-CNC ₆ H ₄	F	H	9.83	IA
13	3-CNC ₆ H ₄	F	H	0.95	IA
14	3-CF ₃ OC ₆ H ₄	F	H	5.08	IA
15	3-ClC ₆ H ₄	F	H	5.81	IA
16	4- <i>i</i> PrOC ₆ H ₄	F	H	2.20	IA
17	3-HOCH ₂ C ₆ H ₅	F	H	2.80	IA

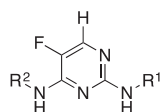
12, in line with other electron withdrawing substituents as shown by **14** and **15**. Introduction of hydrophobic isopropyl ether moieties in **16** or benzyl alcohol hydrogen bond donor groups in **17** did not display any dramatic improvement for inhibition of degranulation activity. Synthesis of compounds shown in Table 1 is similar to compound **1**, with minor modifications to reaction conditions (Supplementary section), Scheme 1.

We turned our attention to the introduction of more polar substituents on the peripheral rings and exploration of alternative 5-pyrimidine substituents as exemplified by compounds **18–26**, Table 2. The general trend from this subset of analogs indicates that polar 3-hydroxyphenyl rings in combination with substituents at the 5-position of pyrimidine consistently lead to more potent compounds. Outliers from this set are compounds **20** and **25**. The 5-trifluoromethyl analog **24** proved to be of interest due to the improvement in anti-IgE mediated degranulation and structurally more desirable in contrast to the 5-bromo compound **22**. Unlike with other 5-substituted pyrimidines the mono-S_NAr product from the reaction of 2,4-dichloro-5-trifluoromethylpyrimidine with amines proved difficult to isolate as we observed nonselective reaction at both the 2- and 4-positions of the pyrimidine. Unsurprisingly

Table 2
SAR on initial hit compound **1** with increased polar character

ID	R ¹	R ²	R ³	R ⁴	Tryptase, EC ₅₀ (μM)	
					Anti-IgE	Iono
18	HO	H	H	H	0.50	IA
19	HO	H	Me	H	0.90	IA
20	HO	H	H	Ph	5.80	IA
21	HO	H	Ph	H	2.90	IA
22	HO	H	Br	H	0.23	IA
23	HO	H	CN	H	0.44	IA
24	HO	H	CF ₃	H	0.27	IA
25	H	HO	F	H	3.40	IA
26	HO	H	F	H	0.35	IA

Table 3
SAR with introduction of polar functionality



ID	R ¹	R ²	Tryptase, EC ₅₀ (μM)	
			Anti-IgE	Iono
27	4-MeO ₂ CCH ₂ OC ₆ H ₄	4-MeO ₂ CCH ₂ OC ₆ H ₄	0.38	1.7
28	4-HO ₂ CCH ₂ OC ₆ H ₄	4-HO ₂ CCH ₂ OC ₆ H ₄	IA	IA
29	4-H ₂ NCOCH ₂ OC ₆ H ₄	4-H ₂ NCOCH ₂ OC ₆ H ₄	IA	IA
30	4-NCCH ₂ OC ₆ H ₄	4-NCCH ₂ OC ₆ H ₄	0.37	IA
31	4-MeO ₂ CCH ₂ OC ₆ H ₄	4-H ₂ NCOCH ₂ OC ₆ H ₄	0.43	2.48
32	4-H ₂ NCOCH ₂ OC ₆ H ₄	4-MeO ₂ CCH ₂ OC ₆ H ₄	0.94	10
33	3-HOC ₆ H ₄	3-HO(CH ₂) ₂ OC ₆ H ₄	0.67	IA
34	3-EtO ₂ CCH ₂ NHC ₆ H ₄	3-HOC ₆ H ₄	0.33	IA
35	3-MeHNCOCH ₂ NHC ₆ H ₄	3-HOC ₆ H ₄	0.29	IA
36	3-HO(CH ₂) ₂ OC ₆ H ₄	3-HO(CH ₂) ₂ OC ₆ H ₄	0.93	IA
37	3-MeO(CH ₂) ₂ OC ₆ H ₄	3-MeO(CH ₂) ₂ OC ₆ H ₄	4.15	IA
38	3-H ₂ NCOCH ₂ NHC ₆ H ₄	3-HOC ₆ H ₄	0.44	IA
39	3-Me ₂ NCOCH ₂ NHC ₆ H ₄	3-HOC ₆ H ₄	0.49	IA
40	4-C ₆ H ₄ OCH ₂ (1H-tetrazol-5-yl)	4-C ₆ H ₄ OCH ₂ (1H-tetrazol-5-yl)	IA	IA
41	4-C ₆ H ₄ OCH ₂ (1Me-tetrazol-5-yl)	4-C ₆ H ₄ OCH ₂ (1Me-tetrazol-5-yl)	0.76	IA
42	4-H ₂ NCOCH ₂ OC ₆ H ₄	3-HOC ₆ H ₄	0.53	10
43	4-NCCH ₂ OC ₆ H ₄	3-HOC ₆ H ₄	0.45	10
44	3-HOC ₆ H ₄	4-H ₂ NCOCH ₂ OC ₆ H ₄	1.55	10
45	3-HOC ₆ H ₄	4-NCCH ₂ OC ₆ H ₄	0.21	10
46	3-MeHNCOCH ₂ OC ₆ H ₄	4- ^t BuC ₆ H ₄	0.43	10
47	3-HO(CH ₂) ₂ OC ₆ H ₄	4-HOCH ₂ C(Me) ₂ C ₆ H ₄	0.28	IA
48	3-MeHNCOCH ₂ OC ₆ H ₄	4-EtOC ₆ H ₄	1.10	IA
49	3-MeHNCOCH ₂ OC ₆ H ₄	4-CF ₃ OC ₆ H ₄	0.40	IA
50	3-MeHNCOCH ₂ OC ₆ H ₄	4-CF ₃ C ₆ H ₄	0.21	IA
51	3-MeHNCOCH ₂ OC ₆ H ₄	4-MorpholinoC ₆ H ₄	1.29	IA

additional electron-withdrawing influence of the 5-trifluoromethyl in contrast to the 5-fluoro moiety made the central pyrimidine core more electrophilic and increased the propensity of reaction with nucleophiles. According to these results we turned our attention in pursuit of 5-fluoropyrimidines in more detail as the chemistry proceeded more efficiently and delivered potent analogs.

The position of the hydroxyl group is important as demonstrated with the 3-isomer **26** showing 10-fold greater potency compared to the corresponding 4-isomer **25**. The former inhibits Syk kinase with $K_i = 0.096 \mu\text{M}$ and $\text{IC}_{50} = 0.29 \mu\text{M}$, we have reported the selectivity and Syk kinase co-crystal structure with **26** elsewhere.^{2c,d} Similar pattern was observed between the 3- and 4-amino isomers **5** and **6**, with respect to tryptase activity and compound **6** inhibits Syk kinase with $\text{IC}_{50} = 0.32 \mu\text{M}$. The dianiline structure of compound **6** makes it significantly less desirable and this was confirmed through positive Ames test. Gratifyingly compound **26** posed on such problems.

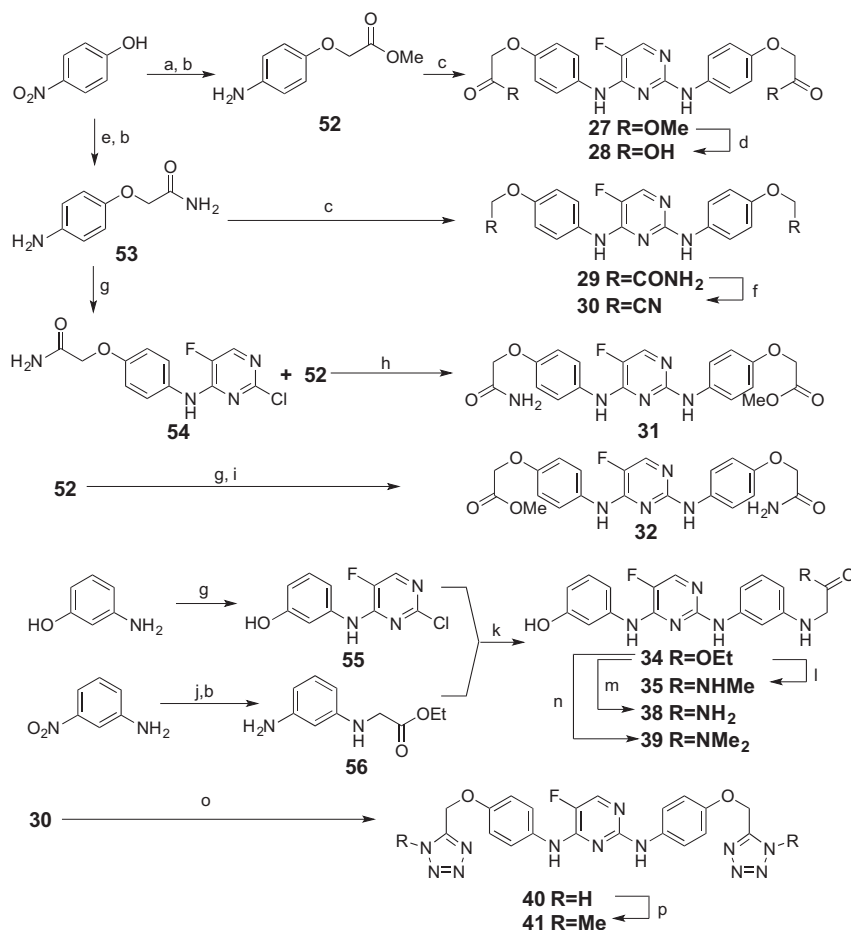
Table 3 outlines SAR to determine the influence of hydrogen bond donor and acceptor functionality, in addition to side-chain homologation on tryptase release by anti-IgE and ionomycin. The bis-methyl ester analog **27** possesses activity in line with other potent analogs. In contrast, the corresponding bis-carboxylic acid and primary bis-amides **28** and **29**, respectively, are inactive. This lack of activity may be attributable to lower cell membrane permeability in contrast the nitrile analog **30** exhibits similar potency to **27**. Combination of structural features from **27** and **29** leads to compounds **31** and **32**, respectively, which contain both primary amide and ester moieties. Indeed compound **31** gains activity presumably as a result of good cell permeability. Unfortunately analog **31** lost selectivity over ionomycin. Presumably, the carboxylic acid bioisostere N-H tetrazole **40**, also lacks sufficient cell permeability and consequently shows no

activity, in contrast the *N*-methyl-tetrazole **41** inhibits anti-IgE tryptase release with $\text{EC}_{50} = 0.76 \mu\text{M}$.

A number of analogs containing hydroxyl groups **33–36**, **38–39**, and **42–45**, **47** proved to be active as shown in Table 3. Similarly, amide containing compounds **46** and **48–50** with hydrophobic substituents at 2-position of pyrimidine showed comparable activity. Overall the SAR suggests that certain polar groups can be utilized to maintain cell-based potency however, hydrophobic amine containing groups, such as in **51** are less tolerated.

The synthesis of compounds shown in Table 3 is outlined in Schemes 2 and 3.⁴ 4-Nitrophenol was alkylated with methyl 2-bromoacetate under reflux conditions with potassium carbonate as base and subsequent hydrogenation to give **52**, this was reacted with 2,4-dichloro-5-fluoropyrimidine in methanol at 100 °C in a sealed tube to give **27**.^{4,5} Hydrolysis of **27** with 2 N NaOH, followed by neutralization and acidification with 2 N HCl to pH 2 produced analog **28**. Using similar methodology compound **29** was synthesized through alkylation of 4-nitrophenol with 2-bromoacetamide to give **53**, followed by double $\text{S}_{\text{N}}\text{Ar}$ reaction and dehydration of the amide with trifluoroacetic anhydride in the presence of pyridine yielded **30**.^{4,6}

The strong inductive effect of 5-fluorine atom dictates the chemoselective activation of the adjacent 4-position of the central pyrimidine ring. Thus under moderate conditions mono- $\text{S}_{\text{N}}\text{Ar}$ intermediate **54** was synthesized from the reaction of **53** with 2,4-dichloro-5-fluoropyrimidine and further elaborated through a second $\text{S}_{\text{N}}\text{Ar}$ reaction with **52** to give analog **31**, Scheme 2. Similarly, analog **32** was synthesized through the 2-step sequential reaction of **52** with 2,4-dichloro-5-fluoropyrimidine and subsequent reaction with aniline **53**. Reaction of 3-aminophenol with 2,4-dichloro-5-fluoropyrimidine proceeded cleanly to produce the mono- $\text{S}_{\text{N}}\text{Ar}$ product **55** and this was reacted with



Scheme 2. Synthesis of **27–32**, **34**, **35**, and **38–41**. Reagents and conditions: (a) BrCH₂CO₂Me, K₂CO₃, acetone, reflux; (b) Pd/C, MeOH, 40 PSI H₂; (c) 2,4-dichloro-5-fluoropyrimidine, MeOH, H₂O 100 °C, sealed tube; (d) 2 N NaOH, THF then 2 N HCl; (e) BrCH₂CONH₂, K₂CO₃, acetone, reflux; (f) (CF₃CO)₂O, pyridine, THF; (g) 2,4-dichloro-5-fluoropyrimidine, MeOH, H₂O, 70 °C; (h) MeOH, H₂O, 100 °C; (i) **53**, MeOH, H₂O, 100 °C, sealed tube; (j) BrCH₂CO₂Et, K₂CO₃, CH₃CN, reflux; (k) EtOH, H₂O, 100 °C; (l) MeNH₂·HCl, DIPEA EtOH, sealed tube, 100 °C; (m) 7 N NH₃ MeOH, sealed tube, 70 °C; (n) Me₂NH·HCl, DIPEA EtOH, sealed tube, 100 °C; (o) NaN₃, NH₄Cl, DMF, HOAc, 70 °C; (p) CH₃I, K₂CO₃, DMF.

intermediate **56** to generate precursor analog **34**. The latter was efficiently converted to congeners **35**, **38** and **39**. We took advantage during synthesis by treating compound **30** with sodium azide, ammonium chloride in conjunction with DMF and acetic acid to generate the di-tetrazole analog **40**. The latter was readily converted to the dimethyl tetrazole **41** through alkylation with methyl iodide.⁷

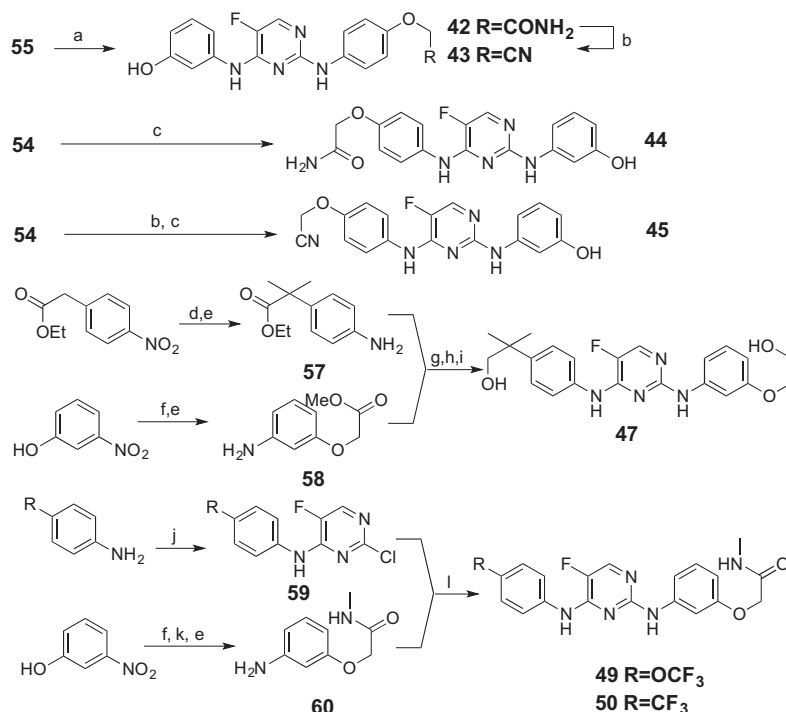
As delineated in Scheme 3, further reaction of **55** with aniline **53** produced the bis-S_NAr product **42** and conversion of the amide functional group led to the nitrile product **43**. Amide derivative **44** was produced by reaction of mono-S_NAr compound **54** with 3-aminophenol. The nitrile analog **45** was synthesized employing dehydration of the mono-S_NAr product **54** and subsequent S_NAr reaction with 3-aminophenol.

The gem-dimethyl intermediate **57** was prepared in 2-steps from ethyl 2-(4-nitrophenyl)acetate via alkylation with methyl iodide in the presence of 18-crown-6 and potassium *tert*-butoxide, followed by palladium catalyzed hydrogenation. Subsequently the mono-S_NAr product from **57** was reacted with **58** to give the penultimate di-ester product and reduction with DIBAL-H produced analog **47**. Analogs **49** and **50** were prepared by reaction of the respective mono-S_NAr product **59** with 2-(3-aminophenoxy)-*N*-methylacetamide **60**.

The SAR outlined in this Letter shows the application of phenotypic screening to the identification of mast cell degranulation inhibitor compound **26**. The compound has the desired biological

selectivity, chemical and pharmaceutic characteristics to serve as a drug candidate for clinical proof of concept.^{2a,c,d} Indeed compound **26**, designated as **R112**, was taken forward to human clinical trials and efficaciously advanced to phase II studies for the treatment of seasonal allergic rhinitis in a park environment.⁸ **R112** is amenable to delivery through intranasal route, which is the preferred route of administration for the clinical study of allergic rhinitis to fully utilize the compounds rapid onset of action.^{2c,d,8,9} The pharmacodynamic effects of **26** were assessed through improvement in global symptom complex, comprised of improvements in symptoms of allergic rhinitis such as sneezes, runny and itchy nose from baseline.⁸ Compound **26** has a rapid onset of action and rapidly cleared following intranasal delivery.^{8,9} In a Phase 1b study, within 5 min after allergen challenge compound **26** decreased prostaglandin D₂ (93.4 ± 23.0 pg/mL vs vehicle 171.6 ± 23.0 pg/mL; *p* = 0.03), a key marker of bronchial airway contraction following mast cell degranulation however, this effect was not durable.⁹

In summary, we have demonstrated the application of functional phenotypic screening using CHMC cells to derive SAR around a series of 2,4-diaminopyrimidines and identified a clinical candidate, **R112**. There are not many reports^{2c,10} of application of primary human mast cells for a thorough derivation of SAR and thus this offers a novel methodology for utilization in phenotypic drug discovery¹¹ space of compounds for the treatment of allergic rhinitis, asthma and other allergic disorders.



Scheme 3. Synthesis of **42–45**, **47**, and **49–50**. Reagents and conditions: (a) **53**, MeOH, H₂O, 100 °C, sealed tube; (b) (CF₃CO)₂O, pyridine, THF; (c) 3-aminophenol, MeOH, H₂O, 100 °C, sealed tube; (d) *t*-BuOK, 18-Crown-6, CH₃I, THF, –78 °C; (e) Pd/C, MeOH, 40 PSI H₂; (f) BrCH₂CO₂Me, K₂CO₃, acetone, reflux; (g) **57**, 2,4-dichloro-5-fluoropyrimidine, MeOH, H₂O, 60 °C; (h) **58**, MeOH, H₂O, 100 °C, sealed tube; (i) DIBAL-H, CH₂Cl₂, 0 °C; (j) 2,4-dichloro-5-fluoropyrimidine, MeOH, H₂O, 60 °C; (k) MeNH₂·HCl, DIPEA, MeOH, sealed tube, 100 °C; (l) **59**, MeOH, 100 °C, sealed tube.

Supplementary data

Supplementary data (synthetic procedure, ¹H NMR, LCMS and yields for compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2015.03.075>.

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Application of cultured human mast cells (CHMC) for the design and structure-activity relationship of IgE-mediated mast cell activation inhibitors

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General experimental

All reagents and solvents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography or high-performance liquid chromatography. NMR was performed on a 300 MHz NMR spectrometer and all chemical shifts are reported relative to a tetramethylsilane internal standard, or by referencing on the deuterated solvent. Reverse-phase high-performance liquid chromatography was performed on standard equipment and was coupled to diode array and mass spectra detectors – the mass-spectra detector operating under the electrospray ionization (ESI) mode.

HPLC column and column-gradient methods are listed below:

7min method

Waters 2695 Alliance High Performance Liquid Chromatography with 996 PDA (210-400 nm) and Waters ZQ single quadrupole mass spectrometer.

Column: Zorbax C18, 5 μ m, 2.1 x 50 mm,

Column temperature: 30°C

Sample temperature: 15°C

Solvent A: 0.05% Formic acid in Water

Solvent B: 0.05% Formic acid in Acetonitrile

Flow rate: 0.8 mL/min

Gradient:

Time (min.)	A%	B%
0	95	5
5	5	95
6	5	95
6.05	95	5

10min method

Waters 2695 Alliance High Performance Liquid Chromatography with 996 PDA (210-400 nm) and Waters ZQ single quadrupole mass spectrometer.

Column: Zorbax C18, 5 μ m, 2.1 x 50 mm,

Column temperature: 30°C

Sample temperature: 15°C

Solvent A: 0.05% Formic acid in Water

Solvent B: 0.05% Formic acid in Acetonitrile

Flow rate: 0.5 mL/min

Gradient:

Time (min.)	A%	B%
0	95	5
1	95	5
8	0	100
10	0	100
10.01	95	5

20min slow method

Waters 2690 Alliance High Performance Liquid Chromatography with 996 PDA (210-400 nm) and Waters ZMD single quadrupole mass spectrometer.

Column: Ultro C18q, 5 μ m, 4.6 x 250 mm,

Column temperature: 30°C

Sample temperature: 20°C

Solvent A: 0.05% Formic acid in Water

Solvent B: 0.05% Formic acid in Acetonitrile

Flow rate: 0.3 mL/min

Gradient:

Time (min.)	A%	B%
0	95	5
10	80	20
18	0	100
18.01	95	5
20	95	5

20m standard method

Waters 2690 Alliance High Performance Liquid Chromatography with 996 PDA (210-400 nm) and Waters ZMD single quadrupole mass spectrometer.

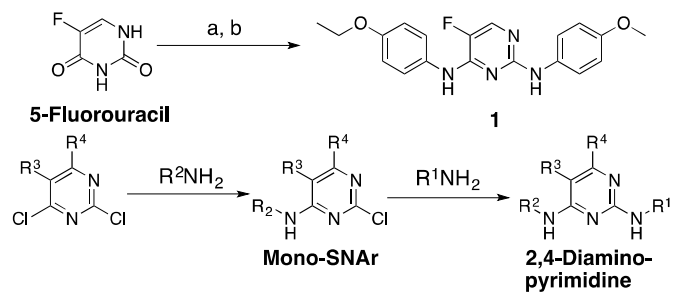
Column: Ultro C18q, 5 μ m, 4.6 x 250 mm,
 Column temperature: 30°C
 Sample temperature: 20°C
 Solvent A: 0.05% Formic acid in Water
 Solvent B: 0.05% Formic acid in Acetonitrile
 Flow rate: 0.3 mL/min

Gradient:

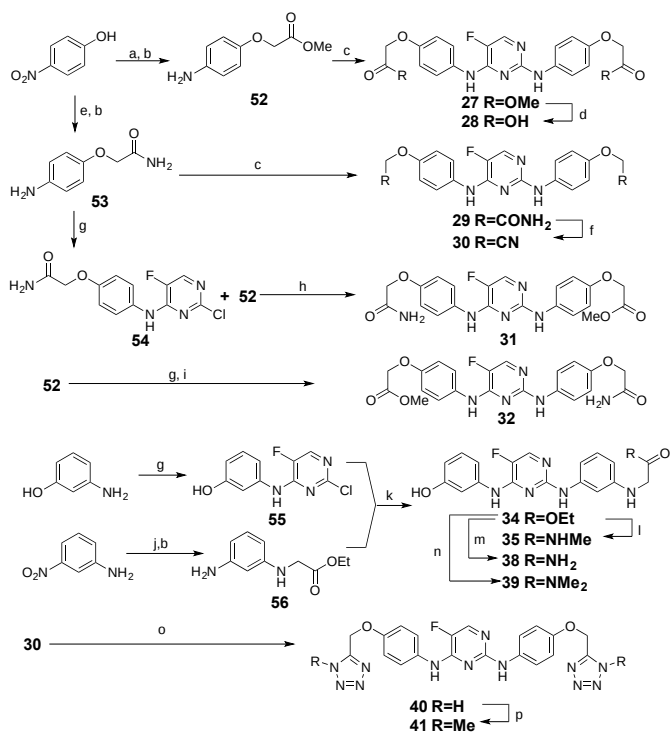
Time (min.)	A%	B%
0	95	5
15	0	100
18	0	100
18.01	95	5
20	95	5

Schemes

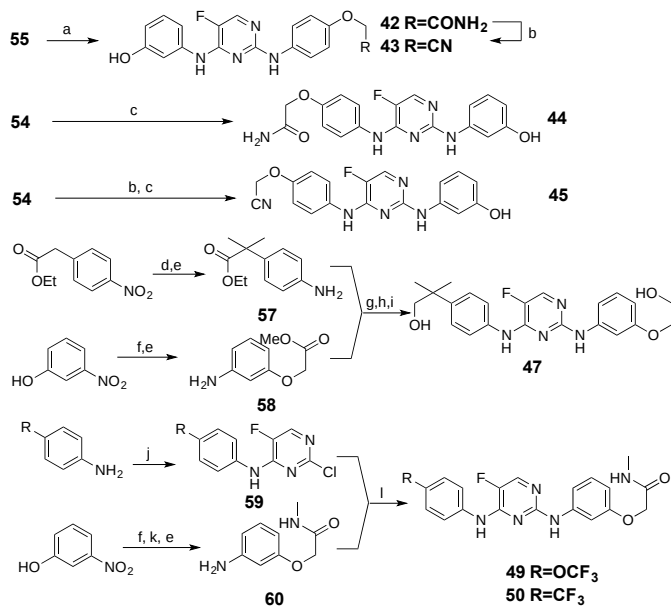
Scheme 1



Scheme 2



Scheme 3



Reaction Conditions to Bis S_NAr [N2, N4-bis(aryl)-2,4-pyrimidinediamines] analogs from 2,4-dichloropyrimidines and anilines

Compound	2,4-Dichloropyrimidine (eq)	Aniline (eq)	Temp (°C)	Time (h)	Solvent	Solvent ratio
2,4	1	2.2	100	24	EtOH:H ₂ O	1:1
3	1	2.2	100	24	EtOH	
5 precursor	1	4	70	24	MeOH:H ₂ O	10:1
6 precursor	1	4	100	20		10:1
7	1	2.2	80	24	EtOH	-
8	1	2.5	70	24		
9	1	4	80	24	MeOH:H ₂ O	4:1
10	1	6	100	48		10:1
11	1	5	100	24		10:1
12,13	1	2.2	80	24	EtOH	-
14, 15	1	2.5	70	24		
16	1	2.5	100	24		
17	1	3	100		MeOH:H ₂ O	20:1
18	1	3	100			5:1
19	1	3	100			5:1
20 precursor	1	3	100	24	MeOH	
22	1	4	100	24	MeOH:H ₂ O	19:1
23	1	5.2	100	72	MeOH	-
24	1	4	100	18	EtOH	
25	1	3	80	24		
26	1	3	100	24	MeOH:H ₂ O	9:1
27	1	3	100	48		2:1
29	1	2.5	70	24		10:1
36	1	3	100	24	MeOH	-
37	1	3	100	24		

General method for the preparation of N2,N4-bis(aryl)-2,4-pyrimidinediamines: 2,4-dichloropyrimidine (1 eq) and aniline (2.2-6 eq) in protic solvent (MeOH or EtOH) or a mixture of EtOH:H₂O (1:1) or MeOH:H₂O (2-20:1) were stirred in a screw capped vial at 70-100 °C for 18-72h. Reaction mixture was cooled to room temperature, diluted with water and acidified with aq. HCl (1N or 2N, pH >2). In some instances, product was precipitated as a solid upon saturating the above acidic homogeneous solution with solid NaCl. Thus precipitated solid was collected by suction filtration and dried to provide N2, N4-bis(aryl)-2,4-pyrimidinediamines. In case of no precipitation observed upon dilution with water, acidification and subsequent saline treatment, saline treated homogeneous

reaction mixture was partitioned with water immiscible organic solvent and discarded aqueous layer. Thus separated organic layer was washed with aq. NaHCO₃ solution, water and brine successively, dried over anhydrous Na₂SO₄, filtered and concentrated. N2, N4-bis(aryl)-2,4-pyrimidinediamines were obtained after the purification of concentrated residue.

Reaction Conditions to N2,N4-diaryl-2,4-pyrimidinediamine analogs from Mono S_NAr intermediate and anilines

Compound	Mono S _N Ar (eq)	Aniline (eq)	Temp (°C)	Time (h)	Solvent	Solvent ratio
31	1	3.4	70, 100	24, 48	MeOH:H ₂ O	10:1
32	1	3	100	24		10:1
33 <i>precursor</i>	1	3	100	24	MeOH:H ₂ O	10:1
34	1	3	100	72	EtOH:H ₂ O	4:1
42	1	3	100	48	MeOH:H ₂ O	10:1
44	1	3	100	72		10:1
45	1	3	100	24		10:1
46	1	1.5	100	24	MeOH	
47 <i>precursor</i>	1	3	100	24	MeOH:H ₂ O	10:1
48	1	3	100	24	MeOH	
49	1	1.5	100	24		
50	1	2	100	24		
51 <i>precursor</i>	1	3.4	100	12		

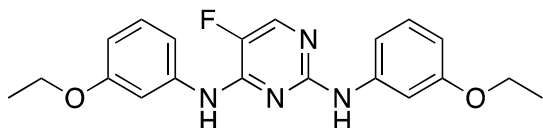
General method for the preparation of N2,N4-diaryl-2,4-pyrimidinediamines: 2,4-dichloropyrimidine (1 eq) and aniline (1.5-3.4 eq) in protic solvent (MeOH or EtOH) or a mixture of EtOH:H₂O (4:1) or MeOH:H₂O (4-10:1) were stirred in a screw capped vial at 70-100 °C for 24-72h. N2,N4-diaryl-2,4-pyrimidinediamines were obtained by following the analogous workup procedure described in the preparation to obtain N2, N4-bis(aryl)-2,4-pyrimidinediamines.

Reaction Conditions to Mono S_NAr intermediate (2-chloro- N4- aryl-4-pyrimidineamine) from 2,4-dichloro-5-fluoropyrimidine and anilines

Compound	Mono S _N Ar Product	2,4- Dichloro- 5-F- pyrimidine	Aniline (eq)	Temp (⁰ C)	Time (h)	Solvent	Ratio
31	54	1	2	70	2	H ₂ O:MeOH	10:1
32		1.4	1	60	12		9:1
33		1.4	1	60	12		9:1
34	55	1	3	70	1		6:1
46		1.4	1	60	12		9:1
47		1	1.2	70	12		9:1
48		1	1.2	rt	1		1:1
49		1.5	1	60, rt	2, 24		
50							
51		1.4	1	60	12		1:1

General method for the preparation of Mono-S_NAr intermediates: N4-Aryl-2-chloro-5-fluoro-4-pyrimidineamine: A screw capped vial containing a mixture of 2,4-dichloro-5-fluoropyrimidine (1.0-1.5 eq) and aniline (1-3 eq) mmol in H₂O: MeOH (1-10:1) was stirred either at room temperature or below 70 °C for 1-24h. In some instances product precipitates during the reaction or upon processing reaction mixture by diluting with water or by acidification (1-2N aq. HCl) or by addition of solid NaCl to the acidified mixture. Subsequently, the solid was collected by filtration, washed with water and dried to provide Mono-S_NAr intermediate (N4-Aryl-2-chloro-5-fluoro-4-pyrimidineamine). Subsequently, it was stirred in 0-5% EtOAc/hexanes and filtered to remove 2,4-dichloro-5-fluoropyrimidine resulting in the pure product. Majority of the Mono S_NAr products described in this communication involved extractive workup and were isolated in quantitative yields by silica gel column chromatographic purification.

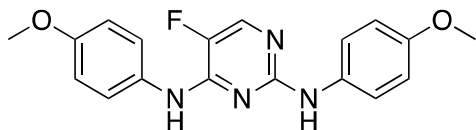
N2,N4-Bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (2):



A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and *m*-phenetidine (0.030 g, 0.22 mmol) in EtOH (0.5 mL): H₂O (0.5 mL) was shaken in a sealed tube at 100 °C for 24h. Reaction mixture was cooled to room temperature, diluted with water (4 mL), acidified with aq. 2N aq. HCl (pH >2) and EtOAc (20 mL) respectively. Upon discarding aqueous layer, organic layer was washed with aq. NaHCO₃ (4 mL), aq. NaCl (3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. Silica gel column chromatographic purification (0-30% EtOAc/hexanes) of the crude concentrate provided

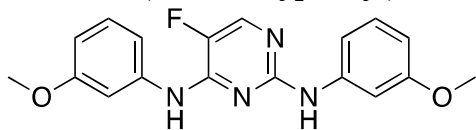
N2,N4-bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**2**). ^1H NMR (CD_3OD): δ 7.96 (1H, J = 4.8 Hz, d), 7.22 (m, 6H), 7.07 (t, J = 1.8 Hz, 1H), 6.95 (dt, J = 7.2, 1.2 Hz, 1H), 6.77 (m, 2H), 3.88 (q, J = 6.3 Hz, 4H), 1.33 (apparent 2t, J = 6.3 Hz, 6H); ^{19}F NMR (CDCl_3): δ - 163.32; LCMS: Purity 97%; MS (m/e) 369 (MH^+).

N2,N4-Bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (3):



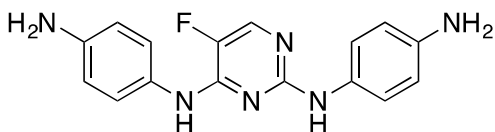
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and *p*-anisidine (0.027 g, 0.22 mmol) in EtOH (1 mL) was shaken in a sealed tube at 100 $^\circ\text{C}$ (24h). N2,N4-Bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**3**) was obtained after acidification of reaction mixture followed by workup and purification analogous to **2**. ^1H NMR (CD_3OD): δ 7.67 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 9.3 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 9.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H), 3.81(s, 3H); LCMS: Purity: 100%; MS (m/e): 341 (MH^+).

N2,N4-Bis(3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (4):



Analogous to the preparation of N2,N4-bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**2**), 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and *m*-anisidine (0.027 g, 0.22 mmol) were reacted to obtain N2,N4-bis(3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**4**) after acidification of reaction mixture followed by workup and purification as described for **2**. ^1H NMR (CD_3OD): δ 7.96 (d, J = 5.4 Hz, 1H), 7.24 (m, 6H), 7.06 (t, J = 2.4 Hz, 1H), 7.00 (dt, J = 1.2 Hz, 1H), 6.79 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H); ^{19}F NMR (CD_3OD): δ - 163.36; LCMS: Purity: 99%; MS (m/e): 341 (MH^+).

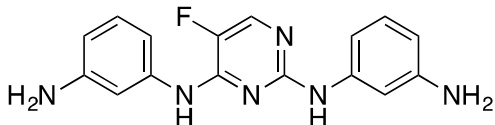
N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (5):



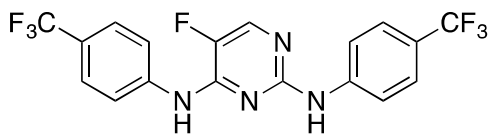
2,4-Dichloro-5-fluoropyrimidine (75 mg, 0.45 mmol) was dissolved in a mixture of MeOH (2 mL) and H_2O (0.2 mL). 4-*tert*-butoxycarbonylaminoaniline (374 mg, 1.8 mmol) was added and the mixture was refluxed for 24h (70 $^\circ\text{C}$ oil-bath temperature). The mixture was cooled to 22 $^\circ\text{C}$, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel (50% EtOAc/hexanes) to give N2,N4-bis[4-(*tert*-butoxycarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (82 mg, 35%). ^1H NMR ($\text{DMSO}-d_6 + \text{CD}_3\text{OD}$): δ 7.96 (d, J = 3.5 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 1.45 (s, 9H), 1.43 (s, 9H); LCMS: Purity: 97.9%; MS (m/e): 511 (MH^+). N2,N4-bis[4-(*tert*-butoxycarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (50 mg) and CH_2Cl_2 (2 mL) at $^\circ\text{C}$ was treated with TFA (1 mL) and stirred. After 1h, dark reaction mixture was

concentrated, neutralized with 2M aq. K_2CO_3 (7 mL) and partitioned with EtOAc (25 mL). Organic layer was separated, dried over $MgSO_4$, filtered and concentrated. Silica gel column chromatographic purification of crude concentrate (3% 2N NH_3 solution in MeOH/ CH_2Cl_2) provided N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (**5**) (22 mg, 73%). ^1H NMR (DMSO- d_6): δ 8.76 (s, 1H), 8.48 (s, 1H), 7.85 (d, J = 3.9 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 8.7 Hz, 2H), 4.85 (br s, 2H), 4.61 (br s, 2H). ^{19}F NMR (DMSO- d_6): δ - 167.24. LCMS: Purity: 100%; MS (m/e): 311.09 (MH^+).

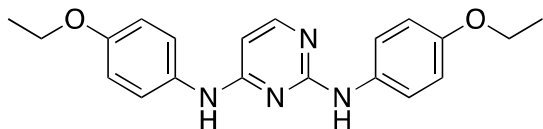
N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (6) :



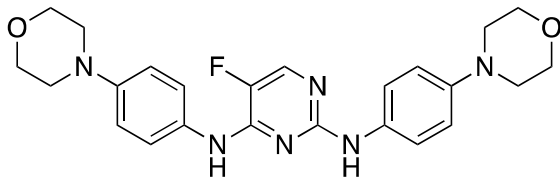
2,4-Dichloro-5-fluoropyrimidine (4.7 g, 28.1 mmol) was dissolved in a mixture of MeOH (150 mL) and H_2O (15 mL). 3-nitroaniline (15.5 g, 112 mmol) was added and the mixture was refluxed for 20h (100 $^{\circ}C$ oil-bath temperature). The mixture was cooled to 22 $^{\circ}C$ and filtered. The residue was washed carefully with 200 mL MeOH- H_2O (1:1; v/v) and dried under vacuum to give 7.89 g (76%) of N2,N4-bis(3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine as yellow crystals. ^1H NMR (DMSO- d_6 + D_2O): δ 8.63 (m, 2H), 8.21 (m, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H); LCMS: Purity: 100%; MS (m/e): 371 (MH^+). N2,N4-Bis(3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (4.0 g, 10.8 mmol) and Pd/C 10% (1.2 g, 50% water content) were suspended in 300 mL EtOH-10% aq. HCl (1 : 1) and hydrogenated (50 PSI) in a Parr shaker apparatus for 6h at room temperature. The suspension was filtered over Celite® and carefully washed with 20 mL DMF- H_2O (1:1; v/v) followed by 50 mL H_2O . The combined filtrates were concentrated under reduced pressure to give pale yellow oil, which was triturated with MeOH to give the product as fine white needles. The precipitate was filtered off and washed with MeOH followed by Et_2O . The remaining crystals were dried under vacuum to give pure material of (**6**, purity >98%, 4 g, 100%) in its salt form. The free amine was obtained by adding aq. 1N NaOH (10 mL) to the stirring solution of above **6.HCl** (1 g) H_2O (5 mL). The resulting precipitate was filtered, washed with H_2O and dried under vacuum for 24h to give N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (**6**) (770 mg) as a white solid. ^1H NMR (CD_3OD): δ 7.92 (d, J = 3.6 Hz, 1H), 7.31 (t, J = 2.1 Hz, 1H), 7.21 (t, J = 2.4 Hz, 1H), 7.08, (t, J = 8.1 Hz, 1H), 6.99 (t, J = 8.1 Hz, 1H), 6.88 (m, 1H), 6.77 (m, 1H), 6.47 (m, 1H), 6.34 (m, 1H); LCMS: Purity: 100%; MS (m/e): 311 (MH^+).

N2,N4-Bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (7):

A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and 4-trifluoromethylaniline (0.035 g, 0.22 mmol) in EtOH (1 mL) was shaken in a sealed tube at 80 °C 24h. N2,N4-bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (**7**) was obtained after acidification of reaction mixture followed by workup and purification analogous to **2**. ¹H NMR (CDCl₃): δ 8.06 (bs, 1H), 7.75 (d, *J* = 9 Hz, 2H), 7.67 (d, *J* = 9 Hz, 2H), 7.63 (d, *J* = 9 Hz, 2H), 7.54 (d, *J* = 9 Hz, 2H), 7.19 (bs, 1H), 6.96 (s, 1H); ¹⁹F NMR (CDCl₃): δ -62.34 (s), -62.62 (s), -164.90 (s); LCMS: Purity: 95%; MS (*m/e*): 417 (MH⁺).

N2, N4-Bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (8):

A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and *p*-phenetidine (0.034 g, 0.25 mmol) in EtOH (1 mL) was shaken in a sealed tube at 70 °C for 24h. Reaction mixture was cooled to room temperature and diluted with water (4 mL) which resulted heterogeneous suspension. The solid was collected by filtration and dried to obtain N2, N4-bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (**8**). ¹H NMR (CD₃OD): δ 7.63 (d, 1H), 7.45 (d, *J* = 9 Hz, 2H), 7.32 (d, *J* = 9.3 Hz, 2H), 6.95 (d, *J* = 6.9 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.23 (d, *J* = 7.2 Hz, 1H), 4.04 (m, 4H), 1.38 (m, 6H); LCMS: Purity: 99%; MS (*m/e*): 351 (MH⁺).

N2,N4-Bis[4-(N-morpholino)phenyl]-5-fluoro-2,4-pyrimidinediamine (9).

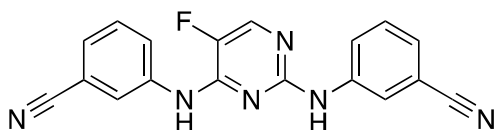
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.033 g, 0.2 mmol) and 4-morpholinoaniline (0.142 g, 0.8 mmol) in MeOH (4 mL): H₂O (1 mL) was shaken in a sealed tube at 80 °C for 24h. Reaction mixture was cooled to room temperature, diluted with water (4 mL) and saturated with solid NaCl. Extractive workup followed by silica gel column chromatographic purification (50-75% EtOAc) provided N2,N4-bis[4-(N-morpholino)phenyl]-5-fluoro-2,4-pyrimidinediamine (**9**) as a beige solid. ¹H NMR (CD₃OD): δ 7.80 (s, 1H), 7.78 (s, partially exchanged, 1H), 7.76 (bs, partially exchanged, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 9 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.86 (bd, 2H), 3.84 (m, 8H), 3.11 (m, 8H); ¹⁹F NMR (CD₃OD): δ -168.97; LCMS: Purity: 99%; MS (*m/e*): 451 (MH⁺).

N2,N4-Bis(4-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (10):



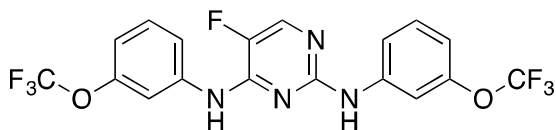
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.1 g, 0.59 mmol) and 4-aminobenzonitrile (0.335 g, 2.9 mmol) in MeOH (10 mL): H₂O (1 mL) was stirred in a sealed tube at 100 °C for (48h). Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (80 mL) and EtOAc (60 mL). The resultant solid was collected by filtration, washed with water and EtOAc to provide white solid of N2,N4-bis(4-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (**10**) (0.16 g, 83%). ¹H NMR (DMSO-*d*₆): δ 9.51 (br, 1 H, NH), 9.49 (br, 1 H, NH), 7.86 (d, *J* = 3.6 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H); ¹⁹F NMR (DMSO-*d*₆): δ -161.48; LCMS: Purity 100%; MS (*m/e*): 331.00 (MH⁺).

N2,N4-Bis(3-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (11):



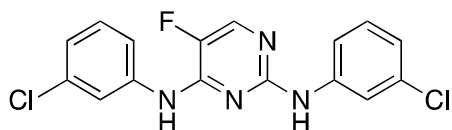
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.05 g, 0.30 mmol) and 4-aminobenzonitrile (0.177 g, 1.5 mmol) in MeOH (10 mL): H₂O (1 mL) was stirred in a sealed tube at 100 °C (24h) and 70 °C (48h). Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl water (80 mL) and EtOAc (60 mL). The resultant solid was collected by filtration, washed with water and dried to provide beige solid of N2,N4-bis(3-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (**11**) (0.075 g, 76%). ¹H NMR (Acetone-*d*₆): δ 9.02 (br s, 1H), 8.98 (br, 1 H, NH), 8.35 (t, *J* = 2.1 Hz, 1 H), 8.31 (m, 1 H), 8.17 (d, *J* = 3.3 Hz, 1 H), 8.09 (ddd, *J* = 8.3, 2.4, 1.2 Hz, 1H), 7.90 (ddd, *J* = 8.4, 2.1, 0.9 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.52-7.46 (m, 2 H), 7.33 (dt, *J* = 7.8, 1.8 Hz, 1 H); ¹⁹F NMR (Acetone-*d*₆): δ -165.80; LCMS: Purity: 98%; MS (*m/e*): 331.01 (MH⁺).

N2,N4-Bis(3-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (12):



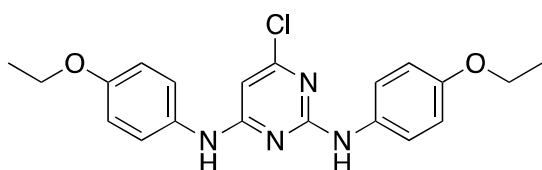
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and 3-trifluoromethoxy aniline (0.039 g, 0.22 mmol) in EtOH (1 mL) was shaken in a sealed tube at 80 °C 24h. N2,N4-Bis(3-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**12**) was obtained after acidification of reaction mixture followed by workup and purification. ¹H NMR (CDCl₃): δ 8.03 (bs, 1H), 7.62 (bs, 2H), 7.48 (bs, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.34 (m, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.01 (m, 2H), 6.88 (m, 2H); ¹⁹F NMR (CDCl₃): δ -164.47, -164.59, -165.57; LCMS: Purity: 93%; MS (*m/e*): 449 (MH⁺).

N2,N4-Bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (13):



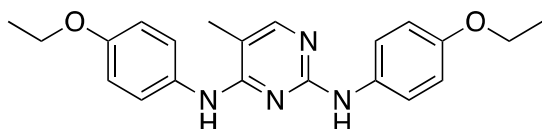
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and 3-chloroaniline (0.039 g, 0.22 mmol) in EtOH (1 mL) was stirred in a sealed tube at 80 °C for 24h. Reaction mixture was cooled to room temperature, diluted with water and 2N aq. HCl. Extractive workup with EtOAc followed by silica gel column chromatographic purification provided N2,N4-Bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (**13**). ¹H NMR (CD₃OD): δ 8.08 (d, *J* = 5.4 Hz, 1H), 7.70 (t, *J* = 1.8 Hz, 1H), 7.57 (t, *J* = 1.2 Hz, 1H), 7.54 (m, 1H), 7.35 (m, 4H), 7.28 (t, *J* = 1.8 Hz, 1H), 7.24 (m, 1H), 7.22 (t, *J* = 1.8 Hz, 1H); ¹⁹F NMR (CD₃OD): δ - 164.57; LCMS: Purity: 99%; MS (*m/e*): 349 (*M*⁺).

N2,N4-Bis(4-ethoxyphenyl)-6-chloro-2,4-pyrimidinediamine (14):



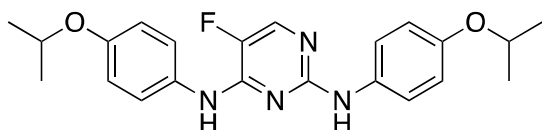
A mixture of 2,4,6-trichloropyrimidine (0.018 g, 0.1 mmol) and *p*-phenetidine (0.034 g, 0.25 mmol) in EtOH (1 mL) was stirred in a sealed tube at 70 °C for 24h. Reaction mixture was cooled to room temperature and diluted with water (4 mL). Extractive workup followed by silica gel column chromatographic purification provided N2,N4-bis(4-ethoxyphenyl)-6-chloro-2,4-pyrimidinediamine (**14**) as a white solid. ¹H NMR (CDCl₃): d 7.42 (d, *J* = 9 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 6.3 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.58 (bs, 1H), 4.02 (m, 4H), 1.43 (m, 6H). LCMS: Purity: 93%; MS (*m/e*): 385 (*MH*⁺).

N2,N4-Bis(4-ethoxyphenyl)-5-methyl-2,4-pyrimidinediamine (15):



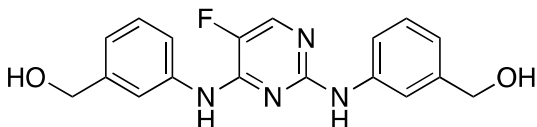
A mixture of 2,4-dichloro-5-methylpyrimidine (0.016 g, 0.1 mmol) and *p*-phenetidine (0.034 g, 0.25 mmol) in EtOH (1 mL) was stirred in a sealed tube at 70 °C for 24h. Reaction mixture was cooled to room temperature and diluted with water (4 mL). The resulting precipitate was collected by filtration and dried to provide N2,N4-bis(4-ethoxyphenyl)-5-methyl-2,4-pyrimidinediamine (**15**). ¹H NMR (CD₃OD): δ 7.55 (s, 1H), 7.40 (d, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.90 (dd, *J* = 8.7 Hz, 4H), 4.04 (q, *J* = 6.6 Hz, 4H), 2.17 (m, 6H); LCMS: Purity: 95%; MS (*m/e*): 365 (*MH*⁺).

N2,N4-Bis(4-isopropoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (16):



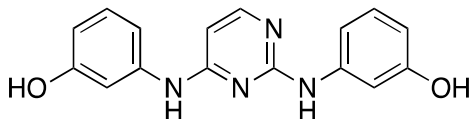
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.016 g, 0.1 mmol) and 4-isopropoxyaniline (0.038 g, 0.25 mmol) in EtOH (1 mL) was stirred in a sealed tube at 100 °C for 24h. Reaction mixture was cooled to room temperature diluted with water (4 mL). Extractive workup followed by silica gel column chromatographic purification provided N2,N4-bis(4-isopropoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**16**) as a white solid. ¹H NMR (CDCl₃): δ 7.89 (bs, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H); LCMS: Purity: 98 %; MS (m/e): 397 (MH⁺).

N2,N4-Bis(3-(hydroxymethyl)phenyl)-5-fluoro-2,4-pyrimidinediamine (17):



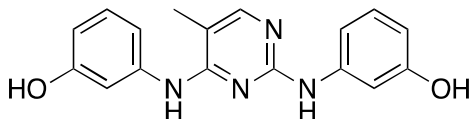
A mixture of 2,4-dichloropyrimidine (0.02 g, 0.12 mmol) and 3-aminobenzyl alcohol (0.044 g, 0.36 mmol) in MeOH (1 mL):H₂O (0.05 mL) was stirred in a sealed tube at 100 °C. Reaction mixture was cooled to room temperature and diluted 2N aq. HCl (2 mL). Extractive workup followed by silica gel column chromatographic purification (30-50% EtOAc/hexanes) provided N2,N4-Bis(3-(hydroxymethyl)phenyl)-5-fluoro-2,4-pyrimidinediamine (**17**). ¹H NMR (CD₃OD): δ 7.90 (d, *J* = 3.3 Hz, 1H), 7.71 (m, 1H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.47 (s, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 6.9 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 4.63 (s, 4H); LCMS: Purity: 100%; MS (m/e): 342 (MH⁺).

N2,N4-Bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (18):



A mixture of 2,4-dichloropyrimidine (0.03 g, 0.2 mmol) and 3-aminophenol (0.065 g, 0.6 mmol) in MeOH (2.5 mL):H₂O (0.5 mL) was stirred in a sealed tube at 100 °C. Reaction mixture was cooled to room temperature and diluted with 2N aq. HCl (2 mL). Extractive workup followed by silica gel column chromatographic purification (1-3% MeOH/CH₂Cl₂) provided N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (**18**). ¹H NMR (DMSO-*d*₆) δ 9.25 (s, 1H), 9.14 (s, 1H), 9.11 (s, 1H), 8.91 (s, 1H), 7.96 (d, *J* = 5.7 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.25 – 7.16 (m, 2H), 7.06 (t, *J* = 8.1 Hz, 1H), 7.02 – 6.93 (m, 2H), 6.40 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.31 (d, *J* = 7.7 Hz, 1H), 6.18 (d, *J* = 5.8 Hz, 1H). LCMS: Purity: 100%; MS (m/e): 295 (MH⁺).

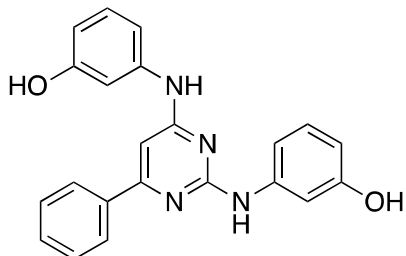
N2,N4-Bis(3-hydroxyphenyl)-5-methyl-2,4-pyrimidinediamine (19):



A mixture of 2,4-dichloro-5-methylpyrimidine (0.033 g, 0.2 mmol) and 3-aminophenol (0.065 g, 0.6 mmol) in MeOH (2.5 mL):H₂O (0.5 mL) was stirred in a sealed tube at 100 °C. Reaction mixture was cooled to room temperature and diluted with 2N aq. HCl (2 mL). Extractive workup followed by silica gel column chromatographic purification (1-

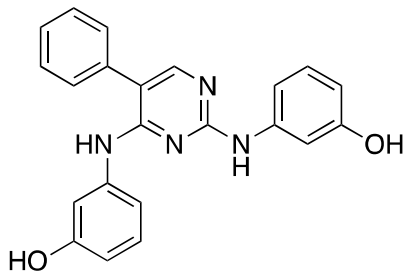
3% MeOH/CH₂Cl₂) provided N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (**18**). ¹H NMR (DMSO-*d*₆) δ 9.22 (s, 1H), 9.04 (s, 1H), 8.73 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 7.13 – 7.02 (m, 3H), 6.91 (t, *J* = 8.1 Hz, 1H), 6.45 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.25 (dd, *J* = 7.9, 2.3 Hz, 1H), 2.07 (s, 3H). LCMS: Purity: 100%; MS (m/e): 309 (MH⁺).

N2,N4-Bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine (20):



A mixture of 2,4,6-trichloropyrimidine (0.183g, 1 mmol) and 3-hydroxyaniline (0.327g, 3 mmol) in MeOH (5 mL) was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H₂O, acidified with 2N aq. HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent and purification by silica gel chromatography (30-70% EtOAc/hexanes) provided N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (0.11g, 11%) as a white solid. ¹H NMR (CD₃OD): δ 7.21 (m, 1H), 7.14-7.03 (m, 5H), 6.50 (m, 1H), 6.44 (m, 1H), 6.16 (s, 1H); LCMS: Purity: 99%; MS (m/e): 329 (M⁺); A screw capped vial containing N2,N4- Bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (13 mg, 0.04 mmol), phenylboronic acid (8 mg, 0.07 mmol), Pd(PPh₃)₄ (3 mg, 0.0025 mmol), 2M aq. NaHCO₃ (0.07 mL, 0.14 mmol), DME (0.7 mL) and a stir bar was purged with nitrogen for 3 min., capped and heated at 75 °C with stirring. After 15h, reaction mixture was diluted with EtOAc (10 mL) and H₂O (1 mL). Organic layer was separated, dried over MgSO₄ and filtered through Celite®. Filtrate was concentrated and purified by silica gel column chromatography (0-70% EtOAc/hexanes) to obtain N2,N4-bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine (7.6 mg, 50%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 9.28 (s, 1H), 9.26 (s, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.62 – 7.43 (m, 3H), 7.37 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.32 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.28 (t, *J* = 2.1 Hz, 1H), 7.14 – 6.97 (m, 3H), 6.69 (s, 1H), 6.42 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H), 6.35 (app ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H). LCMS: Purity: 99 %; MS (m/e): 371 (MH⁺).

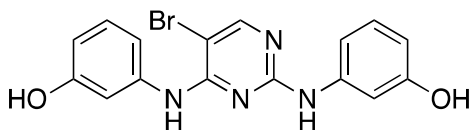
N2,N4-Bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine (21):



A screw capped vial containing N2,N4- bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine (**22**) (15 mg, 0.04 mmol), phenylboronic acid (6.2 mg, 0.051 mmol), Pd(PPh₃)₄ (2 mg, 0.002 mmol), 2M aq. NaHCO₃ (0.05 mL, 0.1 mmol), DME (0.7 mL)

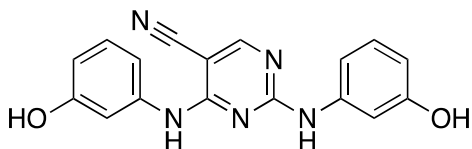
and a stir bar was purged with nitrogen for 3 min., capped and heated at 75 °C with stirring. After 15h, reaction mixture was diluted with EtOAc (10 mL) and H₂O (1 mL). Organic layer was separated, dried over MgSO₄, filtered through Celite® and concentrated. Upon purification of the resultant residue by silica gel column chromatographic purification (0-40% EtOAc/hexanes) provided N2,N4-bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine (9.8 mg, 66%) as an off-white solid. ¹H NMR (CD₃OD): δ 7.85 (bs, 1H), 7.54-7.38 (m, 5H), 7.13-7.11 (m, 2H), 7.10-7.04 (m, 3H), 6.97 (dt, *J* = 8.1 and 1.8 Hz, 1), 6.54 (ddd, 1H, *J* = 7.2, 2.4, 1.9 Hz), 6.44 (dt, *J* = 6.0, 1.8 Hz, 1H); LCMS: Purity: 96 %; MS (*m/e*): 371 (MH⁺).

N2,N4-Bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine (22):



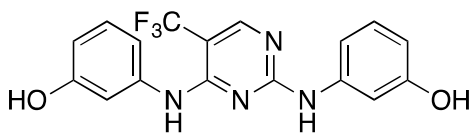
A mixture of 5-bromo-2,4-dichloro-pyrimidine (0.043 g, 0.19 mmol) and 3-aminophenol (0.085 g, 0.78 mmol) in MeOH (0.95 mL):H₂O (0.05 mL) was stirred in a sealed tube at 100 °C for 24h. Reaction mixture was cooled to room temperature and diluted with 10% aq. HCl (3 mL). The resulting solid was collected by filtration, washed with water, Et₂O and CH₂Cl₂ successively. Upon drying the solid under high vacuum provided N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine (**22**) as a white solid (0.04 mg, 52%). ¹H NMR (DMSO-*d*₆): δ 9.99 (bs, 1H), 9.34 (bs, 1H), 8.30 (s, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 7.06-6.97 (m, 2H), 6.94-6.92 (m, 2H), 6.80 (bs, 1H), 6.62 (s, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H); LCMS: Purity: 97%; MS (*m/e*): 374 (MH⁺).

N2,N4-Bis(3-hydroxyphenyl)-5-cyano-2,4-pyrimidinediamine (23):



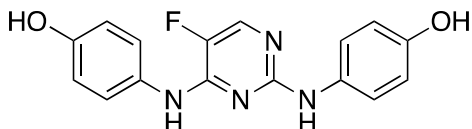
A mixture of 5-cyano-2,4-dichloro-pyrimidine (0.02 g, 0.11 mmol) and 3-aminophenol (0.062 g, 0.57 mmol) in MeOH (0.5 mL) was shaken in a sealed tube at 100 °C for 3 days. Reaction mixture was cooled to room temperature, diluted with EtOAc (15 mL) and washed with 1N aq. HCl (3 mL) followed by aq. NaCl. Usual workup and purification by preparative silica gel TLC purification (40%EtOAc/hexanes) provided N2,N4-bis(3-hydroxyphenyl)-5-cyano-2,4-pyrimidinediamine (**23**) as a white solid. ¹H NMR (DMSO-*d*₆): δ 9.73 (bs, 1H), 9.40 (s, 1H), 9.33 (bs, 1H), 9.24 (s, 1H), 8.47 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.09-7.02 (m, 2H), 6.99-6.89 (m, 3H), 6.54 (d, *J* = 7.2 Hz, 1H), 6.37 (dd, 1H, *J* = 8.4, 1.8 Hz); LCMS: Purity: 97%; MS (*m/e*): 320 (MH⁺).

N2,N4-Bis(3-hydroxyphenyl)-5-trifluoromethyl-2,4-pyrimidinediamine (24):



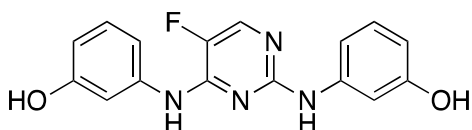
A mixture of 2,4-dichloro-5-trifluoromethylpyrimidine (0.03 g, 0.14 mmol) and 3-aminophenol (0.062 g, 0.57 mmol) in EtOH (1.5 mL) was shaken in a sealed tube at 100 °C for 18h. Upon acidification of reaction mixture followed by extractive work up and silica gel chromatographic purification provided N2,N4-bis(3-hydroxyphenyl)-5-trifluoromethyl-2,4-pyrimidinediamine (**24**). ¹H NMR (DMSO-*d*₆): δ 9.82 (bs, 1H), 8.88 (bs, 1H), 8.36 (s, 1H), 7.18-7.11 (m, 2H), 6.96 (m, 4H), 6.63 (dd, 1H, *J* = 8.1, 2.4 Hz), 6.38 (d, *J* = 8.1 Hz, 1H); ¹⁹F NMR (DMSO-*d*₆): δ -169.79; LCMS: Purity: 95 %; MS (m/e): 363 (MH⁺).

N2,N4-Bis(4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (25):



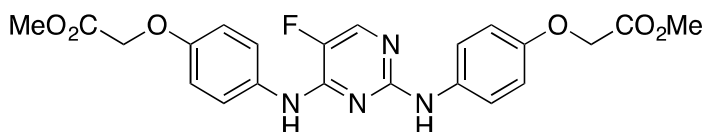
A mixture of 2,4-dichloro-5-fluoropyrimidine (0.016 g, 0.1 mmol) and 4-acetoxyaniline (0.045 g, 0.3 mmol) in EtOH (1 mL) was shaken in a sealed tube at 80 °C for 24h. Extractive workup followed by preparative TLC on silica gel provided N2,N4-Bis(4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**25**). ¹H NMR (CD₃OD): δ 7.74 (d, *J* = 5.6 Hz, 1H), 7.43 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.28 (dd, *J* = 6.3, 2.4 Hz, 2H), 6.74 (dd, *J* = 6.3, 2.4 Hz, 2H), 6.66 (dd, *J* = 7.2, 2.4 Hz, 2H); ¹⁹F NMR (CD₃OD): δ -170.46; LCMS: Purity: 100%; MS (m/e): 313 (MH⁺).

N2,N4-Bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (26):



A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and 3-aminophenol (0.033 g, 0.3 mmol) in MeOH (1.8 mL): H₂O (0.2 mL) was shaken in a sealed tube at 100 °C for 24h, cooled to room temperature, diluted with water (15 mL), acidified with 2N aq. HCl (pH >2). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous sodium sulfate and solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh) using CH₂Cl₂ and (1 -10%) MeOH/CH₂Cl₂ as an eluting solvent to obtain the desired N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.73 (d, *J* = 5.1 Hz, 1H), 7.12-6.90 (m, 6H), 6.64 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.53 (dd, *J* = 5.7, 1.2 Hz, 1H); LCMS: Purity: 100%; MS (m/e): 313 (MH⁺).

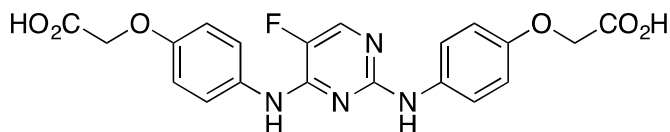
N2, N4-Bis[(4-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (27):



A mixture of 2,4-dichloro-5-fluoropyrimidine (0.017 g, 0.1 mmol) and ethyl 4-aminophenoxyacetate (0.06 g, 0.3 mmol) in MeOH (2 mL): H₂O (1 mL) was shaken in a sealed tube at 100 °C for 48h. Upon acidification of reaction mixture followed by

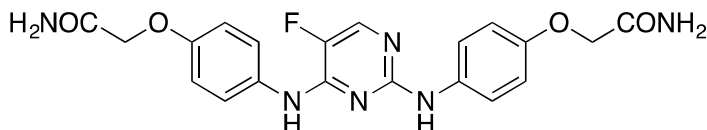
extractive work up and silica gel chromatographic purification provided trans esterified N2, N4-bis[(4-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (**27**) product. ¹H NMR (CD₃OD): δ 7.82 (bs, 1H), 7.50 (d, *J* = 9.3 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.88 (m, 4H), 4.72 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ¹⁹F NMR (CDCl₃): -168.52; LCMS: Purity: 95%; MS (*m/e*): 457 (MH⁺).

N2,N4-Bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine (28):



2N aq. NaOH (0.16 mL, 0.32 mmol) was added to stirring solution of N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**27**) (30 mg, 0.065 mmol) and THF (2 mL) for 5h. The reaction mixture was concentrated, diluted with water (2 mL) and acidified with aq. 2N aq. HCl solution. The resulting precipitate was collected by suction filtration and dried on the funnel to obtain N2,N4-bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine (**28**) as a white solid (19 mg, 67%). ¹H NMR (CD₃OD): δ 7.86 (bs, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.32 (bd, *J* = 9.3 Hz, 2H), 6.95 (m, 4H), 4.66 (s, 2H); LCMS: Purity: 92%; MS (*m/e*): 429 (MH⁺).

N2,N4-Bis[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (29):



4-(Aminocarbonylmethyleneoxy)aniline (500 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (200 mg, 1.2 mmol) were dissolved in methanol (10 mL):water (1 mL) and stirred at 70 °C for 24h. Then methanol was removed under reduced pressure. The remaining aqueous solution was acidified with 1N aq. HCl (80 mL). The resultant white precipitate was collected by filtration to give N2,N4-bis[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (370 mg, 72%) ¹H NMR (Acetone-*d*₆): δ 8.44 (br, 1H, NH), 8.27 (br, 1H, NH), 7.93 (d, *J* = 3.6 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 9.3 Hz, 2H), 7.20 (br, 2H, NH), 6.98 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.81 (br, NH, 2H), 4.50 (s, 2H), 4.46 (s, 2H); LCMS: Purity: 100%; MS (*m/e*): 427 (MH⁺).

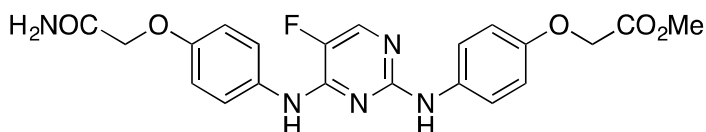
N2,N4-Bis[4-(cyanomethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (30):



To a solution of N2,N4-bis[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (**29**) (200 mg, 0.47 mmol) in THF (10 mL) was added trifluoroacetic anhydride (0.33 mL, 2.35 mmol) and pyridine (0.38 mL, 4.7 mmol) at room temperature and stirred overnight. The mixture was diluted with ethyl acetate (80 mL) and 1 N aq. HCl (80 mL). The organic layer was separated and washed with 1 N aq. HCl (2 x 60

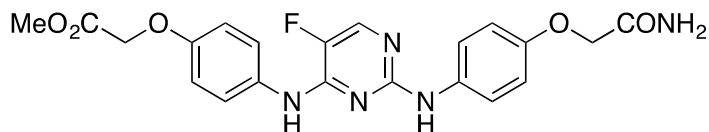
mL), water (2 x 60 mL) and brine (60 mL) successively, stirred in anhydrous Na₂SO₄, filtered and evaporated. The residue was recrystallized from 30% EtOAc/hexanes (15 mL) to give N2,N4-bis[4-(cyanomethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (**30**) (159 mg, 87%) as a white solid. ¹H NMR (Acetone-*d*₆): δ 11.00 (br, 1H, NH), 9.55 (br, 1H, NH), 8.17 (d, *J* = 4.8 Hz, 1H), 7.77 (d, *J* = 9.3 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 9.3 Hz, 2H), 5.16 (s, 2H), 5.09 (s, 2H); LCMS: 96%; MS (m/e): 391 (MH⁺).

N4-(4-Aminocarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (31):



A mixture of methyl 4-aminophenoxyacetate (**52**) (0.18 g, 1 mmol) and N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (**54**) (100 mg, 0.34 mmol) in MeOH (10 mL):H₂O (1 mL) was shaken in a sealed tube at 70 °C (24h) followed by 100 °C (48h). Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (80 mL) and EtOAc (60 mL). N4-(4-Aminocarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (**31**) was precipitated upon addition of solid NaCl to solution. The heterogeneous suspension was filtered and the solid was dried under high vacuum (0.12 g, 80%). ¹H NMR (Acetone-*d*₆): δ 9.78 (br, 1H, NH), 9.46 (br, 1H, NH), 7.71 (d, *J* = 5.1 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.49 (d, *J* = 9.3 Hz, 2H), 6.45 (d, *J* = 8.7 Hz, 2H), 4.33 (s, 2H), 3.98 (s, 2H), 3.25 (s, 3H); LCMS: Purity: 100%; MS (m/e): 442 (MH⁺).

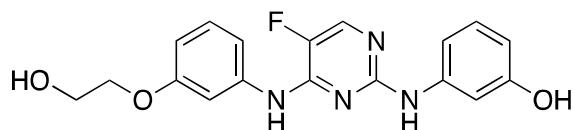
N2-(4-Aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (32):



A screw capped vial containing a mixture of 2,4-dichloro-5-fluoropyrimidine (0.65 g, 3.9 mmol) and methyl 4-aminophenoxyacetate (**52**) (0.50 g, 2.7 mmol) in H₂O (18 mL): MeOH (2 mL) was stirred and heated for 12h at 60 °C. Reaction mixture was cooled to room temperature, concentrated to remove volatiles and extracted into EtOAc (90 mL). Organic layer was washed with water, aq. NaHCO₃ and aq. NaCl successively. Usual workup and purification by silica gel column chromatographic purification (0-30% EtOAc/hexanes) provided 2-chloro-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (0.68 g, 81%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 9.87 (s, 1H), 8.24 (d, *J* = 3.6 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.78 (s, 2H), 3.69 (s, 4H); ¹⁹F NMR (DMSO-*d*₆): δ -154.50; LCMS: Purity: 97%; MS (m/e): 312 (MH⁺). N2-(4-

Aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (**32**) was obtained in an analogous manner to the preparation of **31** by heating the reaction of 2-chloro-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (150 mg, 0.48 mmol) and 4-(aminocarbonylmethyleneoxy)aniline (**54**) (240 mg, 1.44 mmol) at 100 °C for 24h. Yield (145 mg, 68%). ¹H NMR (DMSO-*d*₆): δ 10.39 (br, 1H, NH), 10.13 (br, 1H, NH), 8.21 (d, *J* = 4.8 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.81 (s, 2H), 4.40 (s, 2H), 3.70 (s, 3H); ¹⁹F NMR (DMSO-*d*₆): δ -162.26; LCMS: Purity: 92%; MS (*m/e*): 442 (MH⁺).

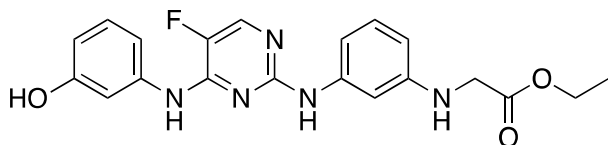
5-Fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (33**):**



2-Chloro-5-fluoro-N4-(3-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (0.72 g, 85%) was prepared in an identical manner to the preparation of 2-chloro-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine and obtained as off-white solid. ¹H NMR (DMSO-*d*₆): δ 9.94 (s, 1H), 8.32 (d, *J* = 3.5 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.33 (ddd, *J* = 8.1, 1.9, 1.1 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.69 (ddd, *J* = 8.0, 2.5, 1.1 Hz, 1H), 4.77 (s, 2H), 3.69 (s, 3H); ¹⁹F NMR (DMSO-*d*₆): δ -153.33; LCMS: Purity: 97%; MS (*m/e*): 312 (MH⁺). A mixture of 3-aminophenol (0.05 g, 0.46 mmol) and 2-chloro-5-fluoro-N4-(3-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (0.05 g, 0.15 mmol) in MeOH (2 mL):H₂O (0.2 mL) was shaken in a screw capped vial at 100 °C for 24h. Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (10 mL) and EtOAc (60 mL). Organic layer was separated, washed with water, aq. NaHCO₃ and aq. NaCl. Usual workup of the organic layer and purification of resultant crude material by silica gel chromatography provided 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.27 (s, 1H), 9.13 (s, 1H), 9.03 (s, 1H), 8.09 (d, *J* = 3.7 Hz, 1H), 7.56 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.35 (t, *J* = 2.2 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.97 (t, *J* = 8.3 Hz, 1H), 6.60 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.30 (ddd, *J* = 8.0, 2.2, 1.2 Hz, 1H), 4.74 (s, 2H), 3.68 (s, 3H). ¹⁹F NMR (DMSO-*d*₆): δ -164.04. LCMS: Purity: 98 %; MS (*m/e*): 385 (MH⁺). DIBAL-H (1M solution in toluene, 1.95 mL, 1.95 mmol) was added slowly over 10 min to a stirring solution of 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (75 mg, 0.195 mmol) in dichloromethane (5 mL) at 0 °C under nitrogen. After 2h, reaction mixture was quenched with MeOH (1 mL), diluted with EtOAc (15 mL), treated with aqueous Rochelle's salt solution (4 mL) and stirred for 30 min. The semi heterogeneous suspension was treated with solid anhydrous Na₂SO₄ (2G), stirred for 10 min, filtered through Celite® and concentrated under reduced pressure. Upon purification of the resulting residue by silica gel flash column chromatography (0-70% EtOAc/hexanes) provided 5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**33**) (34 mg, 49%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 9.23 (s, 1H), 9.14 (s, 1H), 9.06 (s, 1H), 8.07 (d, *J* = 4.1 Hz, 1H), 7.51 (dd, *J* = 1.7 and 7.6 Hz, 1H), 7.30 (app t, *J* = 2.3 and 1.7 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 1H),

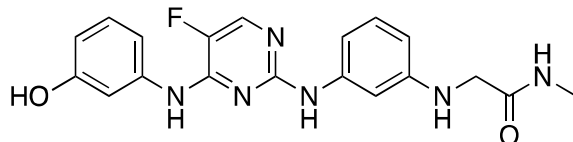
7.13 (br s, 1H), 7.11 (m, 1H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.61 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.28 (dd, $J = 8.2, 2.3$ Hz, 1H), 4.84 (t, $J = 5.8$ Hz, 1H), 3.92 (t, $J = 5.2$ Hz, 2H), 3.68 (app qt, $J = 5.2$ Hz, 2H); LCMS: Purity: 96%; MS (m/e): 357 (MH⁺).

N2-(3-Ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (34):



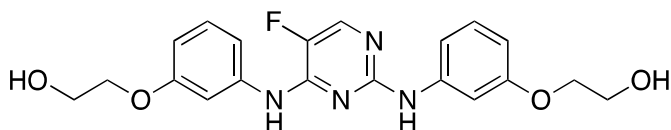
A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.87g, 3.6 mmol) and 3-ethoxycarbonylmethyleneaminophenylaniline (**56**) (2.1g, 10.8 mmol) in EtOH (4 mL):H₂O (1 mL) at 100 °C (72h). Reaction mixture was concentrated and purified by silica gel column chromatography (30-50% EtOAc/hexanes) to obtain N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**34**) as a purple solid. ¹H NMR (DMSO-*d*₆): δ 9.30 (s, 1H), 9.12 (s, 1H), 8.86 (s, 1H), 8.03 (d, $J = 3.7$ Hz, 1H), 7.33 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.12 (t, $J = 2.3$ Hz, 1H), 7.08 (t, $J = 8.0$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 6.93 – 6.85 (m, 2H), 6.47 (dd, $J = 8.0, 2.4$ Hz, 1H), 6.10 (d, $J = 8.1$ Hz, 1H), 5.70 (t, $J = 6.4$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.78 (d, $J = 6.4$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 3H); ¹⁹F NMR (DMSO-*d*₆): δ - 164.34; LCMS: Purity: 96%; MS (m/e): 398 (MH⁺)

5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (35):



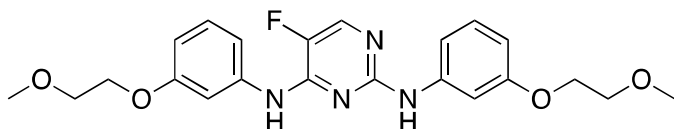
N2-(3-Ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**34**) (50 mg, 0.125 mmol), MeNH₂.HCl (42 mg, 0.622 mmol), *i*-Pr₂NEt (82 mg, 0.11, 0.734 mmol) and EtOH (2 mL) were transferred to a screw capped vial and the mixture was heated at 100 °C for 3h. The reaction mixture was cooled to room temperature, diluted with water (3 mL) and EtOAc (10 mL). The organic phase was separated, dried over MgSO₄, and concentrated under reduced pressure. The residue thus obtained as a solid was subjected to column chromatography on silica gel (chloroform:acetone, 2:1) to give 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (**35**) (19 mg, 39%). ¹H NMR (DMSO-*d*₆) δ 9.32 (s, 1H), 9.13 (s, 1H), 8.91 (s, 1H), 8.03 (d, $J = 3.7$ Hz, 1H), 7.70 (q, $J = 4.7$ Hz, 1H), 7.33 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.13 (t, $J = 2.2$ Hz, 1H), 7.08 (t, $J = 8.1$ Hz, 1H), 7.02 (d, $J = 8.8$ Hz, 1H), 6.91 (t, $J = 8.0$ Hz, 1H), 6.88 (t, $J = 2.1$ Hz, 1H), 6.47 (dd, $J = 7.8, 1.8$ Hz, 1H), 6.08 (dd, $J = 7.6, 1.6$ Hz, 1H), 5.66 (app s, 1H), 3.53 (s, 2H), 2.58 (d, $J = 4.6$ Hz, 3H). ¹⁹F NMR (DMSO-*d*₆): δ - 164.34. LCMS: Purity: 93%; MS (m/e): 383 (MH⁺).

N2, N4-Bis[3-(2-hydroxyethoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (36):



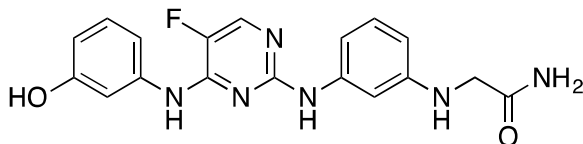
A solution of 2,4-dichloro-5-fluoropyrimidine (0.05 g, 0.30) and 2-(3-aminophenoxy)ethanol (0.13, 0.85 mmol) and MeOH (2 mL) was shaken in a sealed tube at 100 °C for 24h. Upon acidification of reaction mixture followed by workup and silica gel column chromatographic purification provided N2, N4-Bis[3-(2-hydroxyethoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (**36**). ¹H NMR (DMSO-*d*₆): δ 9.50 (br s, 1H), 9.35 (br s, 1H), 8.13 (d, *J* = 4.1 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.26-7.19 (m, 4H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.50 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.0 (br s, 2H), 3.91 (t, *J* = 5.2 Hz, 2H), 3.85 (t, *J* = 5.2 Hz, 2H), 3.68 (qt, *J* = 5.2 Hz, 2H), 3.66 (qt, *J* = 5.2 Hz, 2H); LCMS: Purity: 97%; MS (*m/e*): 401 (MH⁺).

N2,N4-Bis[3-(2-methoxyethyl)oxyphenyl]-5-fluoro-2,4-pyrimidinediamine (37):



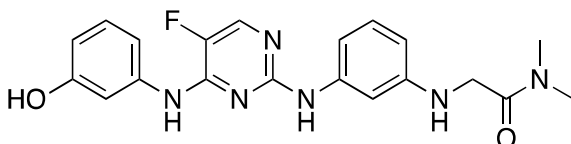
Analogous to the preparation of **36**, N2,N4-Bis[3-(2-methoxyethyl)oxyphenyl]-5-fluoro-2,4-pyrimidinediamine (**37**) was obtained by the reaction of 2,4-dichloro-5-fluoropyrimidine (0.05 g, 0.30 mmol) and 3-(2-methoxyethoxy)aniline (0.15 g, 0.9 mmol). ¹H NMR (CDCl₃): δ 7.96 (d, *J* = 2.9 Hz, 1H), 7.36 (t, *J* = 1.7 Hz, 1H), 7.28 (t, *J* = 1.7 Hz, 1H), 7.25-7.06 (m, 4H), 6.98 (br s, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.70 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.58 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.08-4.03 (m, 4H), 3.74-3.69 (m, 4H), 3.44 (s, 3H), 3.43 (s, 3H); LCMS: Purity: 97%; MS (*m/e*): 429 (MH⁺).

N2-(3-Aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (38):



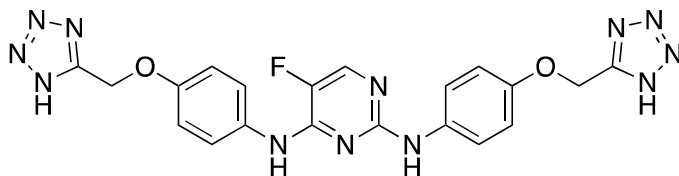
N2-(3-Ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**34**) (50 mg, 0.125 mmol) and 7N NH₃ in MeOH (3 mL) were heated at 100 °C in a similar manner to the preparation of (**35**) as mentioned above to obtain N2-[3-(N,N-dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**38**) (24 mg, 52%) as an off-white solid upon workup and purification. ¹H NMR (DMSO-*d*₆): δ 9.31 (s, 1H), 9.11 (s, 1H), 8.89 (s, 1H), 8.03 (d, *J* = 3.7 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.22 (s, 1H), 7.13 (t, *J* = 2.1 Hz, 1H), 7.11 – 7.03 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.97 – 6.87 (m, 2H), 6.47 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.09 (d, *J* = 9.1 Hz, 1H), 5.54 (t, *J* = 5.8 Hz, 1H), 3.51 (d, *J* = 5.7 Hz, 2H). LCMS: Purity: 95%; MS (*m/e*): 369.03 (MH⁺).

N2-[3-(N,N-Dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (39):



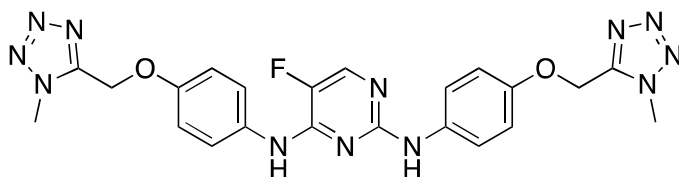
N2-(3-Ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (50 mg, 0.125 mmol), Me₂NH.HCl (50 mg, 0.622 mmol), i-Pr₂NEt (82 mg, 0.11 mL, 0.734 mmol) were reacted in EtOH (2 mL) at 100 °C in the similar manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine as mentioned above to obtain N2-[3-(N,N-dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**39**) (23 mg, 46%) as off-white solid upon workup and purification. ¹H NMR (DMSO-*d*₆): δ 9.29 (s, 1H), 9.12 (s, 1H), 8.83 (s, 1H), 8.04 (d, *J* = 3.7 Hz, 1H), 7.34 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.97 – 6.85 (m, 3H), 6.45 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 6.20 (dt, *J* = 7.0, 2.1 Hz, 1H), 5.17 (t, *J* = 5.0 Hz, 1H), 3.75 (d, *J* = 4.9 Hz, 2H), 2.92 (s, 3H), 2.84 (s, 3H). LCMS: 16.59 min.; Purity: 96.5%; MS (m/e): 397.06 (MH⁺).

N2,N4-Bis[4-(1H-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (40):



To a solution of N2,N4-bis[4-(cyanomethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (**30**) (100 mg, 0.26 mmol) in DMF (10 mL) was added NH₄Cl (136 mg, 2.54 mmol), sodium azide (100 mg, 1.54 mmol), and one drop of acetic acid. The combined reaction mixture was stirred at 70 °C overnight and diluted with ethyl acetate (80 mL) upon cooling to room temperature to give precipitation. The precipitate was collected by filtration, washed with 1N aq. HCl and water to give N2, N4-bis[4-(1H-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (**40**) (66 mg, 54%) as a white solid. ¹H NMR (CD₃OD): δ 7.81 (d, *J* = 4.2 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 5.31 (s, 2H), 7.00 (d, *J* = 9.3 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 5.34 (s, 2H); LCMS: Purity: 88%; MS (m/e): 477 (MH⁺).

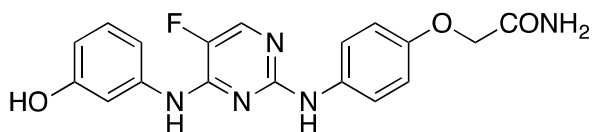
N2,N4-Bis[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (41):



N2,N4-Bis[4-(1H-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (**40**) (30 mg, 0.063 mmol), iodomethane (0.024 mL, 0.38 mmol) and K₂CO₃ (88 mg, 0.64 mmol) in DMF (5 mL) was stirred at room temperature overnight. Then it was diluted with ethyl acetate (50 mL) and water (50 mL). The organic layer was

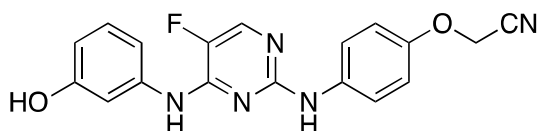
washed with water (50 mL) and brine (50 mL). After separation, the ethyl acetate layer was dried, evaporated and purified by flash column chromatography (EtOAc/hexanes = 2/1, 1/1, EtOAc) which provided N2,N4-bis[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (**41**) (6 mg, 19%). ¹H NMR (CDCl₃): δ 7.90 (br, 1H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.3 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.76 (s, 1H), 6.65 (d, *J* = 3.0 Hz, 1H), 5.36 (s, 2H), 5.33 (s, 2H), 4.38 (s, 3H), 4.37 (s, 3H); ¹⁹F NMR (CDCl₃): δ - 168.52; LCMS: Purity: 94%; MS (m/e): 505 (MH⁺).

N2-[4-(Aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (42**):**



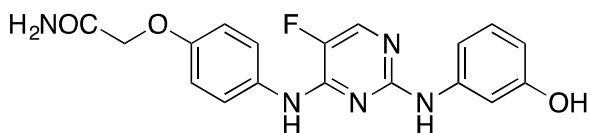
A mixture of 4-(aminocarbonylmethyleneoxy)aniline (198 mg, 1.2 mmol) and 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (**55**) (95 mg, 0.4 mmol) in MeOH (10 mL):H₂O (1 mL) was shaken in a sealed tube at 100 °C (48h). Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (80 mL) and EtOAc (60 mL). The resulting black solid was collected by filtration. Subsequently, filtrate was extracted with EtOAc (3 X 10 mL) and the combined organic layers were mixed, stirred over anhydrous Na₂SO₄ and concentrated to provide dark solid. Recrystallization of combined solids from MeOH/H₂O provided N2-[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**42**) (60 mg, 41%). ¹H NMR (CD₃OD): δ 8.09 (d, 1H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.18 (m, 2H), 7.08 (d, *J* = 9.3 Hz, 2H), 6.75 (dm, *J* = 7.5 Hz, 1H), 4.55 (s, 2H); LCMS; Purity: 99%; MS (m/e): 370 (MH⁺).

N2-(4-Cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (43**):**



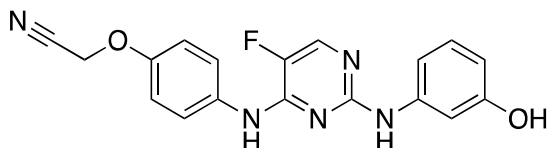
In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**30**), N2-(4-(aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine(**42**) (60 mg, 0.16 mmol), trifluoroacetic anhydride (0.11 mL, 0.8 mmol) and pyridine (0.13 mL, 1.6 mmol) gave N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**43**) (30 mg, 53%) as a white solid. ¹H NMR (Acetone-*d*₆): δ 8.42 (s, 1H, NH), 8.34 (s, 1H, NH), 7.98 (d, *J* = 3.6 Hz, 1H), 7.78 (d, *J* = 9.3 Hz, 2H), 7.38 (t, *J* = 2.1 Hz, 1H), 5.04 (s, 2H), 7.31 (ddd, *J* = 8.1, 2.1, 1.2 Hz, 1H), 7.15 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 9.3 Hz, 2H), 6.60 (ddd, *J* = 8.1, 2.4, 0.9 Hz, 1H); ¹⁹F NMR (Acetone-*d*₆): δ - 168.06; LCMS: Purity: 97%; MS (m/e): 352 (MH⁺).

N4-[4-(Aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (44):



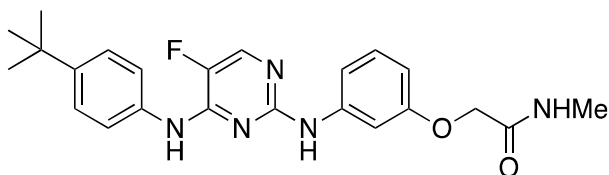
A mixture of 3-aminophenol (0.110 g, 1.0 mmol) and 2-chloro-N4-[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine (**54**) (0.08 g, 0.27 mmol) in MeOH (10 mL):H₂O (1 mL) was shaken in a sealed tube at 100°C (72h). Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (80 mL) and EtOAc (80 mL). Upon removal of volatiles under reduced pressure, solid NaCl was added to the solution and the resultant solid was collected on the funnel to provide N4-[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**44**) (75 mg, 76%). ¹H NMR (Acetone-*d*₆): δ 8.27 (d, *J* = 6.0 Hz, 1H), 7.70 (dd, *J* = 9.0, 2.4, 2H), 7.06-7.14 (m, 5H), 6.64 (dm, *J* = 8.4 Hz, 1H), 4.51 (s, 2H); ¹⁹F NMR (Acetone-*d*₆): δ - 164.00; LCMS: Purity: 94%; MS (*m/e*): 370 (MH⁺).

N4-[4-(Cyanomethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (45):



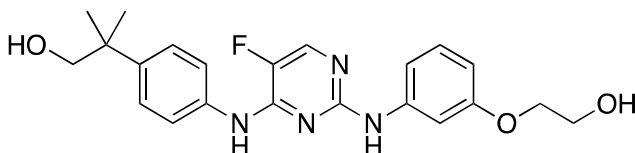
To a solution of N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (**54**) (178 mg, 0.6 mmol) in THF (10 mL) was added trifluoroacetic anhydride (0.17 mL, 1.2 mmol) and pyridine (0.15 mL, 1.84 mmol) and stirred at room temperature overnight. The mixture was diluted with ethyl acetate (50 mL) and 1 N aq. HCl (35 mL). The organic layer was separated, washed with 1 N aq. HCl (2 x 30 mL), water (2 x 30 mL) and brine (40 mL) successively, stirred in anhydrous Na₂SO₄, filtered and evaporated. Upon recrystallization of concentrated residue from 30% EtOAc/hexanes (15 mL) provided 2-chloro-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine (110 mg, 66%) as a white solid. ¹H NMR (Acetone-*d*₆): δ 5.22 (s, 2 H), 7.24 (d, *J* = 9.3 Hz, 2 H), 7.62 (d, *J* = 9.0 Hz, 2 H), 8.94 (d, *J* = 1.8 Hz, 1 H); ¹⁹F NMR (Acetone-*d*₆): δ -137.60; LCMS: Purity: 89%; MS (*m/e*): 279 (MH⁺). A mixture of 3-aminophenol (94 mg, 0.86 mmol) and 2-chloro-N4-(4-(cyanomethyleneoxy)phenyl)-5-fluoro-4-pyrimidineamine (80 mg, 0.29 mmol) in MeOH (10 mL):H₂O (1 mL) was shaken in a sealed tube at 100°C (24h). Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (80 mL) and EtOAc (80 mL). Organic layer was separated, washed with aq. HCl (1N, 2 x 60 mL) and water (2 x 60 mL), dried, filtered and concentrated. The resulting solid residue was recrystallized from MeOH/Et₂O/hexanes to provide g N4-[4-(cyanomethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (**45**) (65 mg, 64%) as off-white solid. ¹H NMR (Acetone-*d*₆): δ 11.33 (s, 1 H, NH), 10.04 (s, 1H, NH), 8.30 (d, *J* = 5.4 Hz, 1H), 7.77 (d, *J* = 9.3 Hz, 2H), 7.19 (d, *J* = 9.3 Hz, 2H), 7.08-7.16 (m, 2H), 7.03 (t, *J* = 2.1 Hz, 1H), 6.64 (ddd, *J* = 7.5, 2.4, 1.8, 1H), 5.16 (s, 2 H); ¹⁹F NMR (Acetone-*d*₆): δ - 163.52; LCMS: Purity: 100%; MS (*m/e*): 352 (MH⁺).

N4-(4-*tert*-Butylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (46):



N4-(*t*-Butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (0.76 g, 81%) was prepared in an identical manner to the preparation of 2-chloro-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine and obtained as off-white solid. ¹H NMR (DMSO-*d*₆): δ 9.92 (s, 1H), 8.27 (d, *J* = 4.0 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 1.26 (s, 9H); ¹⁹F NMR (DMSO-*d*₆): δ - 154.05; LCMS: Purity: 96%; MS (m/e): 280 (MH⁺). N4-(*t*-Butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (0.76 g, 81%). A mixture of N-methyl 3-aminophenoxyacetamide (**60**) (0.05 g, 0.27 mmol) and N4-(*t*-butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (0.05 g, 0.18 mmol) in MeOH (2 mL) was shaken in a sealed tube at 100 °C (24h). Reaction mixture was cooled to room temperature, diluted with water and extracted into EtOAc. Organic layer was separated, washed with water, dried, filtered, concentrated and purified by silica gel column chromatography (2% 2N NH₃ in MeOH/CH₂Cl₂) to obtain N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (**46**) (0.56 g, 48%). ¹H NMR (CD₃OD): δ 7.90 (d, *J* = 3.3 Hz, 1H), 7.61 (d *J* = 8.7 Hz, 2H), 7.40-7.33 (m, 3H), 7.14-7.11 (m, 2H), 6.62-6.57 (m, 1H), 4.36 (s, 2H), 2.79 (s, 3H), 1.31 (s, 9H); ¹⁹F NMR (CD₃OD): δ - 168.32; LCMS: Purity: 93 %; MS (m/e): 424 (MH⁺).

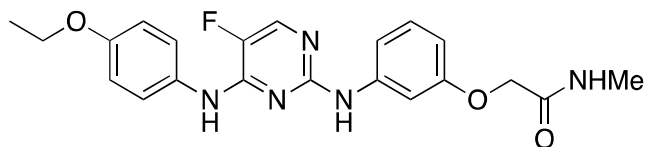
5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine (47):



A screw capped vial containing a mixture of 2,4-dichloro-5-fluoropyrimidine (0.17 g, 1.0 mmol) and ethyl-2-(4-aminophenyl)-2-methylpropanoate (0.25 g, 1.2 mmol) in MeOH (1 mL): H₂O (9 mL) was stirred and heated in a screw capped vial for 12h at 70 °C. Reaction mixture was cooled to room temperature, concentrated to remove volatiles and extracted into EtOAc (90 mL). Organic layer was washed with water, aq. NaHCO₃ and aq. NaCl successively. Usual workup and purification by silica gel column chromatography (0-30% EtOAc/hexanes) provided 2-chloro-5-fluoro-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine (**57**) (0.28 g, 84%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 9.99 (s, 1H), 8.30 (d, *J* = 3.5 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 4.04 (qt, *J* = 7.0 Hz, 2H), 1.47 (s, 6H), 1.10 (t, *J* = 7.0 Hz, 3H); ¹⁹F NMR (DMSO-*d*₆): δ - 153.82; LCMS: Purity: 97%; MS (m/e): 338 (MH⁺). A mixture of methyl 3-aminophenoxyacetate (0.09 g, 0.44 mmol) and 2-chloro-5-fluoro-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine (0.05 g, 0.15 mmol) in MeOH (2 mL):H₂O (0.2 mL) was shaken in a screw capped vial at 100 °C for

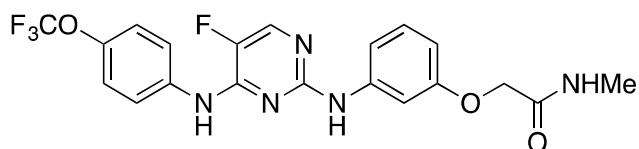
24h. Reaction mixture was cooled to room temperature, diluted with 1N aq. HCl (10 mL) and EtOAc (60 mL). Organic layer was separated, washed with water, aq. NaHCO₃ and aq. NaCl. Usual workup of the organic layer and purification of resultant crude material by silica gel chromatography provided 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 10.06 (s, 1H), 9.85 (s, 1H), 8.22 (d, *J* = 4.7 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.22 (q, *J* = 2.3, 1.7 Hz, 1H), 7.19 – 7.10 (m, 2H), 6.64 – 6.53 (m, 1H), 4.70 (s, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 1.48 (s, 6H), 1.10 (t, *J* = 7.1 Hz, 3H). ¹⁹F NMR (DMSO-*d*₆): δ -161.86; LCMS: Purity: 99 %; MS (*m/e*): 411 (MH⁺). Analogous to the preparation of **33**, DIBAL-H (1M solution in toluene, 0.6 mL, 0.60 mmol) reduction of 5-fluoro-N2-(3-hydroxyphenyl)-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine (50 mg, 0.12 mmol) provided 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine (**47**) (16 mg, 36%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 9.27 (s, 1H), 9.11 (s, 1H), 8.07 (d, *J* = 3.5 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.38-7.24 (m, 4H), 7.06 (t, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 4.83 (t, *J* = 5.3 Hz, 1H), 4.66 (t, *J* = 5.3 Hz, 1H), 3.88 (t, *J* = 5.3 Hz, 2H), 3.67 (t, *J* = 5.3 Hz, 1H), 3.66 (t, *J* = 5.3 Hz, 1H), 3.38 (d, *J* = 5.3 Hz, 2H), 1.20 (s, 6H); LCMS: Purity: 96%; MS (*m/e*): 413 (MH⁺).

N4-(4-Ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (48**):**



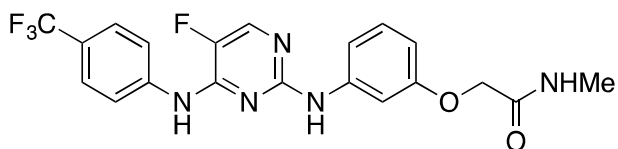
A screw capped vial containing a mixture of 2,4-dichloro-5-fluoropyrimidine (0.83 g, 5.0 mmol) and *p*-phenetidine (0.82 g, 6.0 mmol) in MeOH (2 mL): H₂O (10 mL) was stirred at room temperature for 1h. The reaction mixture was acidified with 2N aq. HCl upon cooling to room temperature. The solid from resulting heterogeneous mixture was collected by filtration, washed with water and dried to provide 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine ¹H NMR (CDCl₃): δ 8.01 (d, *J* = 3Hz, 1H), 7.49 (bdd, *J* = 8.7 Hz, 2H), 6.92 (bdd, *J* = 9.6 Hz, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); LCMS: Purity: 99%; MS (*m/e*): 268 (MH⁺). A mixture of N-methyl 3-aminophenoxyacetamide (**60**) (0.22 g, 1.5 mmol) and 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine (0.13 g, 0.5 mmol) in MeOH (4 mL) was shaken in a sealed tube at 100 °C (24h). Reaction mixture was cooled to room temperature, diluted with water and extracted into EtOAc. Organic layer was separated, washed with water, dried, filtered, concentrated and purified by preparative silica gel TLC to obtain N4-(4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (**48**). ¹H NMR (DMSO-*d*₆): δ 9.18 (s, 1H), 9.12 (s, 1H), 8.03 (d, *J* = 3.8 Hz, 1H), 7.92 (q, *J* = 4.7 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.36 (t, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.08 (t, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.46 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.33 (s, 1H), 3.98 (q, *J* = 6.9 Hz, 2H), 2.63 (d, *J* = 4.6 Hz, 3H), 1.31 (t, *J* = 6.9 Hz, 3H). ¹⁹F NMR (DMSO-*d*₆): δ -164.57. LCMS: Purity: 96%; MS (*m/e*): 412 (MH⁺).

5-Fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (49):



A mixture of 2,4-dichloro-5-fluoropyrimidine (0.23 g, 1.5 mmol) and 4-trifluoromethoxyaniline (0.18 g, 1.0 mmol) in MeOH (2 mL): H₂O (2 mL) was shaken in a screw capped vial at 60 °C (2h) and 100 °C (24h). The reaction mixture was acidified with 2N aq. HCl upon cooling to room temperature. The solid from resulting heterogeneous was collected by filtration, washed with water and dried to provide 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine (**59**). ¹H NMR (CDCl₃): δ 8.11 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 7.6, 2.4 Hz, 2H), 7.26 (dd, *J* = 8.7, 3 Hz, 2H), 7.0 (bs, 1H); ¹⁹F NMR (CD₃OD): δ -58.51 and 157.73; LCMS: Purity: 94%; MS (*m/e*): 308 (MH⁺). A mixture of N-methyl 3-aminophenoxyacetamide (0.11 g, 0.6 mmol) and 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine (0.3 g, 0.9 mmol) in MeOH (2 mL) was shaken in a sealed tube at 100 °C (24h). Reaction mixture was cooled to room temperature and diluted with 1N aq. HCl. The resulting solid was collected by filtration and neutralized with aq. NaHCO₃ to provide 5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (**49**). ¹H NMR (DMSO-*d*₆): δ 10.05 (bs, 1H), 9.74 (bd, *J* = 1.5 Hz, 1H), 8.22 (d, *J* = 4.2 Hz, 1H), 7.99 (bd, *J* = 4.5 Hz, 1H), 7.86 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.26 (s, 1H), 7.16 (m, 2H), 6.58 (m, 1H), 4.36 (s, 2H), 2.65 (bd, 3H); LCMS: Purity: 92%; MS (*m/e*): 452 (MH⁺).

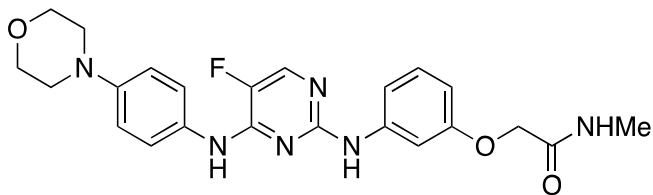
5-Fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine (50):



2-Chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine (**60**) was obtained in an identical manner to the preparation of 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine (**59**) by the reaction of 2,4-dichloro-5-fluoropyrimidine (0.23 g, 1.5 mmol) and 4-trifluoromethylaniline (0.16 g, 1.0 mmol). ¹H NMR (CDCl₃): δ 8.15 (d, *J* = 2.1 Hz), 7.80 (d, 7.1 Hz, 2H), 7.66 (d, *J* = 9 Hz, 2H), 7.10 (bs, 1H); ¹⁹F NMR (CDCl₃): δ -62.64 and -157.16; LCMS: Purity: 91%; MS (*m/z*): 292 (MH⁺). A mixture of N-methyl 3-aminophenoxyacetamide (0.11 g, 0.6 mmol) and 2-chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine (0.09 g, 0.3 mmol) in MeOH (2 mL) was shaken in a sealed tube at 100 °C (24h). Reaction mixture was cooled to room temperature and diluted with 1N aq. HCl. The resulting solid was collected by filtration and neutralized with aq. NaHCO₃ to provide 5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine (**50**). ¹H NMR (DMSO-*d*₆): δ 10.10 (bs, 1H), 9.72 (d, *J* = 1.2 Hz, 1H), 8.26 (d, *J* = 4.2 Hz, 1H), 8.00 (m, 3H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.31 (bs, 1H), 7.17

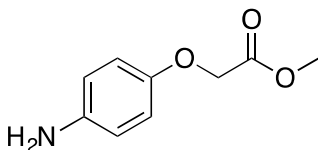
(d, $J = 5.4$ Hz, 2H), 6.59 (m, 1H), 4.36 (s, 2H), 2.62 (d, $J = 4.8$ Hz, 3H); LCMS: Purity: 92%; MS (m/e): 436 (MH^+).

5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (51):



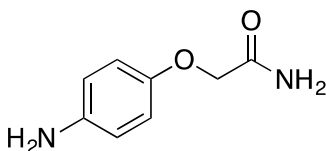
A screw capped vial containing a mixture of 2,4-dichloro-5-fluoropyrimidine (0.30 g, 3.9 mmol) and 4-morpholinoaniline (0.5 g, 2.8 mmol) in MeOH (5 mL): H_2O (5 mL) was stirred at 60°C for 12h. Reaction mixture was concentrated and neutralized with aq. NaHCO_3 (10 mL) and partitioned into EtOAc (50 mL). Organic layer was separated, washed with water, dried and concentrated. The crude solid was purified by silica gel column chromatography (0-50% EtOAc/hexanes) to provide a white solid of 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine as (0.71 g, 79%). ^1H NMR ($\text{DMSO}-d_6$) δ 9.79 (s, 1H), 8.21 (d, $J = 3.6$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 2H), 6.94 (d, $J = 9.1$ Hz, 2H), 3.85 – 3.58 (m, 4H), 3.22 – 2.90 (m, 4H); ^{19}F NMR ($\text{DMSO}-d_6$): δ - 154.67. LCMS: Purity: 97%; MS (m/e): 309 (MH^+). 3-[(Methoxycarbonylmethyleneoxy)aniline (200 mg, 1.1 mmol) and 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine (100 mg, 0.32 mmol) were reacted in methanol at 100°C overnight in a sealed tube. The reaction mixture was cooled to room temperature and diluted with water. The resultant precipitate was collected by filtration, washed with water, suction dried and purified by silica gel column chromatography (50% EtOAc/hexanes) to obtain 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^1H NMR (CDCl_3): δ 7.90 (d, $J = 3.3$ Hz, 1H), 7.49 (d, $J = 9.0$ Hz, 2H), 7.33 (t, $J = 2.1$ Hz, 1H), 7.20 (br, 1H, NH), 7.17 (t, $J = 8.4$ Hz, 1H), 7.06 (ddd, $J = 8.4, 2.1, 0.9$ Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 2H), 6.76 (br s, 1H, NH), 6.55 (ddd, $J = 8.1, 2.7, 0.9$ Hz, 1H), 4.55 (s, 2H), 3.88 (t, $J = 4.8$ Hz, 4H), 3.80 (s, 3H), 3.15 (t, $J = 4.8$ Hz, 4H); ^{19}F NMR (CDCl_3): δ - 167.19; LCMS: Purity: 97 %; MS (m/e): 454 (MH^+). 5-Fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (30 mg, 0.066 mmol), $\text{MeNH}_2\cdot\text{HCl}$ (30 mg, 0.44 mmol) and NEt_3 (0.2 mL) in MeOH (2 mL) were stirred and heated in a screw capped vial at 100°C overnight. Reaction mixture was cooled to room temperature and diluted with water. The white solid was collected by filtration, washed with water and dried to provide 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (51). ^1H NMR ($\text{DMSO}-d_6$): δ 9.15 (br, 1H), 9.12 (br, 1H), 8.02 (d, $J = 3.9$ Hz, 1H), 7.94 (br, 1H), 7.60 (dd, $J = 3.3$ and 8.7 Hz, 2H), 7.37 (s, 1H), 7.26 (d, $J = 7.8$ Hz, 1H), 7.08 (t, $J = 8.1$ Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.46 (dd, $J = 7.8$ Hz, 1H), 4.32 (s, 2H), 3.72 (t, $J = 4.8$ Hz, 4H), 3.04 (t, $J = 4.8$ Hz, 4H), 2.63 (d, $J = 4.5$ Hz, 3H); ^{19}F NMR ($\text{DMSO}-d_6$): δ - 167.17; LCMS: Purity: 99.47%; MS (m/e): 453.21 (MH^+).

Methyl 4-aminophenoxyacetate (52):



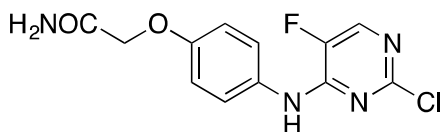
A screw capped vial containing 4-nitrophenol (3.0 g, 21.5 mmol), methyl bromoacetate (4.3 g, 2.64 mL, 28.11 mmol), K_2CO_3 (4.0 g, 28.9 mmol), dry acetone (10 mL) and a stir bar was sealed and heated at 70 °C for 6h with stirring. The heterogeneous reaction mixture was cooled, poured onto water (50 mL) and stirred for 30 min. The resulting precipitated product, methyl 4-nitrophenoxyacetate, was collected on the Buchner funnel by suction filtration and dried overnight (3.2 g, 82%). ^1H NMR (DMSO- d_6) δ 8.19 (d, J = 9.2 Hz, 2H), 7.15 (d, J = 9.2 Hz, 2H), 4.99 (s, 2H), 3.70 (s, 3H). A solution of methyl 4-nitrophenoxyacetate (3.0 g, 14.2 mmol) in MeOH (100 mL) was hydrogenated at 40 PSI for 2h in the presence of 10% Pd/C (0.3 g, 10% by weight) on a par shaker. Reaction mixture was filtered through Celite® and upon concentration of the solvent under reduced pressure provided methyl 4-aminophenoxyacetate (**52**) (2.4 g, 93%) as a pale red viscous material. Material was used with no further purification. ^1H NMR (DMSO- d_6): δ 6.63 (d, J = 8.8 Hz, 2H), 6.48 (d, J = 8.8 Hz, 2H), 4.63 (s, 2H), 4.57 (s, 2H), 3.66 (s, 3H); LCMS: Purity: 97%; MS (m/e): 182 (MH⁺).

4-(Aminocarbonylmethyleneoxy)aniline (**53**):



A mixture of 4-nitrophenol (7.65 g, 55 mmol), 2-bromoacetamide (6.90 g, 50 mmol) and K_2CO_3 (13.8 g, 0.1 mol) in acetone (50 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water, and acetone was removed under reduced pressure. Thus formed light-yellow precipitate was collected by filtration, washed with water and dried to give 1-aminocarbonylmethyleneoxy-4-nitrobenzene (8.28 g, 84%). ^1H NMR (DMSO- d_6) δ 8.20 (d, J = 9.2 Hz, 2H), 7.63 (s, 1H), 7.43 (s, 1H), 7.12 (d, J = 9.2 Hz, 2H), 4.60 (s, 2H). Hydrogenation of 1-aminocarbonylmethyleneoxy-4-nitrobenzene (3 g, 15 mmol) in methanol (50 mL) catalyzed by 10% Pd/C (500 mg) and Na_2SO_4 (500 mg) at 50 psi for 2h gave 4-(aminocarbonylmethyleneoxy)aniline (**53**) (2.5 g, 98%) as a white solid. ^1H NMR (DMSO- d_6): δ 7.36 (s, 1H), 7.32 (s, 1H), 6.66 (d, J = 8.9 Hz, 2H), 6.48 (d, J = 8.9 Hz, 2H), 4.63 (s, 2H), 4.21 (s, 2H); LCMS: Purity: 97%; MS (m/e): 167 (MH⁺).

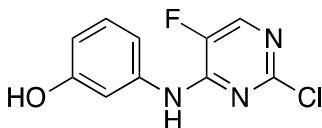
N4-(4-Aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (**54**):



A mixture of 2,4-dichloro-5-fluoropyrimidine (0.2 g, 1.2 mmol) and 4-(aminocarbonylmethyleneoxy)aniline (0.40 g, 2.4 mmol) in H_2O (10 mL): MeOH (1 mL) was shaken in a screw capped vial for 2h at 70 °C. Reaction solution was cooled to room

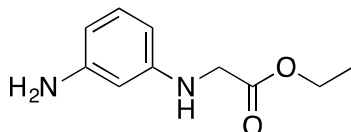
temperature, acidified with 1N aq. HCl (80 mL), volatiles removed and saturated with solid NaCl. The solid precipitated was collected by filtration, washed with cold water and dried to provide beige solid of N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (0.27 g, 76%) under reduced pressure. ^1H NMR (DMSO- d_6): δ 9.87 (s, 1H), 8.24 (d, J = 3.5 Hz, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.37 (s, 1H), 6.95 (d, J = 9.0 Hz, 2H), 4.41 (s, 2H); ^{19}F NMR (DMSO- d_6): δ - 154.55; LCMS: Purity: 100%; MS (m/e): 298 (MH^+).

2-Chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (55):



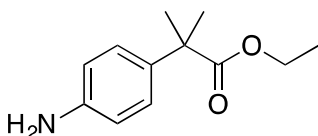
2,4-Dichloro-5-fluoropyrimidine (4.0 g, 24 mmol) and 3-aminophenol (7.8 g, 71 mmol) in H_2O (10 mL): MeOH (10 mL) was stirred at 70 $^\circ\text{C}$ for 1h. Reaction mixture was cooled, diluted with water (30 mL). Upon filtering resulting heterogeneous mixture, filter cake was washed with MeOH: H_2O (1:1) and dried to provide 2-chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (55) (3.2 g, 55%). ^1H NMR (CD_3OD): δ 8.06 (bd, 1H), 7.26 (bd, 1H), 7.20-7.00 (m, 2H), 6.57 (d, J = 7.2 Hz, 1H); ^{19}F NMR (CD_3OD): - 157.24; LCMS: Purity: 100%; MS (m/e): 240 (M^+).

Ethyl 2-[(3-aminophenyl)amino]acetate (56):



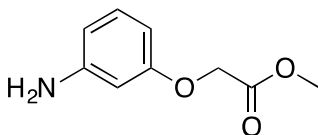
A mixture of 3-nitroaniline (20 g, 0.144 mol), ethyl bromoacetate (24.1 mL, 36.3 g, 0.217 mole) and K_2CO_3 (30 g, 0.217 mol) in acetonitrile (100 mL) was refluxed at 100 $^\circ\text{C}$ for 20h. The reaction mixture was diluted with water/MeOH (1:1, 100 mL) upon cooling to room temperature until homogeneous solution obtained, cooled at -18 $^\circ\text{C}$ for 2h. The crystalline solid thus obtained was collected on the funnel by suction filtration, washed with H_2O /MeOH (1:1, 20 mL) and dried on the funnel to obtain ethyl 2-[(3-nitrophenyl)amino]acetate as a pale brown crystalline needles (2.4 g, 7.4%). ^1H NMR (DMSO- d_6): δ 7.41 – 7.35 (m, 1H), 7.35 – 7.28 (m, 2H), 6.97 (ddd, J = 7.8, 2.5, 1.3 Hz, 1H), 6.74 (t, J = 6.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.00 (d, J = 6.4 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). Ethyl 2-[(3-nitrophenyl)amino]acetate (2.0 g) was reduced by hydrogenation with 10% Pd/C (200 mg) in EtOH (120 mL) at 40 psi for 2h and filtered through Celite®. Ethyl 2-[(3-aminophenyl)amino]acetate (56) was obtained as a dark clear viscous liquid (1.6 g, 93%) upon concentration of filtrate under reduced and used with no further purification. ^1H NMR (DMSO- d_6): δ 6.69 (t, J = 8.0 Hz, 1H), 5.82 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 5.77 – 5.64 (m, 2H), 5.58 (t, J = 6.5 Hz, 1H), 4.71 (s, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.74 (d, J = 6.5 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); LCMS: Purity: 93%; MS (m/e): 195 (MH^+).

Ethyl-2-(4-aminophenyl)-2-methylpropanoate (57):



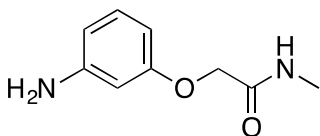
A dry reaction flask charged with ethyl 4-nitrophenylacetate (5.0 g, 23.89 mmol), iodomethane (8.48 g, 3.72 mL, 59.74 mmol), 18-crown-6 (1.57 g, 5.93 mmol) in dry THF (200 mL) was cooled to -78°C under nitrogen atmosphere. While stirring the contents, *t*-BuOK (5.90 g, 52.57 mmol) was added in portions. The resulting violet precipitate was stirred at -78°C for 2h and allowed the contents to warm to room temperature. The reaction was stirred at room temperature for 6h. At this time, once again the contents were cooled to -78°C another portion of iodomethane, *t*-BuOK, and 18-crown-6 were added successively and stirred at the same temperature for 2h. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (75 mL), the resulting homogenous mixture extracted with ether (4 x 200 mL), dried over anhydrous Na_2SO_4 , and concentrated. The concentrate was purified by silica gel column chromatography with 1%EtOAc/hexanes to provide ethyl 2-methyl-2-(4-nitrophenyl)propanoate as a pale yellow oil (2.38, 42%). ^1H NMR (CDCl_3): δ 8.17 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 4.12 (qt, J = 7.0 Hz, 2H), 1.60 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H). Thus obtained ethyl 2-methyl-2-(4-nitrophenyl)propanoate (2.0 g) was reduced by hydrogenation with 10% Pd/C (200 mg) in EtOH (75 mL) at 40 psi for 2h and filtered through Celite®. Ethyl-2-(4-aminophenyl)-2-methylpropanoate was obtained as a clear viscous liquid (1.67 g, 96%) upon concentration of filtrate under reduced pressure and used with no further purification. ^1H NMR (CDCl_3): δ 7.16 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 4.09 (qt, J = 7.0 Hz, 2H), 3.62 (br s, 2H), 1.52 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H); LCMS: Purity: 97%; MS (m/e): 182 (MH^+).

Methyl 3-aminophenoxyacetate (**58**):



Methyl 3-nitrophenoxyacetate was obtained in analogous manner to Methyl 4-nitrophenoxyacetate by alkylation of 3-nitrophenol (3.0 g, 21.5 mmol) with methyl bromoacetate (4.3 g, 2.64 mL, 28.11 mmol). Methyl 3-nitrophenoxyacetate (3.9 g, 85%) was isolated as a white solid after aqueous dilution of the reaction mixture followed by filtration. ^1H NMR ($\text{DMSO}-d_6$) δ 7.83 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 7.72 (t, J = 2.3 Hz, 1H), 7.57 (t, J = 8.2 Hz, 1H), 7.43 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 4.97 (s, 2H), 3.70 (s, 3H). Reduction of methyl 3-nitrophenoxyacetate (3.0 g, 14.2 mmol) by hydrogenation was conducted in the similar to the preparation of methyl 4-aminophenoxyacetate provided methyl 3-aminophenoxyacetate (**58**) (2.3 g, 90%) as a pale red viscous material. ^1H NMR ($\text{DMSO}-d_6$): δ 6.87 (t, J = 8.0 Hz, 1H), 6.15 (ddd, J = 8.0, 2.0, 0.9 Hz, 1H), 6.08 (t, J = 2.2 Hz, 1H), 6.02 (ddd, J = 8.1, 2.5, 0.9 Hz, 1H), 5.05 (s, 2H), 4.62 (s, 2H), 3.67 (s, 3H); LCMS: Purity: 97%; MS (m/e): 182 (MH^+).

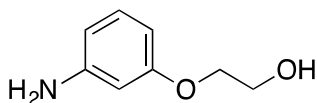
N-Methyl 3-Aminophenoxyacetamide (**60**):



A dry reaction flask equipped with a reflux condenser, N₂ inlet and a magnetic stirring bar was charged with 3-nitrophenol (76.45 g, 550 mmol), K₂CO₃ (76.45 g, 550 mmol) and dry acetone (500 mL) under N₂ atmosphere. To this at room temperature was added ethyl bromoacetate (55.44 mL, 500 mmol) over a period of 15 min. The reaction mixture was refluxed for 16h, cooled and poured over ice-water (4 Kg). The resulting aqueous solution was extracted with CH₂Cl₂ (3 x 500 mL), dried over anhydrous Na₂SO₄ and solvent was removed to obtain 103g (92%) of the desired ethyl 3-nitrophenoxyacetate. ¹H NMR (CDCl₃): δ 7.88 (dt, *J* = 8.7, 1.2 Hz, 1H), 7.71 (t, *J* = 2.4 Hz, 1H), 7.45 (t, *J* = 8.4 Hz, 1H), 7.27 (dt, *J* = 8.4, 2.4 Hz, 1H), 4.70 (s, 2H), 4.29 (q, *J* = 6.9 Hz, 2H), 1.30 (t, *J* = 6.9Hz), 3H); LCMS: Purity: 96%. A mixture of ethyl 3-nitrophenoxyacetate (9.12g, 40 mmol), methylamine hydrochloride (26.8g, 400 mmol) and diisopropylethylamine (35.5 mL, 200 mL) in MeOH (100 mL) was stirred in a pressure vial at 90 °C for 6h. The reaction was cooled to room temperature and diluted with water (1 L). The resultant solid formed was collected on the funnel by suction filtration, washed with water and dried to get the desired N-methyl 3-nitrophenoxyacetamide (**60**) (8g, 95%). ¹H NMR CDCl₃: δ 7.91 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.78 (t, *J* = 2.4 Hz, 1H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.29 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.50 (bs, 2H), 4.57 (s, 2H), 2.95 and 2.93 (2s, 3H); LCMS: Purity 100%, MS (m/e) 211 (MH⁺). A solution of N-methyl 3-nitrophenoxyacetamide (8 g, 39 mmol) in EtOH (200 mL) was hydrogenated at 40 PSI for 40 minutes over 10% Pd/C (0.8 g, 10% by weight). After filtration through Celite® and concentration of the filtrate under reduced pressure provided off-white solid of N-methyl 3-aminophenoxyacetamide (**60**) (6 g, 86%). ¹H NMR (CD₃OD): δ 6.99 (t, *J* = 8.1 Hz, 1H), 6.37-6.25 (m, 3H), 4.41 (s, 2H), 2.80 (s, 3H); LCMS: Purity: 97%; MS (m/e): 181 (MH⁺).

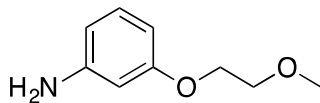
Preparation of Anilines:

2-(3-Aminophenoxy)ethanol:



2-(3-Aminophenoxy)ethanol was obtained analogous to the procedure of methyl 4-aminophenoxyacetate from 3-nitrophenol (3.0 g, 21.5 mmol) alkylation with 2-bromoethanol (1.8 mL, 3.2 g, 25.6 mmol) and subsequent hydrogenation of resulting 2-(3-nitrophenoxy)ethanol. 2-(3-Nitrophenoxy)ethanol (81%, off-white solid): ¹H NMR (DMSO-*d*₆) δ 7.79 (ddd, *J* = 8.1, 2.1, 0.8 Hz, 1H), 7.70 (t, *J* = 2.4 Hz, 1H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.41 (ddt, *J* = 8.3, 2.6, 0.8 Hz, 1H), 4.89 (s, 1H), 4.24 – 4.01 (m, 2H), 3.72 (t, *J* = 4.9 Hz, 2H). 2-(3-Aminophenoxy)ethanol: (95%, clear pale red viscous liquid): ¹H NMR (DMSO-*d*₆): δ 6.86 (t, *J* = 8.3 Hz, 1H), 6.14 – 6.07 (m, 2H), 6.07 – 5.99 (m, 1H), 4.99 (s, 2H), 4.77 (t, *J* = 5.6 Hz, 1H), 3.84 (t, *J* = 5.2 Hz, 2H), 3.65 (q, *J* = 5.4 Hz, 2H); LCMS: Purity: 98%; MS (m/e): 154 (MH⁺).

3-(2-Methoxyethoxy)aniline:



1-(2-Methoxyethoxy)-3-nitrobenzene was obtained by the alkylation of 3-nitrophenol (3.0 g, 21.5 mmol) with 1-bromo-2-methoxyethane (2.4 mL, 3.6 g, 25.9 mmol) in the similar manner to the preparation 4-nitrophenoxyacetate. However, aq. dilution of the reaction mixture did not result in precipitation of the alkylated product. Subsequently, volatiles were removed from diluted reaction mixture and partitioned with EtOAc (100 mL). Organic layer washed with water (30 mL), aq. NaCl (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. Upon silica gel column chromatographic purification (0-30% EtOAc/hexanes) of thus concentrated pale yellow viscous liquid provided 1-(2-methoxyethoxy)-3-nitrobenzene as a clear oil (2.25 g, 53%). ^1H NMR ($\text{DMSO}-d_6$) δ 7.79 (ddd, $J = 8.1, 2.2, 1.0$ Hz, 1H), 7.70 (t, $J = 2.3$ Hz, 1H), 7.55 (t, $J = 8.2$ Hz, 1H), 7.41 (ddd, $J = 8.4, 2.6, 1.0$ Hz, 1H), 4.30 – 4.12 (m, 2H), 3.74 – 3.59 (m, 2H), 3.28 (s, 3H). Reduction of 1-(2-methoxyethoxy)-3-nitrobenzene (2.0 g, 10.1 mmol) by hydrogenation analogous to the preparation of methyl 4-aminophenoxyacetate provided 3-(2-methoxyethoxy)aniline (1.5 g, 89%) as a orange viscous liquid. ^1H NMR ($\text{DMSO}-d_6$): δ 6.86 (t, $J = 8.2$ Hz, 1H), 6.16 – 6.08 (m, 2H), 6.05 (ddd, $J = 8.1, 2.2, 1.1$ Hz, 1H), 5.00 (s, 2H), 3.99 – 3.89 (m, 2H), 3.66 – 3.53 (m, 2H), 3.29 (s, 3H); LCMS: Purity: 97%; MS (m/e): 168 (MH^+).