CHEMISTRY
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To be cited as: *Chem. Asian J.* 10.1002/asia.201801762

Link to VoR: http://dx.doi.org/10.1002/asia.201801762

A Journal of
ACES Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

10.1002/asia.201801762

Synthesis and Evaluation of Imidazo[1,2-*a*]pyridine Analogues of the ZSTK474 Class of Phosphatidylinositol 3-Kinase Inhibitors

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10.1002/asia.201801762

Abstract: Using a scaffold-hopping approach, imidazo[1,2-*a*]pyridine analogues of the ZSTK474 (benzimidazole) class of phosphatidylinositol 3-kinase (PI3K) inhibitors have been synthesized for biological evaluation. Compounds were prepared using a heteroaryl Heck reaction procedure, involving the palladium-catalysed coupling of 2-(difluoromethyl)imidazo[1,2-*a*]pyridines with chloro, iodo or trifluoromethanesulfonyl-oxy (trifloxy) substituted 1,3,5-triazines or pyrimidines, with the iodo intermediates being preferred in terms of higher yields and milder reaction conditions. The new compounds maintain the PI3K isoform selectivity of their benzimidazole analogues, but in general show less potency.

Introduction

Phosphatidylinositol 3-kinases (PI3Ks) comprise three separate classes (I, II and III) of lipid kinase enzymes that play crucial roles in both cell and tissue physiology.[1] The three class-Ia PI3Ks (PI3Kα/β/δ) link growth factor receptors to a wide range of downstream pathways, while the single class-Ib PI3K (PI3Kγ) links to G-protein coupled receptors (GPCRs).[2] The four enzymes have different mechanisms of activation and display different kinetic properties, but all produce phosphatidyl-inositol-3,4,5-trisphosphate (PIP3) from phosphatidylinositol-4,5-bisphosphate (PIP2).[3] The amount of PIP3 produced in cells is in turn tightly controlled by phosphatases such as PTEN, which converts PIP3 back to PIP2.[4] Defects in both kinase and phosphatase activities are often seen with tumors, and a large percentage of human cancers depend strongly on PI3Kα for their survival and resistance to treatment.[5] As a result, the design and development of small molecule inhibitors that target the p110α isoform of PI3K has been intensely investigated, and a number of inhibitors have now entered human clinical trial.[6]

ZSTK474 (**1**) (Figure 1) is a pan-class I PI3K inhibitor, that has demonstrated antitumor activity *in vivo* against human tumor xenografts, and has been evaluated in phase I/II clinical trials for the treatment of solid tumors.[7] An X-ray crystal structure obtained with the p110δ isoform of PI3K showed that ZSTK474 bound with one of the morpholine oxygen atoms making an important H-bond to the Val828 residue, while the benzimidazole N-3 atom formed a second H-bond to Lys779.[8] We showed

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that the addition of a methoxy group at the 4-position of the benzimidazole unit, to give **2**, improved selectivity for the p110α isoform over the other PI3K isoforms,[9] and we further demonstrated that one of the morpholine groups could be replaced by piperazinesulfonamide derivatives, to give compounds such as **3**.[10] Unfortunately, compounds like **3** did not possess good bioavailability, due to limited aqueous solubility (similar to **1** itself), which led us to prepare more soluble derivatives. These included SN32976 (**4**),[11] and PWT33597 (**5**),[12] also known as VDC-597, which proceeded to human clinical trial.

In order to further investigate this important class of PI3K inhibitors, we have now employed a scaffold hopping approach to prepare imidazo[1,2-*a*]pyridine analogues of compounds **1**-**5** (Figure 1). We also synthesized imidazo[1,2-*a*]pyridine analogues of piperazine-amides **6**-**9**,[13] including the p110β selective inhibitor MIPS-9922 (**8**), to determine whether PI3K isoform selectivity was conserved. Continuing this theme, the imidazo[1,2-*a*]pyridine analogue of the p110δ selective inhibitor AS2541019 (**10**)[14] was also prepared.

Our justification for selecting imidazo[1,2-*a*]pyridine derivatives was not only that their structure represented a privileged scaffold with good stability that is present in several commercial drugs, in a variety of different therapeutic areas,[15] but also that they are known bioisosteres of benzimidazoles, both in the PI3K field,[16] and elsewhere. For example, we previously investigated the antibacterial activity of imidazo[1,2-*a*]pyridine urea derivatives as analogues of benzimidazole urea inhibitors of DNA Gyrase and Topoisomerase IV.[17]

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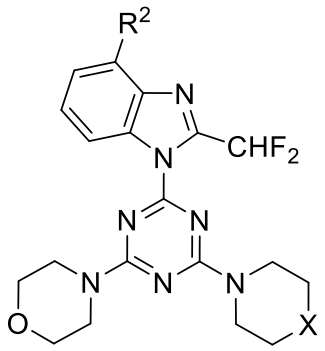
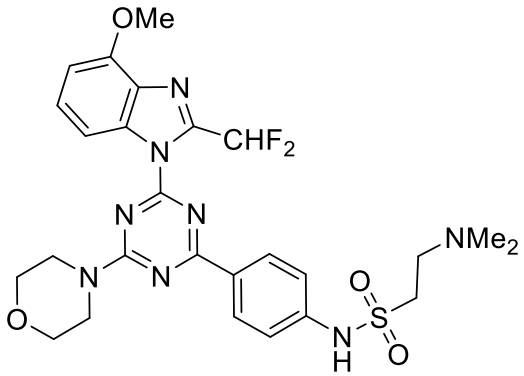
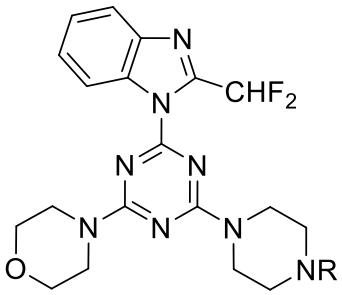


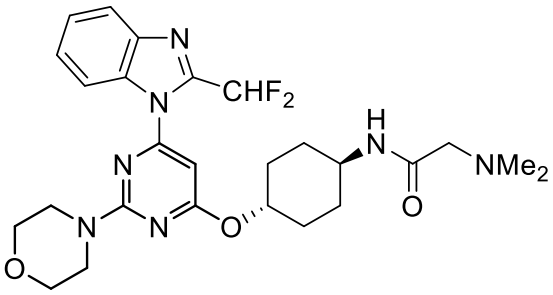
1. R = H, X = O (ZSTK474)
2. R = OMe, X = O
3. R = OMe, X = NSO_2Me
4. R = OMe, X = $NSO_2(CH_2)_2NMe_2$ (SN 32976)



5. (PWT33597 / VDC-597)



6. R = L-Ala
7. R = D-Ala
8. R = L-Phe (MIPS-9922)
9. R = D-Pro



10. (AS2541019)

Figure 1. Structures of ZSTK474 and related phosphatidylinositol 3-kinase inhibitors

Results and Discussion

We began our work by investigating an existing literature route to morpholino-triazinyl-imidazo[1,2-*a*]pyridines.[18] Reaction of moroxydine hydrochloride (**11**) with the imidazo[1,2-a]pyridine ester **12** did give the desired triazine product **13** (Scheme 1), but in very low yield, and even though the subsequent steps performed much better, this route was abandoned.

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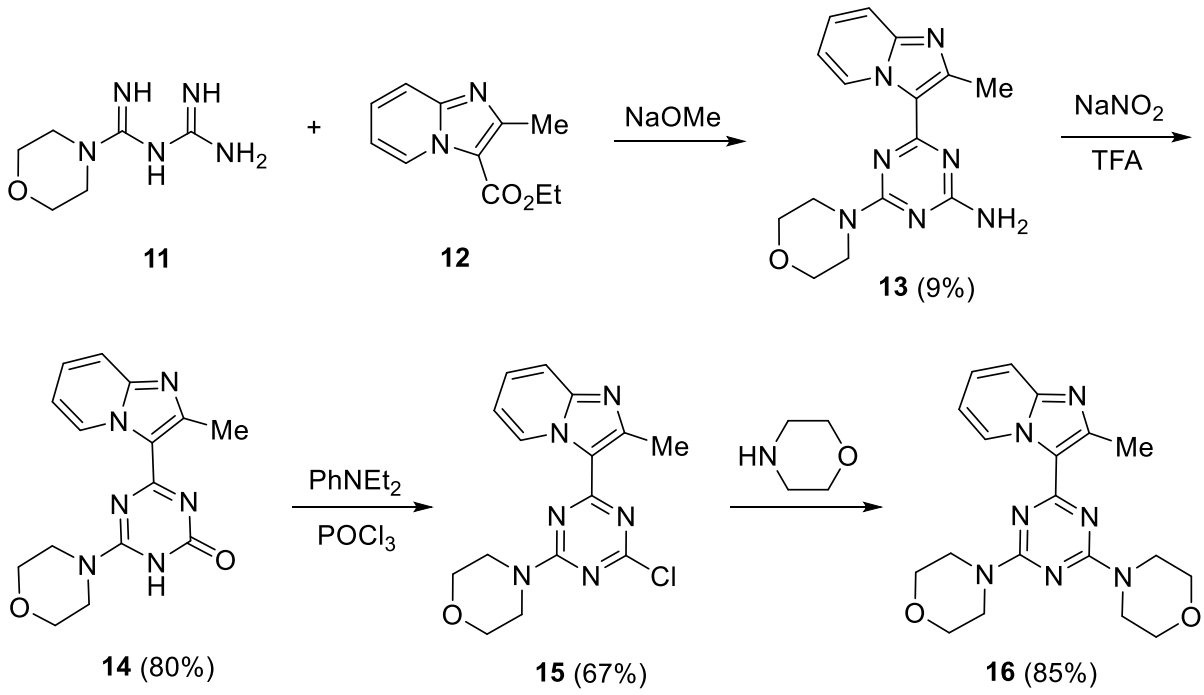

Scheme 1. Synthesis of **16**.

We next turned our attention to the use of palladium catalyzed direct arylation (heteroaryl Heck reaction) of C-3 unsubstituted imidazo[1,2-*a*]pyridines with halotriazine derivatives (Scheme 2), which is an established procedure in the PI3K field.[15] Our initial investigations utilized the readily available 2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (**17**)[19] in reactions with the 2-chlorotriazine **18**,[20] giving product **20** in moderate yield when triphenylphosphine was used as the palladium ligand. Improved yields were obtained using di(1-adamantyl)-*n*-butylphosphine (*n*-BuPAd$_2$), a ligand known to be more effective for chlorinated substrates in Heck reactions involving imidazo[1,2-*a*]pyridines,[21] and this phosphine was retained for all subsequent work. The use of the 2-iodotriazine **19**[22] was also found to give superior results compared to chloride **18**, in terms of higher product yield and milder reaction conditions.

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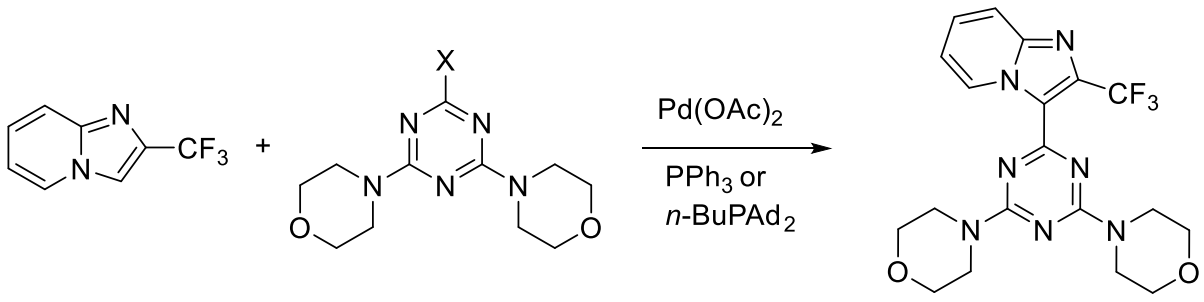
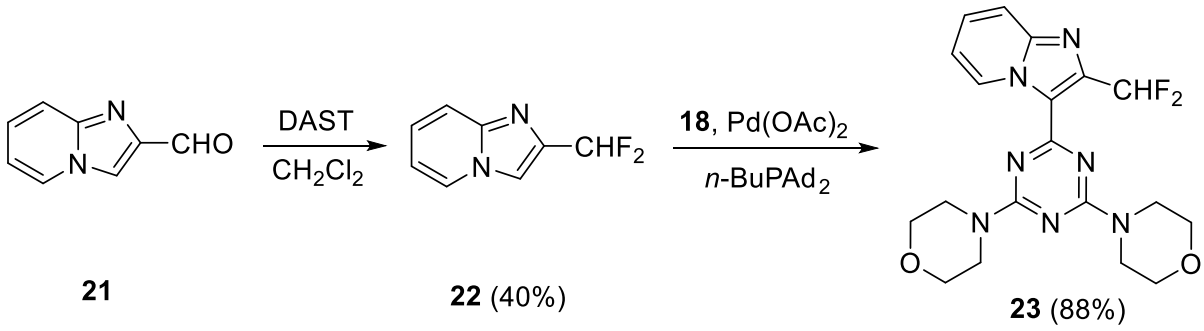


17 **18**. X = Cl; **19**. X = I **20** (X = Cl, 52%; X = I, 92%)

Scheme 2. Synthesis of **20**. *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine.

In order to prepare the direct imidazo[1,2-*a*]pyridine analogue of ZSTK474 (**1**) it was first necessary to prepare 2-(difluoromethyl)imidazo[1,2-*a*]pyridine (**22**), which was readily formed by treatment of the known aldehyde **21**[23] with DAST (Scheme 3). Heck reaction of **22** with chloride **18** gave the desired ZSTK474 analogue **23** in good yield.



21 **22** (40%) **23** (88%)

Scheme 3. Synthesis of **23**. DAST = (diethylamino)sulfur trifluoride; *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine.

For synthesis of the 4-methoxy analogue of **23**, a similar approach was used (Scheme 4), with aldehyde **25** first being prepared from 2-aminopyridine **24**. Again Heck reaction of imidazo[1,2-*a*]pyridine **26** with chloride **18**, occurred in very good yield to give the target compound **27**.

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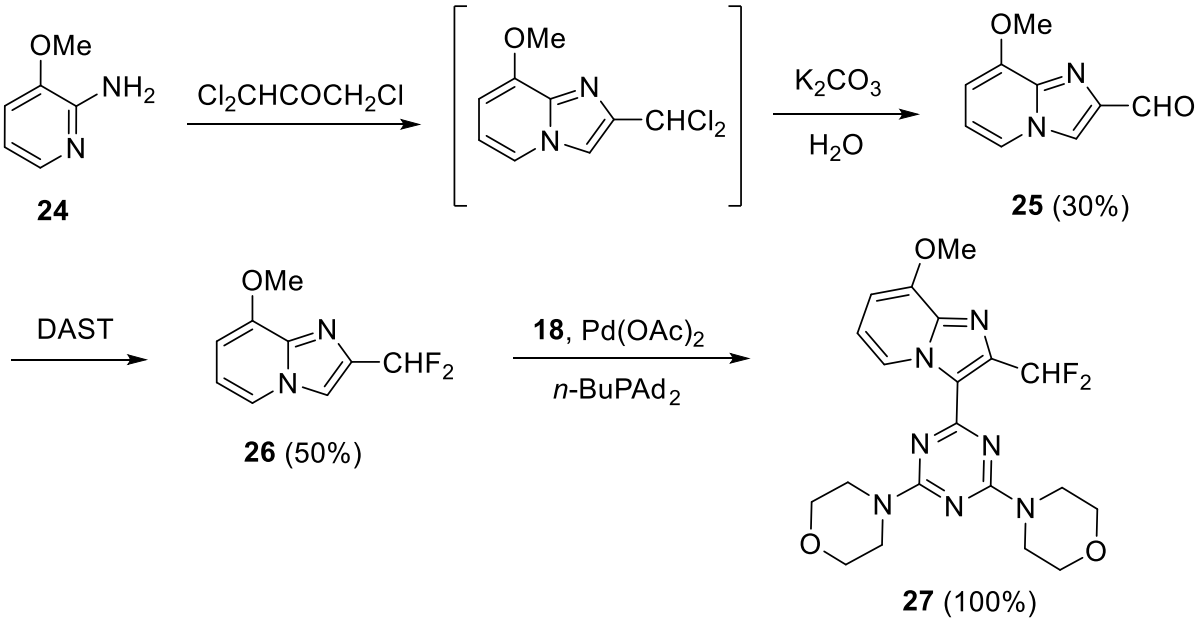

Scheme 4. Synthesis of **27**. DAST = (diethylamino)sulfur trifluoride; *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine.

For the synthesis of imidazo[1,2-*a*]pyridine analogues of the piperazinesulfonamides **3** and **4** (SN32976), we first prepared the iodotriazine **30** (Scheme 5). This was readily prepared from diiodide **29,** which was obtained from dichloride **28**[24] by treatment with aqueous hydriodic acid. Heck reaction of **26** with **30** gave Boc-piperazine **31** in good yield, and after removal of the Boc protecting group, sulfonamides **32** and **33** were readily prepared. Reaction of the vinyl sulfonamide **33** with dimethylamine then gave the desired SN32976 analogue **34**.

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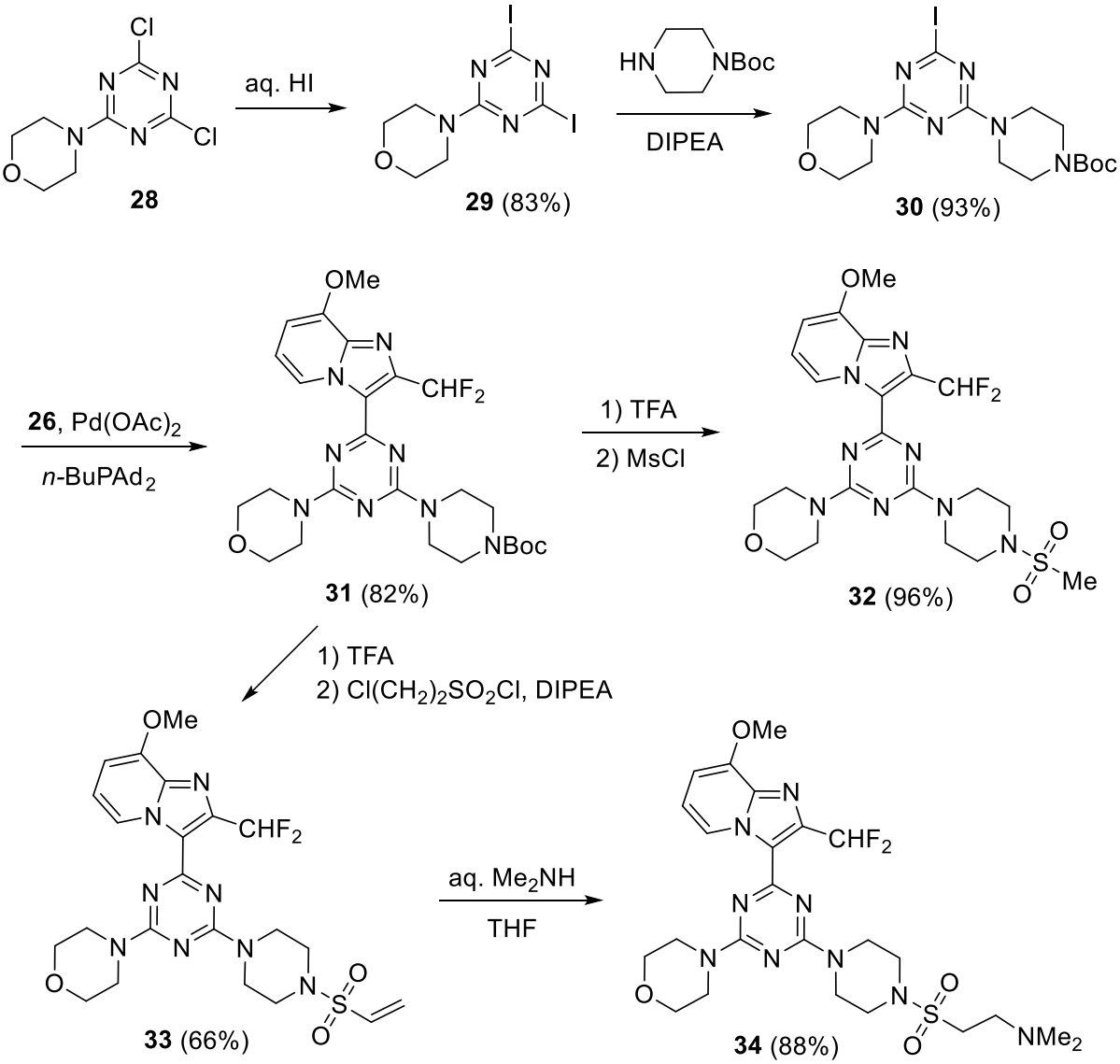

Scheme 5. Synthesis of **34**. DIPEA = *N,N*-diisopropylethylamine; *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine.

For the synthesis of the imidazo[1,2-*a*]pyridine analogue of PWT33597 (**5**), we utilized the triflate intermediate **38**, which was prepared by standard procedures (Scheme 6). Heck reaction of **26** with **38** gave compound **39** in moderate yield, and this was then successfully elaborated to target **41,** by similar procedures to that used in the synthesis of **34**.

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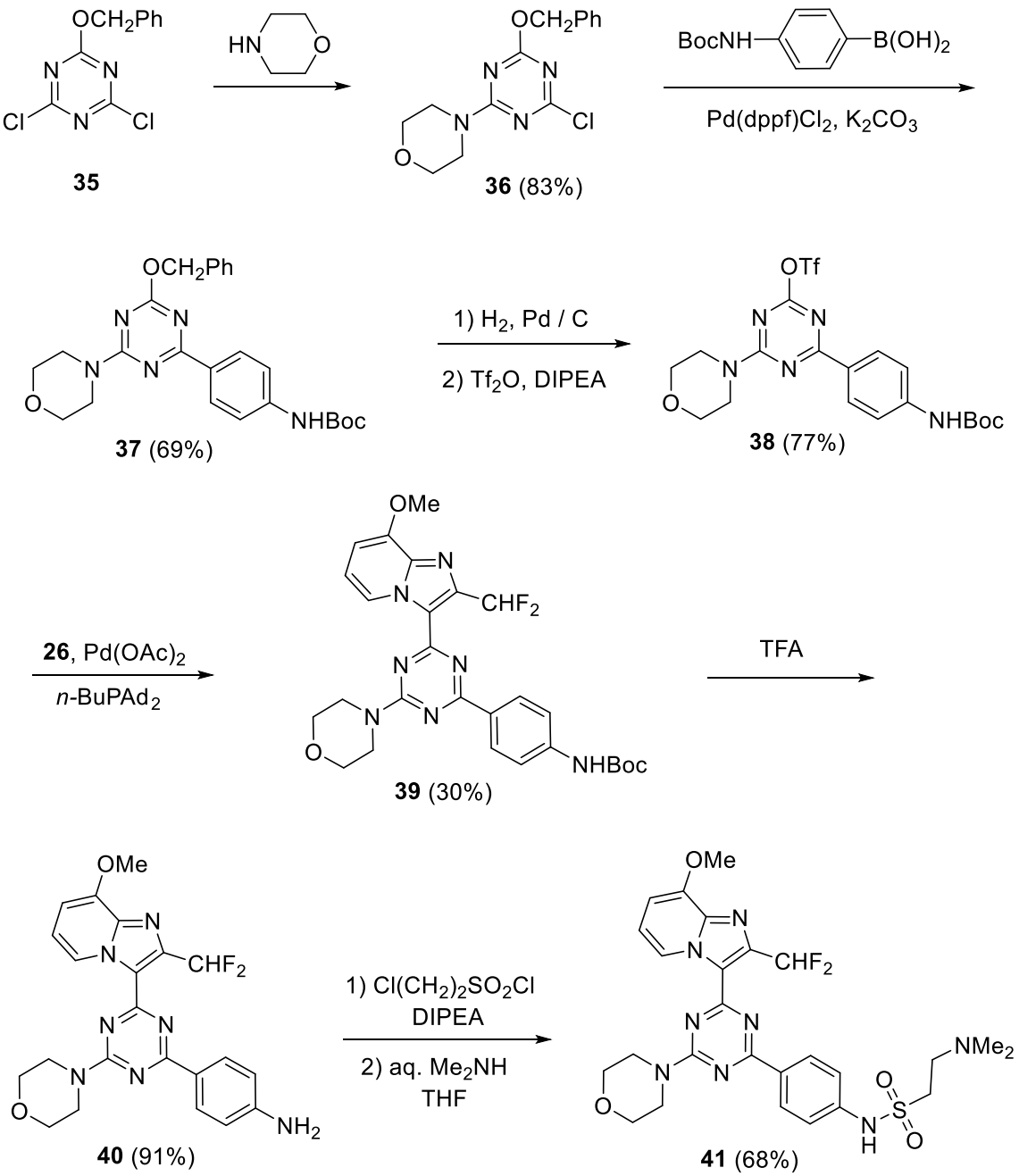

Scheme 6. Synthesis of **41**. dppf = 1,1'-bis(diphenylphosphino)ferrocene; *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine; DIPEA = *N,N*-diisopropylethylamine.

For the synthesis of imidazo[1,2-*a*]pyridine analogues of the PI3K isoform selective derivatives **6**-**9**, Heck reaction of existing intermediates **22** and **30** gave Boc-piperazine **42**, which was deprotected to give amine **43** (Scheme 7). Coupling of **43** with Boc-protected aminoacids gave amides **44** - **47**, from which targets **48** - **51** were obtained.

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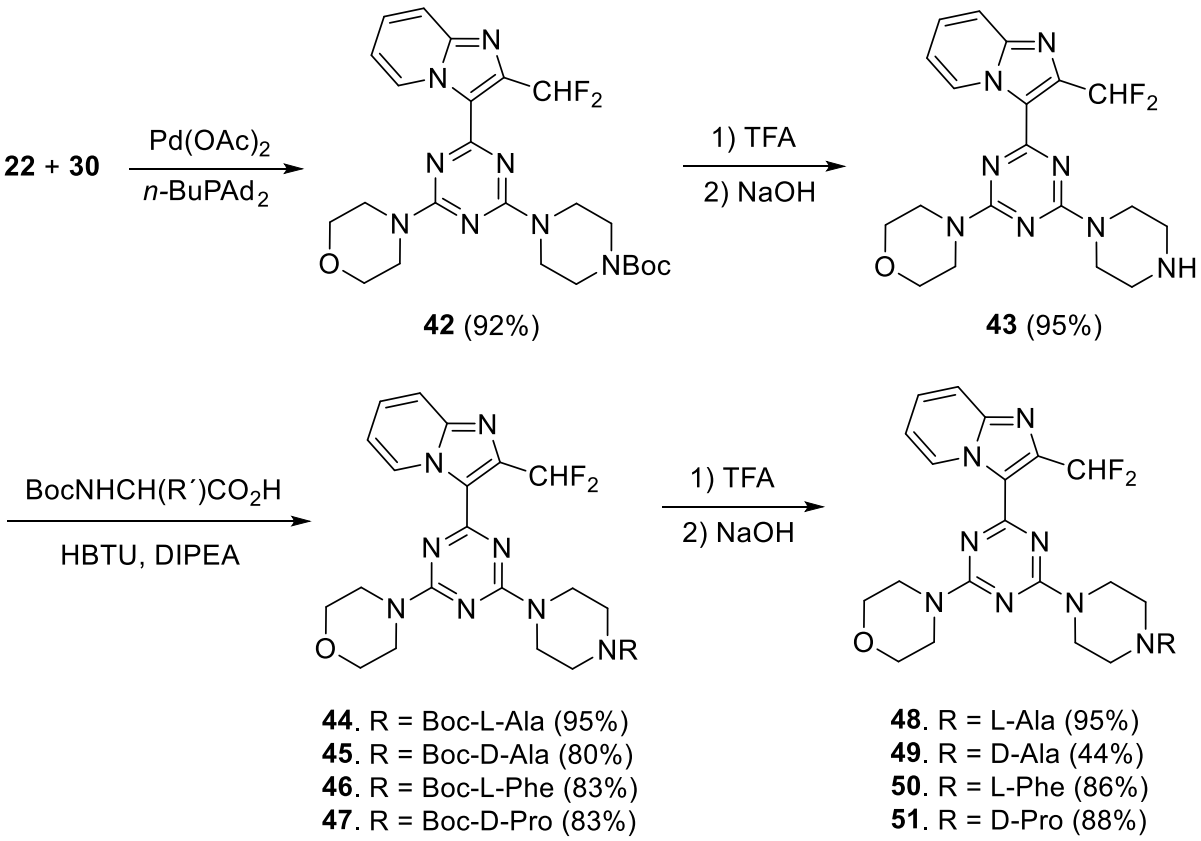

Scheme 7. Synthesis of **48**-**51**. *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine; HBTU = *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate; DIPEA = *N,N*-diisopropylethylamine.

Finally, synthesis of the imidazo[1,2-*a*]pyridine analogue of the p110δ selective inhibitor AS2541019 (**10**) was achieved as shown in Scheme 8. Condensation of *tert*-butyl (*trans*-4-hydroxycyclohexyl)carbamate with 4,6-dichloro-2-(methylthio)-pyrimidine (**52**) successfully gave ether **53**, but this compound failed to react cleanly with imidazo[1,2-*a*]pyridine **22** under palladium catalysed conditions. Accordingly, **53** was oxidized to the analogous sulfone, and this was treated with morpholine to give an approximately 1:1 mixture of the desired chloro derivative **54**, plus sulfone **55**. Fortunately, these were readily separable by chromatography, and chloride **54** was then converted to iodide **56**, in 83% overall yield, via a 3-step procedure involving Boc removal, iodination, and re-addition of the Boc protecting group. Heck reaction of **56** with imidazo[1,2-*a*]pyridine **22** gave **57** in excellent yield, and this was then elaborated by standard procedures to target **58**.

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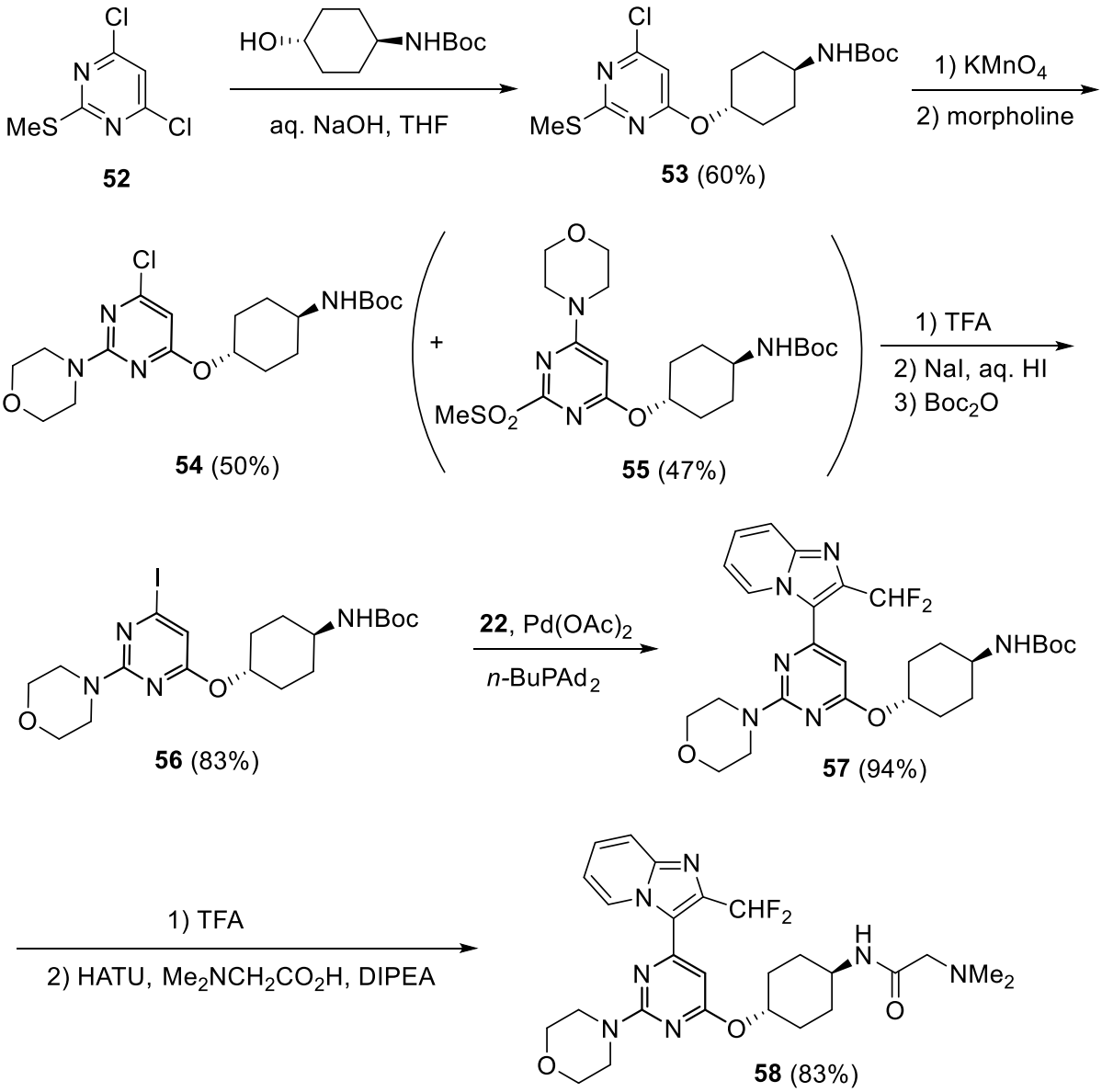

Scheme 8. Synthesis of **58**. *n*-BuPAd$_2$ = di(1-adamantyl)-*n*-butylphosphine; HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate ; DIPEA = *N,N*-diisopropylethylamine.

The target compounds were tested for their biochemical inhibitory activity against the p110α, p110β, and p110δ isoforms of PI3K using Homogeneous Time Resolved Fluorescence (HTRF) assays, and their results are compared with those of reference compounds **1**-**10** in Table 1.

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Table 1. Biological data for benzimidazole and imidazo[1,2-*a*]pyridine analogues

Cpd	Type[a]	Enzyme IC_{50} (nM)[b]		
		p110α	p110β	p110δ
1	B	9	58	38
23	I	89	750	137
2	B	4	182	19
27	I	44	750	240
3	B	6	1,500	41
32	I	18	>3,000	315
4	B	5	743	206
34	I	20	680	255
5	B	6	317	57
41	I	21	150	180
6	B	77	2	14
48	I	231	21	200
7	B	106	44	9
49	I	436	1186	234
8	B	87	3	16
50	I	310	11	228
9	B	165	221	3
51	I	732	535	110
10	B	547	734	7
58	I	340	1,386	16

[a] B = benzimidazole; I = imidazo[1,2-*a*]pyridine

[b] IC_{50} values are the mean of duplicate or triplicate measurements

Comparison of the benzimidazole/imidazo[1,2-*a*]pyridine pairs (**1** and **23**, **2** and **27**, **3** and **32**, **4** and **34**, **5** and **41**, **6** and **48**, **7** and **49**, **8** and **50**, **9** and **51**, **10** and **58**) shows that the benzimidazole derivatives are generally more potent (lower IC_{50} values), although PI3K isoform selectivity is maintained. Thus, imidazo[1,2-*a*]pyridines **23**, **27**, **32**, **34** and **41** retain the p110α selectivity of benzimidazoles **1**-**5**,

imidazo[1,2-*a*]pyridines **48** and **50** retain the p110β selectivity of benzimidazoles **6** and **8**, and imidazo[1,2-*a*]pyridines **49**, **51** and **58** retain the p110δ selectivity of benzimidazoles **7**, **9** and **10**.

A possible explanation for the greater potency of the benzimidazoles, compared to the imidazo[1,2-*a*]pyridines, might be due to the greater basicity of the latter. For example, the parent imidazo[1,2-*a*]pyridine has a pKa of 6.79,[25] whereas the pKa of unsubstituted benzimidazole is 5.53.[26] Since the benzimidazole 3-nitrogen atom (and presumably the imidazo[1,2-*a*]pyridine 1-nitrogen atom) is involved in H-bonding to a lysine amino group in the ATP binding pocket of the PI3K (Lys802 in p110α, Lys805 in p110β, Lys779 in p110δ and Lys833 in p110γ),[8, 9] the greater proportion of protonation of the imidazo[1,2-*a*]pyridines would leave less molecules available to form H-bonds with the lysine amino group.

Conclusions

We have developed an efficient route to imidazo[1,2-*a*]pyridine analogues of the ZSTK474 class of PI3K inhibitors. Comparison of the new compounds with the existing benzimidazole inhibitors shows that while the latter are still the most preferred in terms of potency, the imidazo[1,2-*a*]pyridines retain the PI3K isoform selectivity of their benzimidazole analogues.

Experimental Section

General information

Elemental analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal IA9100 melting point apparatus and are as read. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for proton spectra, 376 MHz for fluorine spectra, and 100 MHz for carbon spectra, referenced to Me_4Si or solvent resonances. Low-resolution atmospheric pressure chemical ionization (APCI) mass spectra were measured for methanol solutions on an Agilent Technologies 6120 Quadrapole LC/MS connected to an Agilent Technologies1260 Infinity autosampler.

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High-resolution mass spectra were obtained with organic solutions on an Agilent Technologies 6500 Series quadrupole time-of-flight (Q-TOF) LC/MS system. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F254), with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel, (Merck 230 - 400 mesh) unless otherwise stated. Tested compounds were >95% purity, as determined by combustion analysis, or by HPLC conducted on an Agilent 1100 system, using a reversed-phase C8 column with diode array detection.

Materials and Methods

Reference compounds **1**-**10** were available from earlier work,[9-12] or were prepared by literature procedures.[13, 14]

4,4'-(6-(2-Methylimidazo[1,2-*a*]pyridin-3-yl)-1,3,5-triazine-2,4-diyl)dimorpholine (16)

A mixture of moroxydine hydrochloride (**11**) (1.81 g, 8.75 mmol) and NaOMe (1.2152 g, 22.5 mmol) in MeOH (30 mL) was stirred for 35 min, and a solution of ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**12**)[27] (1.77 g, 8.75 mmol) in MeOH (10 mL) was added. The resulting mixture was heated at 65 °C for 48 h, and concentrated under reduced pressure. Purification by flash column chromatography with silica using CH_2Cl_2/MeOH (9:1) gave 4-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-amine (**13**) (0.14 g, 9%): ^{1}H NMR (DMSO-d_6) δ=10.03 (dt, 7.1, 1.1 Hz, 1H), 7.60 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.42-7.39 (m, 1H), 7.04 (dt, *J* = 6.9, 1.3 Hz, 1H), 6.95 (br s, 2H), 3.76-3.75 (m, 4H), 3.68-3.66 ppm (m, 4H); MS (APCI) m/z 312.8 (MH^+).

To a solution of **13** (0.345 g, 1.11 mmol) in TFA (9 mL) at 0 °C was added $NaNO_2$ (0.12 g, 1.74 mmol), and the mixture was stirred overnight. After dilution with water (5 mL), the mixture was neutralized with ammonia, and extracted with CH_2Cl_2. After drying and removal of the solvent, the crude product was recrystallized from CH_2Cl_2-MeOH to give 4-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-

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2(1*H*)-one (**14**) (0.277 g, 80%) as a white powder: ^{1}H NMR (DMSO-d_6) δ=9.69 (br s, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.75-7.71 (m, 1H), 7.35 (t, *J* = 6.8 Hz, 1H), 3.79-3.78 (m, 4H), 3.71-3.69 ppm (m, 4H); MS (APCI) m/z 313.8 (MH^+).

A mixture of **14** (0.171 g, 0.55 mmol), $POCl_3$ (0.12 mL, 1.29 mmol) and diethylaniline (0.08 mL, 0.50 mmol) was heated to reflux for 5 h, cooled to room temperature, and poured into ice-water. After being stirred for 30 min, the resultant mixture was diluted with saturated aqueous Na_2CO_3 solution and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica using CH_2Cl_2-EtOAc (1:3) gave 4-(4-chloro-6-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-1,3,5-triazin-2-yl)morpholine (**15**) (0.122 g, 67%) as a white powder: ^{1}H NMR (DMSO-d_6) δ=9.69 (dt, 7.0, 1.0 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.55 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.22 (dt, *J* = 7.0, 1.3 Hz, 1H), 3.88 (d, *J* = 4.6 Hz, 2H), 3.80-3.70 (m, 6H), 2.77 ppm (s, 3H); elemental analysis calcd (%) for $C_{15}H_{15}ClN_6O$: C 54.5, H 4.5, N 25.4; found: C 54.7, H 4.6, N, 25.6.

To a solution of **15** in THF (2 mL) was added morpholine (0.05 mL, 0.57 mmol) and the reaction mixture was heated at 60 °C for 2 h. After cooling and dilution with water, the resulting solid was collected by filtration and dried, to give **16** (0.029 g, 85%) as a white powder: m.p. 250-252 °C; ^{1}H NMR ($CDCl_3$) δ=9.75 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.60 (d, *J* = 8.9, 1.1 Hz, 1H), 7.28 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 6.90 (dt, *J* = 6.9, 1.3 Hz, 1H), 3.89-3.85 (m, 4H), 3.80-3.77 (m, 4H), 2.87 ppm (s, 3H); ^{13}C NMR ($CDCl_3$) δ=165.7 (C), 164.8 (C), 151.3 (C), 146.5 (C), 128.8 (CH), 126.2 (CH), 118.2 (C), 116.9 (CH), 112.7 (CH), 66.9 (CH_2), 44.0 (CH_2), 18.3 ppm (CH_3); HRMS (APCI): *m*/*z* calcd for $C_{19}H_{23}N_7O_2$+H^+: 382.1986 [*M*+H^+]; found: 382.2000.

4,4'-(6-(2-(Trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-1,3,5-triazine-2,4-diyl)dimorpholine (20)

Method A: A mixture of 2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (**17**)[19] (82 mg, 0.044 mmol), 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl)dimorpholine (**18**)[20] (125.7 mg, 0.044 mmol), $Pd(PPh_3)_4$ (254 mg, 0.022 mmol), $Pd(OAc)_2$ (49 mg, 0.022 mmol), K_2CO_3 (122 mg, 0.088 mmol) in dioxane (5 mL) and water (1 mL) was degassed, flushed with nitrogen, and heated under reflux overnight. After dilution with water and

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extraction with CH_2Cl_2, the crude product was chromatographed on silica eluting with hexanes/EtOAc (1:1), to give **20** (100.8 mg, 52%); mp (MeOH) 271-274 °C; ^{1}H NMR ($CDCl_3$) δ=9.63 (dt, J = 7.1, 1.1 Hz, 1H), 7.79 (dt, J = 9.1, 1.1 Hz, 1H), 7.41 (ddd, J = 9.0, 6.8, 1.2 Hz, 1H), 7.04 (td, J = 7.0, 1.2 Hz, 1H), 3.92-3.84 (br, 8 H), 3.79-3.76 ppm (m, 8H); ^{13}C NMR ($CDCl_3$) δ=164.6 (C), 163.7 (C), 145.2 (C), 138.5 (q, J_{CF} = 38.0 Hz, C), 128.6 (CH), 127.4 (CH), 122.0 (q, J_{CF} = 269.4 Hz, C), 121.2 (C), 118.9 (CH), 114.7 (CH), 67.0 (CH_2), 43.9 ppm (CH_2); ^{19}F NMR ($CDCl_3$) δ=-60.43 ppm (s); HRMS (APCI): m/z calcd.for $C_{19}H_{20}F_3N_7O_2$+H^+: 436.1703 [M+H^+]; found: m/z 436.1695.

Method B: A mixture of **17** (49 mg, 0.026 mmol), 4,4'-(6-iodo-1,3,5-triazine-2,4-diyl)dimorpholine (**19**)[22] (94 mg, 0.025 mmol), $Pd(OAc)_2$ (1.2 mg, 0.0053 mmol), n-$BuPAd_2$ (3.5 mg, 0.0098 mmol), K_3PO_4 (110 mg, 0.052 mmol) in dry DMF (2 mL) was flushed with nitrogen and heated in an oil bath at 90 °C for 2 h. After dilution with water and extraction with CH_2Cl_2, the crude product was chromatographed on silica, eluting first with CH_2Cl_2/EtOAc (49:1), and then CH_2Cl_2/EtOAc (4:1), to give **20** (100 mg, 92% yield); identical to above.

4,4'-(6-(2-(Difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-1,3,5-triazine-2,4-diyl)dimorpholine (23)

A solution of imidazo[1,2-*a*]pyridine-2-carbaldehyde (**21**)[23] (2.15 g, 14.72 mmol) in CH_2Cl_2 was treated with (diethylamino)sulfur trifluoride (DAST) (4 mL, excess) and the mixture was stirred for 1h, when further DAST (3 mL) was added and stirring was continued for a another 2 h. The reaction mixture was poured into ice water, basified with aq NH_3, extracted into CH_2Cl_2 (4x 30 mL) and dried (Na_2SO_4). Evaporation of the solvents and chromatography of the residue on silica, eluting with CH_2Cl_2/hexanes (1:1) followed by CH_2Cl_2/EtOAc (9:1) gave 2-(difluoromethyl)imidazo[1,2-*a*]pyridine (**22**)[28] (1.0 g, 40%): ^{1}H NMR ($CDCl_3$) δ=8.13 (td, J = 6.8, 1.0 Hz, 1H), 7.79 (brs, 1H),7.61 (dd, J = 9.2, 0.6 Hz, 1H), 7.24 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 6.88 (t, J_{HF} = 55.6 Hz, 1H), 6.88 ppm (dt, J = 6.8, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=146.6 (C), 140.5 (t, J_{CF} = 27.5 Hz, C), 126.4 (CH), 126.0 (CH), 118.5 (CH), 113.6 (CH), 111.9 (t, J_{CF} = 235.7 Hz, CH), 110.7 ppm (CH); ^{19}F NMR ($CDCl_3$) δ= -113.8 ppm (d, J_{FH} = 55.1 Hz).

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A mixture of **18** (449 mg, 1.2 mmol), **22** (220 mg, 1.3 mmol), and K_2CO_3 (259 mg, 2 eq) in DMA (2 mL) was degassed with N_2 for 10 min, then $Pd(OAc)_2$ (30 mg, 0.1 eq) and *n*-$BuPAd_2$ (74 mg, 0.16 mmol) was added and the mixture was heated at 120 °C for 4 h. The reaction mixture was diluted with EtOAc, stirred and the resulting precipitate was collected by filtration and washed with more EtOAc. The combined filtrate was evaporated to dryness. Further material was isolated by extracting the precipitate with CH_2Cl_2 (5x30 mL). The combined material was chromatographed on silica eluting with CH_2Cl_2/EtOAc (0-10%) to give **23** (353 mg, 88%): mp (CH_2Cl_2/hexane) 272-274 °C. ^{1}H NMR ($CDCl_3$) δ 9.74 (td, J = 7.1, 1.1 Hz, 1H), 7.80 (td, J = 9.0, 1.1 Hz, 1H), 7.71 (t, J_{HF} = 54.5 Hz, 1H), 7.41 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.03 (dt, J = 6.9, 1.2 Hz, 1H), 3.89-3.86 (m, 8H), 3.80-3.78 (m, 8H); ^{13}C NMR ($CDCl_3$) δ=164.5 (C), 164.3 (C), 146.7 (C), 143.9 (t, J_{CF} = 24.1 Hz, C), 128.9 (CH), 127.4 (CH), 120.9 (t, J_{CF} = 6.5 Hz, C), 118.8 (CH), 114.3 (CH), 110.5 (t, J_{CF} = 234.5 Hz, CH), 66.9 (CH_2), 44.0 ppm (CH_2); ^{19}F NMR ($CDCl_3$) δ=-116.36 ppm (d, J_{FH} = 54.5 Hz); elemental analysis calcd (%).for $C_{19}H_{21}F_2N_7O_2$: C 54.7, H 5.1, N 23.5; found: C 54.9, H 4.9, N 23.7.

4,4'-(6-(2-(difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridin-3-yl)-1,3,5-triazine-2,4-diyl)dimorpholine (27)

A solution of 3-methoxypyridin-2-amine (**24**) (2.32 g, 18.69 mmol) in 1,2-dimethoxyethane (DME) was treated with 1,1,3-trichloroacetone (3 mL, 22.4 mmol) in DME (10 mL). The reaction mixture was stirred at 20 °C for 4 h and the resulting solid was collected by filtration. The solid was suspended in ethanol (30 mL) and the mixture was heated under reflux overnight. After cooling, the solvent was removed under vacuum, and the residue was suspended in aq K_2CO_3 and heated to 90 °C for 3 h. After cooling, the mixture was extracted with CH_2Cl_2, and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on silica, eluting with CH_2Cl_2/EtOAc (9:1) gave 8-methoxyimidazo[1,2-*a*]pyridine-2-carbaldehyde (**25**) (1.27 g, 30%): mp (CH_2Cl_2/hexane) 186-188°C, ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H), 8.13 (s, 1H), 7.80 (dd, J = 6.8, 0.8 Hz, 1H), 6.82 (t, J = 8.0, 1H), 6.53 (d, J = 7.5 Hz, 1H), 4.05 (s, 3H); elemental analysis calcd (%) for $C_9H_8N_2O_2$: C 61.4, H 4.6, N 15.9; found C 61.5; H 4.5, N 16.0.

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To a solution of **25** (1.16 g, 6.6 mmol) in CH_2Cl_2 (10 mL) was added DAST (2 ml, excess) and the mixture was stirred at 20 °C for 2 h. More DAST (2 mL, excess) was added and after 2 h an additional amount of DAST (2 mL) was added, and stirring was continued for a further 2h.The reaction mixture was slowly poured into ice, basified with aq. NH_3 and the solvent evaporated to dryness. The residue was chromatographed on silica, eluting with CH_2Cl_2/hexane (4:1), followed by CH_2Cl_2/EtOAc (9:1) to give 2-(difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridine (**26**) (658 mg, 50%): mp (*i*-Pr_2O) 122-124 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (t, J = 1.4 Hz, 1H), 7.77 (d, J = 0.8 Hz, 1H), 6.87 (t, J_{HF} = 55.5 Hz, 1H), 6.77 (t, J = 7.2 Hz, 1H), 6.51 (d, J = 7.5 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.7 (C), 140.2 (C), 139.8 (C), 119.1 (CH), 113.7 (CH), 112.1 (t, J_{CF} = 235.3 Hz, CH), 111.6 (t, J_{CF} = 4.1 Hz, CH), 101.4 (CH), 56.1 (CH_3); ^{19}F NMR ($CDCl_3$) δ -113.2 (d, J_{HF} = 56.0 Hz); MS (APCI) *m/z*: 199.2 (MH^+); elemental analysis calcd (%) for $C_9H_8F_2N_2O$: C 54.5, H 4.1, N 14.1; found: C 54.7, H 3.8, N 14.2.

A mixture of compound **26** (154 mg, 0.78 mmol), compound **18** (266 mg, 0.94 mmol) and K_2CO_3 (215 mg, 1.56 mmol), in DMA (1 mL) was degassed and flushed with a balloon of nitrogen. $Pd(OAc)_2$ (18 mg, 0.1 eq) and *n*-$BuPAd_2$ (45 mg, 0.16 eq) were then added and the mixture was degassed and flushed with nitrogen again. The reaction mixture was heated for 2 h at 120 °C and the DMA was removed under vacuum. The resulting residue was chromatographed on silica eluting with CH_2Cl_2/EtOAc (4:1) to give **27** (386 mg, 100%): mp (CH_2Cl_2/MeOH) 316-320 °C; ^{1}H NMR ($CDCl_3$) δ=9.33 (dd, J = 7.0, 0.8 Hz, 1H), 7.64 (t, J_{HF} = 54.4 Hz, 1H), 6.92 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 7.2 Hz, 1H), 4.05 (s, 3H), 3.88-3.85 (m, 8H), 3.79-3.77 ppm (m, 8H); elemental analysis calcd (%) for $C_{20}H_{23}F_2N_7O_3$: C 53.7, H 5.2, N 21.9; found: C 53.8, H 5.1, N 22.0.

2-(Difluoromethyl)-8-methoxy-3-[4-[4-(methylsulfonyl)-1-piperazinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]imidazo[1,2-*a*]pyridine (**32**)

To a solution of 3-methoxypyridin-2-amine (**24**) (0.68 g, 5.5 mmol) in DME (10 mL) was added dropwise a solution of 1-bromo-3,3-difluoroacetone (1 g, 5.8 mmol) in DME (1 mL), and the mixture was stirred for 4 h. The white precipitate was collected

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by filtration, washed with DME, and dissolved in EtOH (10 mL). The solution was heated under reflux overnight and the solvent was removed. The residue was basified with aq. Na_2CO_3 and extracted with CH_2Cl_2. After drying, the solvent was removed to give **26** (0.826 g, 76%); identical to above.

4-(4,6-Dichloro-1,3,5-triazin-2-yl)morpholine (**28**)[24] (2.50 g, 10.6 mmol) was added portion-wise to 57% aq. HI (20 mL) at 0 °C, and the resulting suspension was allowed to warm to room temperature. After stirring overnight, the reaction mixture was poured onto ice and carefully neutralized with saturated Na_2CO_3 solution. The resulting solid was extracted into CH_2Cl_2 and washed with 1 M Na_2SO_3 and brine. The organic layer was dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give 4-(4,6-diiodo-1,3,5-triazin-2-yl)morpholine (**29**) (3.41 g, 83%) as a crystalline white solid: mp (hexane) 191-193 °C; ^{1}H NMR ($CDCl_3$) δ=3.83-3.79 (m, 4H), 3.76-3.71 ppm (m, 4H); ^{13}C NMR ($CDCl_3$) δ=159.9 (C), 138.0 (C), 140.6 (C), 66.6 (CH_2), 44.3 ppm (CH_2); MS (APCI) *m/z*: 418.9 (MH^+); elemental analysis calcd (%) for $C_7H_8I_2N_4O$: C 20.1, H 1.9, N 13.4; found: C 20.4, H 2.0, N 13.3.

To a solution of **29** (3.41 g, 8.8 mmol) and DIPEA (2.06 g, 16.0 mmol) in THF (30 mL) was added *N*-Boc-piperazine (2.08 g, 11.2 mmol). This mixture was stirred at room temperature for 1 h and water was added. The resulting white solid was collected by filtration, washed well with water and dried in a vacuum oven to give *tert*-butyl 4-(4-iodo-6-morpholino-1,3,5-triazin-2-yl)piperazine-1-carboxylate (**30**) (3.89 g, 93%) as a white solid: mp (MeOH) 210-215 °C; ^{1}H NMR ($CDCl_3$) δ=3.79-3.67 (m, 12H), 3.47-3.42 (m, 4H), 1.48 ppm (s, 9H); ^{13}C NMR ($CDCl_3$) δ=162.2 (C), 154.9 (C), 140.6 (C), 80.43 (C), 66.9 (CH_2), 66.7 (CH_2), 44.0 (CH_2), 43.7 (CH_2), 43.4 (CH_2), 43.2 (CH_2), 28.6 ppm (CH_3); MS (APCI) *m/z*: 477.1 (MH^+); elemental analysis calcd (%) for $C_{16}H_{25}IN_6O_3$: C 40.4, H 5.3, N 17.6; found: C 40.6, H 5.4, N 17.5.

A mixture of 2-(difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridine (**26**) (0.238 g, 1.2 mmol), **30** (0.476 g, 1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.005 mmol), *n*-BuPAd$_2$ (36 mg, 0.01 mmol) and K_3PO_4 (440 mg, 2 mmol) in DMF (20 mL) was degassed, flushed with nitrogen, and heated at 90 °C for 3 h. After cooling, dilution with water gave a

precipitate, which was collected and washed with water. After drying the solid was chromatographed on silica, eluting with CH_2Cl_2/EtOAc (4:1) to give *tert*-butyl 4-(4-(2-(difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazine-1-carboxylate (**31**) (0.446 g, 82%): mp (MeOH) 234-236 °C; ^{1}H NMR ($CDCl_3$) δ=9.32 (dd, J = 7.1, 0.7 Hz, 1H); 7.64 (t, J_{HF} = 54.5 Hz, 1H); 6.92 (t, J = 7.4 Hz, 1H); 6.68 (t, J = 7.5 Hz, 1H); 4.05 (s, 3H); 3.89-3.82 (m, 8H), 3.81-3.76 (m, 4H), 3.56-3.50 (m, 4H), 1.50 ppm (s, 9H); MS (APCI) *m/z*: 547.3 (MH^+).

A mixture of **31** (0.109 g, 0.2 mmol) and TFA (1 mL) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 h. After cooling in ice, the mixture was basified with aq. NH_3. The CH_2Cl_2 solution was dried, and removed, to give 2-(difluoromethyl)-8-methoxy-3-[4-(4-morpholinyl)-6-(1-piperazinyl)-1,3,5-triazin-2-yl]imidazo[1,2-*a*]pyridine: ^{1}H NMR (DMSO-d_6) δ 9.30 (dd, J = 7.00, 0.6 Hz, 1H), 7.72 (t, J_{HF} = 54.3 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H); 6.99 (d, J = 7.7 Hz, 1H), 3.99 (s, 3H), 3.83-3.75 (m, 8H), 3.72-3.66 (m, 4H), 2.96-2.87 (m, 4H); MS (APCI) *m/z*: 447.3 (MH^+).

The above crude amine (0.2 mmol) was dissolved in CH_2Cl_2 (25 mL) with DIPEA (65 mg, 5 mmol) and the mixture was cooled to 0 °C in an ice-bath. Methanesulfonyl chloride (27 mg, 0.24 mmol) was added, and the mixture was stirred overnight at room temperature. Water was added, and the organic layer was separated and dried, to give **32** (0.101 g, 96%): mp (MeOH) 311-314 °C; ^{1}H NMR ($CDCl_3$) δ=9.29 (dd, J = 7.1, 0.8 Hz, 1H), 7.60 (t, J_{HF} = 54.5, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.69 (dd, J = 7.4, 0.4 Hz, 1H), 4.05 (s, 3H), 4.03-3.99 (m,4H), 3.89-3.83 (m, 4H), 3.81-3.77 (m, 4H), 3.34-3.30 (m, 4H), 2.81 ppm (s, 3H); ^{13}C NMR ($CDCl_3$) δ=164.5 (C), 164.46 (C), 164.42 (C), 149.6 (C), 143.0 (t, J_{CF} = 24.8 Hz, C), 141.1 (C), 121.7 (t, J_{CF} = 5.7 Hz, C), 121.3 (CH), 114.4 (CH), 110.5 (t, J_{CF} = 236.4 Hz, CH), 103.5 (CH), 66.9 (CH_2), 56.2 (CH_3), 45.8 (CH_2), 44.0 (CH_2), 43.2 (CH_2), 34.8 ppm (CH_3); HRMS (APCI): *m/z* calcd for $C_{21}H_{26}F_2N_8O_4$+H^+: 525.1865 [M+H^+]; found: 525.1863.

2-((4-(4-(2-(Difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3, 5-triazin-2-yl)piperazin-1-yl)sulfonyl)-*N,N*-dimethylethan-1-amine (34)

A mixture of **31** (0.191 g, 0.35 mmol) and TFA (2 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. After cooling in ice, the mixture was basified with aq.

NH_3 and extracted with CH_2Cl_2 to give crude 2-(difluoromethyl)-8-methoxy-3-[4-(4-morpholinyl)-6-(1-piperazinyl)-1,3,5-triazin-2-yl]imidazo[1,2-*a*]pyridine (identical to above) which was combined with DIPEA (113 mg, 0.875 mmol) in CH_2Cl_2 (50 mL). The solution was cooled to -15 °C in an ice-salt bath and 2-chloroethanesulfonyl chloride (85 mg, 0.52 mmol) was added slowly over 10 min, and the mixture was stirred at -15 °C for 1 h. After dilution with water the organic layer was separated, dried (Na_2SO_4), and removed. The residue was chromatographed on silica, eluting with CH_2Cl_2/EtOAc (4:1) to give 2-(difluoromethyl)-8-methoxy-3-[4-(4-morpholinyl)-6-[4-(vinylsulfonyl)-1-piperazinyl]-1,3,5-triazin-2-yl]imidazo[1,2-*a*]pyridine (**33**) (0.124 g, 66%): ^{1}H NMR ($CDCl_3$) δ=9.29 (dd, J = 7.0, 0.8 Hz, 1H), 7.59 (t, J_{HF} = 54.4 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 6.43 (dd, J = 16.6, 9.8 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 6.08 (d, J = 9.8 Hz, 1H), 4.05 (s, 1H), 4.02-3.97 (m, 4H), 3.89-3.83 (m 4H), 3.81-3.76 ppm (m, 4H), 3.27-3.32 (m, 4H); MS (APCI) *m/z*: 536.9 (MH^+).

Crude **33** was combined with 40% aq. Me_2NH (10 mL) in THF (40 mL), and after 30 min the solvents were removed, and the residue was extracted with CH_2Cl_2. After drying, the solvent was removed, and the residue was recrystallized from MeOH to give **34** (118 mg, 88%): mp 258-261 °C; ^{1}H NMR ($CDCl_3$) δ=9.30 (dd, J = 7.1, 0.8 Hz, 1H), 7.60 (t, J_{HF} = 54.4, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.69 (dd, J = 7.4, 0.4 Hz, 1H), 4.05 (s, 3H), 4.01-3.95 (m, 4H), 3.90-3.84 (m, 4H), 3.81-3.77 (m, 4H), 3.41-3.36 (m, 4H) (s, 3H); 3.13 (t, J = 7.3 Hz, 2H), 2.80 (d, J = 7.3 Hz, 2H), 2.28 ppm (s, 6H); HRMS (APCI): *m*/*z* calcd for $C_{24}H_{33}F_2N_9O_4$+H^+: 582.2417 [M+H^+]; found: 582.2420.

_N_-(4-(4-(2-(Nifluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-2-(dimethylamino)ethane-1-sulfonamide (41)

A mixture of 2-(benzyloxy)-4,6-dichloro-1,3,5-triazine (**35**)[29] (1.106 g, 4.34 mmol) and morpholine (755 mg, 8.68 mmol) in CH_2Cl_2 (30 mL) was stirred at 20 °C for 2h. The solvent was evaporated at room temperature, and the resulting residue was stirred in water (150 mL), the precipitate was collected and chromatographed on silica, eluting with CH_2Cl_2/hexane (95:5) to give 4-(4-(benzyloxy)-6-chloro-1,3,5-triazin-2-yl)morpholine (**36**) (1.11g, 83%); mp (CH_2Cl_2/hexanes) 141-142 °C, ^{1}H NMR

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($CDCl_3$) δ=7.44-7.42 (m, 2H), 7.38-7.30 (m, 3H), 5.39 (s, 2H), 3.88-3.83 (m, 4H), 3.74-3.71 ppm (m, 4H); MS (APCI) *m/z*: 307.0 (MH^+).

A mixture of **36** (2.01g, 6.54 mmol), 4-(Boc-amino)phenylboronic acid (804 mg, 3.39 mmol) and 2M K_2CO_3 (2.5 mL) in dioxane was degassed and flushed with N_2, then treated with Pd(dppf)Cl_2 and refluxed under N_2 for 2h, evaporated to dryness and the residue was chromatographed on silica, eluting with CH_2Cl_2/hexanes (1:1) and then CH_2Cl_2 to give *tert*-butyl (4-(4-(benzyloxy)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-carbamate (**37**) (718 mg, 69%): ^{1}H NMR ($CDCl_3$) δ=8.38 – 8.36 (m, 2H), 7.50-7.43 (m, 4H), 7.38-7.29 (m, 3H), 6.64 (br s, 1H), 5.48 (s, 2H), 4.01 and 3.88 (2 br, 4H), 3.76 (br, 4H), 1.53 ppm (s, 9H); MS (APCI) *m/z*: 464.0 (MH^+).

A solution of **37** (2.51g, 5.42 mmol) in THF (30 mL) was hydrogenated over 10% Pd/C for 4h, MeOH (50 mL) and CH_2Cl_2 (50 mL) added to dissolve the precipitated product, and the solution filtered through a pad of celite. Removal of the solvents gave *tert*-butyl (4-(4-hydroxy-6-morpholino-1,3,5-triazin-2-yl)phenyl)carbamate (1.94 g, 95%); ^{1}H NMR (DMSO-d_6) δ=11.83 (br s, 1H), 9.78 (s, 1H), 8.13 (br d, *J* = 8.9 Hz, 2H), 7.59 (br d, *J* = 8.9 Hz, 2H), 3.82 (br, 4H), 3.66-3.63 (m, 4H), 1.49 ppm (s, 9H); MS (APCI) *m/z*: 374.0 (MH^+).

A suspension of the above compound (780 mg, 2.1 mmol) and DIPEA (1.5 mL, 8.4 mmol) in CH_2Cl_2 (30 mL) was treated with triflic anhydride (0.7 mL, 4.2 mmol) and the mixture was stirred for 2h, when more triflic anhydride (0.4 mL) and DIPEA (1 mL) were added. Stirring was continued for a further 2h before the volatiles were removed under vacuum. The resulting residue was chromatographed on silica, eluting with CH_2Cl_2/hexanes (9:1) to give 4-(4-((*tert*-butoxycarbonyl)amino)phenyl)-6-morpholino-1,3,5-triazin-2-yl trifluoromethanesulfonate (**38**) (859 mg, 81%): mp (CH_2Cl_2/hexane) >320 °C; ^{1}H NMR ($CDCl_3$) δ=8.34-8.30 (m, 2H), 7.47 (br d, *J* = 8.8 Hz, 2H), 6.69 (br s, 1H), 4.07 (br t, *J* = 4.9 Hz, 2H), 3.87 (br t, *J* = 4.7 Hz, 2H), 3.83-3.77 (m, 4H), 1.54 ppm (s, 9H); MS (APCI) *m/z*: 505.9 (MH^+).

A mixture of **26** (307 mg, 1.55 mmol), **38** (850 mg, 1.68 mmol), and K_2CO_3 (354, mg 2.56 mmol) in DMF (3 mL) in a sealed tube was degassed and flushed with N_2. Then $Pd(OAc)_2$ (28 mg, 0.1 eq), *n*-$BuPAd_2$ (73 mg, 0.16 eq) was added. The reaction

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mixture was heated to 120 °C for 2 h. The solvents were removed under vacuum and the resulting residue was chromatographed on silica, eluting with CH_2Cl_2 to give unreacted **26** (216 mg, 70%). Further elution with CH_2Cl_2/EtOAc (17:3) gave *tert*-butyl (4-(4-(2-(difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)carbamate (**39**) (257 mg, 30%): ^{1}H NMR ($CDCl_3$) δ=9.58 (dd, J = 7.0, 0.7 Hz, 1H), 8.40 (br d, J = 8.8 Hz, 2H), 7.77 (t, J_{HF} = 54.3 Hz, 1H), 7.52 (br d, J = 8.8 Hz, 2H), 7.02-6.99 (m, 1H), 6.74 (br d, J = 7.3 Hz, 1H), 6.69 (br s, 1H), 4.07 (br, 2H), 4.07 (s, 3H), 3.94 (br, 2H), 3.86-3.84 (m, 4H), 1.55 ppm (s, 9H).

A solution of **39** (240 mg, 0.43 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (3 mL) and the mixture was stirred for 20 h. The solvents and excess TFA were evaporated, and the resulting residue was stirred in aq NH_3 and the precipitate collected by filtration and washed with water to give 4-(4-(2-(difluoromethyl)-8-methoxy-imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)aniline (**40**) (179 mg, 91%); ^{1}H NMR [DMSO-d_6] δ=9.50 (dd, J = 6.9, 0.5 Hz, 1H), 8.15 (br d, J = 8.7 Hz, 2H), 7.86 (t, J_{HF} = 54.3 Hz, 1H), 7.27-7.21 (m, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.67 (br d, J = 8.8 Hz, 2H), 5.99 (br s, 2H), 4.01 (s, 3H), 3.97 (br, 2H), 3.86 (br, 2H), 3.74 ppm (br, 4H); MS (APCI) *m/z*: 453.9 (MH^+).

A mixture of **40** (207 mg, 0.46 mmol) and pyridine (6 mL) at 0 °C was treated with 2-chloroethylsulfonyl chloride (0.5 mL, excess). The reaction mixture was stirred 4 h, allowing it to warm up to 20 °C. The mixture was diluted with water, the resulting precipitate was collected by filtration, and chromatographed on silica, eluting with CH_2Cl_2/hexane (1:1) to give crude *N*-(4-(4-(2-(difluoromethyl)-8-methoxyimidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)ethenesulfonamide which was treated directly with 40% aq dimethylamine (5 mL) in THF (20 mL), and the reaction mixture was stirred for 20 h. The volatiles were removed under vacuum and the residue was diluted with H_2O. The resulting solid was collected and purified by column chromatography on silica, eluting with CH_2Cl_2/MeOH (96:4) to give **41** (183 mg, 68%): ^{1}H NMR (DMSO-d_6) δ=9.47 (d, J = 7.1 Hz, 1H), 8.39 (br d, J = 8.8 Hz, 2H), 7.85 (t, J_{HF} = 54.2 Hz, 1H), 7.38 (br d, J = 8.8 Hz, 2H), 7.27-7.22 (m, 1H), 7.05 (d, J = 7.5 Hz, 1H), 4.01 (s, 3H), 4.01 (br, 2H), 3.87 (br 2H), 3.76 (br, 4H), 3.38-3.34 (m, 2H), 2.67-2.64 (m, 2H), 2.08 ppm (s, 6H); MS (APCI) *m/z*: 589.0 (MH^+).

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Methanesulfonate: mp (MeOH/EtOAc) 243-246 °C; ^{1}H NMR (DMSO-d_6) δ=10.67 (s, 1H), 9.48 (br d, J = 6.6 Hz, 2H), 8.43 (br d, J = 8.8 Hz, 2H), 7.87 (t, J_{HF} = 54.2 Hz, 1H), 7.42 (br d, J = 8.8 Hz, 2H), 7.28-7.24 (m, 1H), 7.08 (d, J = 7.6 Hz, 1H), 4.01 (s, 3H), 4.01 (br, 2H), 3.89 (br 2H), 3.76 – 3.48 (m, 6H), 2.83 (br s, 6H), 2.31ppm (s, 3H); elemental analysis calcd (%) for $C_{27}H_{34}F_2N_8O_7S_2 \cdot H_2O$: C 46.1, H 5.1, N 15.9; found: C 46.2, H 5.1, N 15.6.

(*S*)-2-Amino-1-(4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazin-1-yl)propan-1-one (48)

2-(Difluoromethyl)imidazo[1,2-*a*]pyridine (**22**) (200 mg, 1.19 mmol), *tert*-butyl 4-(4-iodo-6-morpholino-1,3,5-triazin-2-yl)piperazine-1-carboxylate (**30**) (515 mg, 1.08 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), *n*-BuPAd$_2$ (39 mg, 0.11 mmol) and K_3PO_4 (548 mg, 2.38 mmol) were all weighed into a pressure tube (50 mL), dry DMF (20 mL) added, and the solution degassed and sealed under N_2. This mixture was heated with stirring at 90 ^{o}C for 2 h. Upon cooling, the reaction mixture was diluted to 100 mL with water then extracted with EtOAc (3x50 mL). The combined EtOAc fractions were then washed with water (3x50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give a crude solid. This solid was purified by flash column chromatography on silica gel using a gradient of 2-20% EtOAc in hexanes to elute *tert*-butyl 4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazine-1-carboxylate (**42**) as a cream solid (531 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.74 (dt, J = 7.1, 1.1 Hz, 1H), 7.80 (dd, J = 9.1, 1.1 Hz, 1H), 7.70 (t, J_{HF} = 54.6 Hz, 1H), 7.41 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.04 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 3.84-3.90 (m, 8H), 3.66-3.83 (m, 4H), 3.46-3.57 (m, 4H), 1.51 ppm (s, 9H); MS (APCI) *m/z*: 517 (MH^+).

A mixture of **42** (414 mg, 0.80 mmol) and TFA (3 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature for 0.5 h. All solvent was removed under reduced pressure and the remaining oily residue was dissolved in a small amount of water, cooled (ice/water), and basified through the dropwise addition of 2 M NaOH. The resulting solid was collected by filtration, washed well with water and dried under vacuum to give 4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-(piperazin-1-yl)-1,3,5-triazin-2-yl)morpholine (**43**) as a beige solid (318 mg, 95%): ^{1}H NMR (400 MHz,

$CDCl_3$) δ=9.75 (dt, J = 7.1, 1.1 Hz, 1H), 7.78 (dt, J = 9.0, 1.1 Hz, 1H), 7.73 (t, J_{HF} = 54.6 Hz, 1H), 7.40 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.02 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 3.83-4.08 (m, 8H), 3.73-3.82 (m, 4H), 2.90-2.98 ppm (m, 4H); MS (APCI) *m/z*: 417 (MH^+),

N-Boc-L-Alanine (154 mg, 0.82 mmol) was dissolved in DMF (10 mL) under N_2, to which was added HBTU (310 mg, 0.82 mmol) and DIPEA (0.29 mL, 1.63 mmol). After stirring for 10 minutes at room temperature, **43** (170 mg, 0.41 mmol) was added and the entire mixture stirred for 2 hours. The reaction mixture was diluted with EtOAc (80 mL), and this solution was washed with 1 M citric acid, brine, saturated $NaHCO_3$, brine, water, brine (all 40 mL), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, 50% EtOAc in hexanes as eluant, to give *tert*-butyl (*S*)-(1-(4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate (**44**) as a white foam (229 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.72 (d, J = 7.1 Hz, 1 H), 7.81 (d, J = 9.0 Hz, 1 H), 7.68 (t, J_{HF} = 54.7 Hz, 1 H), 7.40 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 7.03 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H), 5.47 (br s, 1 H), 4.65-4.72 (m, 1 H), 3.52-4.05 (m, 16 H), 1.45 (s, 9 H), 1.34 ppm (d, J = 6.9 Hz, 3 H); MS (APCI) *m/z*: 588 (MH^+).

Trifluoroacetic acid was added to a solution of **44** (229 mg, 0.39 mmol) in CH_2Cl_2 (2 mL), and this mixture was stirred at room temperature under N_2 for 2 hours. Removal of all solvent under reduced pressure gave an oil that was dissolved in CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Trituration with diethyl ether gave the title compound **48** as a cream solid (180 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.73 (d, J = 7.1 Hz, 1 H), 7.82 (d, J = 9.1 Hz, 1 H), 7.69 (t, J_{HF} = 54.6 Hz, 1 H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 7.04 (ddd, J = 8.1, 7.0, 1.2 Hz, 1 H), 3.54-3.96 (m, 17 H), 1.31 ppm (d, J = 6.8 Hz, 3 H); HRMS (APCI): *m*/*z* calcd for $C_{22}H_{28}F_2N_9O_2+H^+$: 488.2329 [$M$+$H^+$]; found 488.2334.

(*R*)-2-Amino-1-(4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazin-1-yl)propan-1-one (49)

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N-Boc-D-Alanine was reacted with **43** according to the procedure for **44**. *tert*-Butyl (*R*)-(1-(4-(4-(2-(Difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate (**45**) was isolated as a transparent glass (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.72 (d, J = 7.1 Hz, 1 H), 7.81 (d, J = 8.9 Hz, 1 H), 7.67 (t, J_{HF} = 54.7 Hz, 1 H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 7.04 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H), 5.47 (br s 1 H), 4.69 (q, J = 7.2 Hz, 1 H), 3.50-4.07 (m, 16 H), 1.45 (s, 9 H), 1.34 ppm (d, J = 6.9 Hz, 3 H); MS (APCI) *m/z*: 587 (MH^+).

Compound **45** was deprotected according to the procedure for **48**. Following trituration with diethyl ether, the title compound **49** was isolated as a cream solid (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.73 (d, J = 7.1 Hz, 1 H), 7.81 (d, J = 9.1 Hz, 1 H), 7.68 (t, J_{HF} = 54.5 Hz, 1 H), 7.42 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 7.04 (ddd, J = 8.1, 7.0, 1.1 Hz, 1 H), 3.53-3.97 (m, 17 H), 1.30 ppm (d, J = 6.8 Hz, 3 H); HRMS (APCI): *m*/*z* calcd for $C_{22}H_{28}F_2N_9O_2$+H^+: 488.2329 [M+H^+]; found 488.2327.

(*S*)-2-Amino-1-(4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one (50)

N-Boc-L-Phenylalanine was reacted with **43** according the procedure for **44**. *tert*-Butyl (*S*)-(1-(4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (**46**) was isolated as a white foam (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.68 (br s, 1 H), 7.80 (d, J = 9.1 Hz, 1 H), 7.64 (t, J_{HF} = 54.7 Hz, 1 H), 7.42 (ddd, J = 8.0, 6.8, 1.1 Hz, 1 H), 7.17-7.34 (m, 5 H), 7.04 (ddd, J = 8.1, 7.0, 1.2 Hz, 1 H), 5.41 (br s, 1 H), 4.88 (br s, 1 H), 3.42-4.90 (m, 14 H), 2.95-3.14 (m, 4 H), 1.44 ppm (s, 9 H); MS (APCI) *m/z*: 664 (MH^+).

Compound **46** was deprotected according to the procedure for **48**. The title compound **50** was isolated as a cream solid (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.70 (d, J = 7.0 Hz, 1 H), 7.81 (d, J = 9.0 Hz, 1 H), 7.64 (t, J_{HF} = 54.9 Hz, 1 H), 7.42 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 7.16-7.36 (m, 5 H), 7.04 (ddd, J = 8.1, 7.0, 1.2 Hz, 1 H), 3.67-4.04 (m, 12 H), 3.53-4.03 (m, 2 H), 3.36-3.47 (m, 1H), 3.06-3.24 (m, 2 H), 2.84-3.03 ppm (m, 2 H); HRMS (APCI): *m*/*z* calcd for $C_{28}H_{32}F_2N_9O_2$+H^+: 564.2642 [M+H^+]; found 564.2641.

(*R*)-4-(4-(2-(Difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-(4-prolylpiperazin-1-yl)-1,3,5-triazin-2-yl)morpholine (51)

N-Boc-D-Proline was reacted with **43** according to the procedure for **44**. *tert*-Butyl (*R*)-2-(4-(4-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-morpholino-1,3,5-triazin-2-yl)piperazine-1-carbonyl)pyrrolidine-1-carboxylate (**47**) was isolated as a white foam (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.73 (d, J = 7.1 Hz, 1 H), 7.77-7.84 (m, 1 H), 7.68 (t, J_{HF} = 54.5 Hz, 1 H), 7.37-7.46 (m, 1 H), 7.01-7.07 (m, 1 H), 3.93-4.04 (m, 2 H), 3.51-3.92 (m, 12 H), 3.30-3.50 (m, 5 H), 2.00-2.30 (m, 2 H), 1.84-1.95 (m, 2 H), 1.46 ppm (s, 9 H); MS (APCI) *m/z*: 614 (MH^+),

Compound **47** was deprotected according to the procedure for **48**. Following trituration with diethyl ether, the title compound **51** was isolated as a white solid (88%). ^{1}H NMR (400 MHz, $CDCl_3$)=δ 9.72 (d, J = 7.1 Hz, 1 H), 7.82 (d, J = 9.1 Hz, 1 H), 7.68 (t, J_{HF} = 54.5 Hz, 1 H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 7.04 (ddd, J = 8.1, 7.0, 1.2 Hz, 1 H), 3.52-4.04 (m, 17 H), 3.16-3.26 (m, 1 H), 2.85-2.96 (m, 1 H), 2.50-2.63 (m, 1 H), 1.77-1.96 ppm (m, 3 H); HRMS (APCI): *m*/*z* calcd for $C_{24}H_{30}F_2N_9O_2$+H^+: 514.2485 [M+H^+]; found 514.2488.

***N*-(*trans*-4-((6-(2-(difluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-2-morpholino-pyrimidin-4-yl)oxy)cyclohexyl)-2-(dimethylamino)acetamide (58)**

A mixture of 4,6-dichloro-2-(methylthio)pyrimidine (**52**) (7.804g, 0.04 mol), *tert*-butyl (*trans*-4-hydroxycyclohexyl)carbamate (2.87 g, 13.3 mmol), 4 M NaOH (17 mL), and THF (50 mL) was heated under reflux for 36 h, then cooled and diluted with water. The white solid was collected and dried. Chromatography on silica, eluting with CH_2Cl_2/hexanes (2:1) gave 4-chloro-2,6-bis(methylthio)pyrimidine (0.17 g): ^{1}H NMR ($CDCl_3$) δ=6.85 (s, 1H), 2.56 ppm (s, 6H); MS (APCI) *m/z*: 207.1 (MH^+).

Further elution with CH_2Cl_2 gave *tert*-butyl (*trans*-4-((6-chloro-2-(methylthio)pyrimidin-4-yl)oxy)cyclohexyl)carbamate (**53**) (3.0 g, 60%): mp (*i*-Pr_2O) 179-182 °C; ^{1}H NMR ($CDCl_3$) δ=6.35 (s, 1H), 5.08-4.99 (m, 1H), 4.47-4.35 (m, exchangeable with D_2O, 1H), 3.58-3.44 (m, 1H), 2.52 (s, 3H), 2.16-2.04 (m, 4H), 1.59-1.49 (m, 2H), 1.45 (s, 9H), 1.35-1.23 ppm (m, 2H); ^{13}C NMR ($CDCl_3$) δ =172.8 (C), 169.2 (C), 160.6 (C),

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155.4 (C), 103.1 (CH), 79.6 (C), 74.9 (CH), 48.8 (CH), 30.9 (CH_2), 30.0 (CH_2), 28.6 (CH_3), 14.4 ppm (CH_3); MS (APCI) *m/z*: 374.2 (MH^+).

Acidification of the original aqueous filtrate gave 6-chloro-2-(methylthio)pyrimidin-4(3*H*)-one: ^{1}H NMR (DMSO-d_6) δ=13.11 (br s, 1H), 6.29 (s, 1H), 2.49 ppm (s, 3H), MS (APCI) *m/z*: 169.2 (MH^+).

To a solution of **53** (3.74 g, 10 mmol) in a mixture of acetone (500 mL) and acetic acid (50 mL) was added $KMnO_4$ (5 g, 32 mmol) in water (100 mL), and the mixture was stirred at room temperature overnight. The mixture was diluted with water, extracted with CH_2Cl_2, and washed with aq. Na_2CO_3 until gas evolution ceased. Drying (Na_2SO_4) and removal of solvent gave *tert*-butyl (*trans*-4-((6-chloro-2-(methylsulfonyl)pyrimidin-4-yl)oxy)cyclohexyl)carbamate (3.99 g, 98%): ^{1}H NMR ($CDCl_3$) δ=6.86 (s, 1H), 5.24-5.15 (m, 1H), 4.47-4.34 (m, 1H), 3.59-3.46 (m, 1H), 3.34 (s, 3H), 2.18-2.04 (m, 4H), 1.67-1.56 (m, 2H), 1.45 (s, 9H), 1.38-1.26 ppm (m, 2H); MS (APCI) MH^+ not observed.

The above crude carbamate (3.99 g, 9.8 mmol) was dissolved in THF (100 mL) and morpholine (1.8 g, 21 mmol) in THF (10 mL) was added. The mixture was stirred at room temperature for 2 h, diluted with water, and extracted with CH_2Cl_2. Chromatography on silica, eluting with CH_2Cl_2/EtOAc (95:5) gave *tert*-butyl (*trans*-4-((6-chloro-2-morpholinopyrimidin-4-yl)oxy)cyclohexyl)carbamate (**54**) (2.06 g, 51%): mp (*i*-Pr_2O) 152-155 °C; ^{1}H NMR ($CDCl_3$) δ 5.97 (s, 1H), 4.89 (tt, *J* = 10.5, 3.8 Hz, 1H), 4.46-4.35 (m, 1H), 3.74 (m, 8H), 3.58-3.43 (m, 1H), 2.14-2.04 (m, 4H), 1.62-1.49 (m, 2H), 1.45 (s, 9H), 1.34-1.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.2 (C), 161.1 (C), 161.0 (C), 155.4 (C), 96.2 (CH), 79.6 (C), 74.0 (CH), 66.9 (CH_2), 48.9 (CH), 44.5 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 28.6 (CH_3); MS (APCI) *m/z*: 413.2 (MH^+).

Further elution with CH_2Cl_2/EtOAc (95:5) gave *tert*-butyl (*trans*-4-((2-(methylsulfonyl)-6-morpholinopyrimidin-4-yl)oxy)cyclohexyl)carbamate (**55**) (2.14 g, 48%): mp (*i*-Pr_2O) 177-179 °C; ^{1}H NMR ($CDCl_3$) δ=5.86 (s, 1H), 5.08-4.99 (m, 1H), 4.47-4.36 (m, 1H), 3.78-3.74 (m, 4H), 3.63-3.58 (m, 4H), 3.56-3.46 (m, 1H), 3.25 (s, 3H), 2.15-2.02 (m, 4H), 1.60-1.49 (m, 2H), 1.45 (s, 9H), 1.35-1.23 ppm (m, 2H); ^{13}C NMR ($CDCl_3$) δ=170.7 (C), 164.7 (C), 164.1 (C), 155.4 (C), 87.9 (CH), 79.6 (C), 74.7 (CH), 66.5

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(CH_2), 48.8 (CH), 44.8 (CH_2), 38.9 (CH_3), 30.9 (CH_2), 30.2 (CH_2), 28.6 ppm (CH_3); MS (APCI) *m/z*: 457.2 (MH^+).

A solution of **54** (1.239 g, 3 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (5 mL) for 2h, and the solvents were removed under vacuum. The residue was dissolved in 57% HI (20 mL) and NaI (6 g) was added. The mixture was stirred at room temperature for 4 days, and poured onto ice. Neutralization with aq. Na_2CO_3, and extraction with CH_2Cl_2, gave (*trans*-4-((6-iodo-2-morpholinopyrimidin-4-yl)oxy)cyclohexan-1-amine as a white solid: ^{1}H NMR ($CDCl_3$) *δ*=6.42 (s, 1H), 4.87 (tt, *J* = 10.7, 4.2 Hz, 1H), 3.73 (s, 8H), 2.77 (tt, *J* = 10.6, 4.0 Hz, 1H), 2.12-2.04 (m, 2H), 1.96-1.88 (m, 2H), 1.53-1.41 (m, 4H, reduced to 2H after D_2O exchange), 1.23 ppm (dq, *J* = 13.3, 3.4, 2H); MS (APCI) *m/z*: 405.1 (MH^+).

The crude solid was dissolved in MeCN (200 mL), di-*tert*-butyldicarbonate (0.98 g, 1.5 equiv.) was added, and the mixture was stirred at room temperature overnight. Dilution with water gave *tert*-butyl (*trans*-4-((6-iodo-2-morpholinopyrimidin-4-yl)oxy)cyclohexyl)carbamate (**56**) (1.253 g, 83%): mp (*i*-Pr_2O) 191-193 °C; ^{1}H NMR ($CDCl_3$) *δ*=6.42 (s, 1H), 4.86 (tt, *J* = 10.5, 3.8 Hz, 1H), 4.49-4.32 (m, 1H), 3.73 (m, 8H), 3.56-3.41 (m, 1H), 2.12-2.03 (m, 4H), 1.61-1.47 (m, 2H), 1.44 (s, 9H), 1.33-1.21 ppm (m, 2H); ^{13}C NMR ($CDCl_3$) *δ*=168.2 (C), 160.1 (C), 155.4 (C), 128.8 (C), 107.8 (CH), 79.6 (C), 73.7 (CH), 66.9 (CH_2), 48.8 (CH), 44.4 (CH_2), 31.0 (CH_2), 30.0 (CH_2), 28.6 ppm (CH_3); MS (APCI) *m/z*: 505.1 (MH^+).

A mixture of iodide **56** (505 mg, 1 mmol), 2-(difluoromethyl)imidazo[1,2-*a*]pyridine (**22**) (200 mg, 1.2 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), *n*-$BuPAd_2$ (36 mg, 0.1 mmol), K_3PO_4 (440 mg, 2.05 mmol) in dry DMF (20 mL) was degassed, flushed with nitrogen, and heated at 90 °C for 5 h. After cooling, the mixture was diluted with water, to give a solid, which was collected and dried. Chromatography on silica, eluting with CH_2Cl_2/EtOAc (95:5) gave *tert*-butyl (*trans*-4-((6-(2-(difluoromethyl)-imidazo[1,2-*a*]pyridin-3-yl)-2-morpholinopyrimidin-4-yl)oxy)cyclohexyl)carbamate (**57**) (0.51 g, 94%): mp (*i*-Pr_2O) 171-173 °C; ^{1}H NMR ($CDCl_3$) *δ*=9.03 (d, *J* = 7.1 Hz, 1H), 7.73 (d, *J* = 9.1, 1H), 7.35 (ddd, *J* = 9.1, 6.7, 1.2 Hz, 1H), 7.03 (t, J_{HF} = 54.0 Hz, 1H), 6.93 (dt, *J* = 6.9, 1.2 Hz, 1H), 6.89 (s, 1H), 5.04-4.95 (m, 1H), 4.47-4.36 (m, 1H), 3.81 (br d, *J* = 1.8 Hz, 8H), 3.59-3.46 (m, 1H), 2.22-2.08 (m, 4H), 1.67-1.57 (m, 2H),

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1.46 (s, 9H), 1.35-1.26 ppm (m, 1H); ^{13}C NMR ($CDCl_3$) δ=170.3 (C), 161.8 (C), 155.8 (C), 155.4 (C), 146.0 (C), 139.4 (t, J_{CF} = 25.4 Hz, C), 126.94 (CH), 126.91 (CH), 122.3 (t, J_{CF} = 5.1 Hz, C), 118.8 (CH), 113.9 (CH), 111.2 (t, J_{CF} = 235.7 Hz, CH), 96.9 (CH), 79.6 (C), 73.8 (CH), 67.0 (CH_2), 48.9 (CH), 44.5 (CH_2), 31.1 (CH_2), 30.1 (CH_2), 28.6 ppm (CH_3); MS (APCI) *m/z*: 545.3 (MH^+).

A solution of **57** (408 mg, 0.75 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (5 mL) and the mixture was stirred at room temperature for 2 h, before being poured onto ice. Neutralization with aq. NH_3 gave *trans*-4-((6-(2-(difluoromethyl)imidazo[1,2-a]pyridin-3-yl)-2-morpholinopyrimidin-4-yl)oxy)cyclohexan-1-amine (0.33 g, 99%) as an oil: ^{1}H NMR ($CDCl_3$) δ=9.05 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.73 (dt, *J* = 9.1, 1.0, 1H), 7.03 (t, J_{HF} = 54.0 Hz, 1H), 6.93 (dt, *J* = 7.0, 1.2 Hz, 1H), 6.31 (s, 1H), 5.01 (tt, *J* = 10.7, 4.2 Hz, 1H), 3.84-3.78 (m, 8H), 2.81 (tt, *J* = 10.6, 3.9 Hz, 1H), 2.22-2.14 (m, 2H), 2.01-1.93 (m, 2H), 1.62-1.50 (m, 2H), 1.48 (br, exchangeable with D_2O, 2H), 1.35-1.23 ppm (m, 2H); MS (APCI) *m/z*: 445.2 (MH^+).

The above crude amine (0.33 g, 0.74 mmol) and dimethylglycine hydrochloride (0.114 g, 0.82 mmol) were dissolved in DMF (10 mL) containing DIPEA (0.21 g, 1.6 mmol). HATU (0.31 g, 0.81 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was diluted with water, and extracted with CH_2Cl_2. Chromatography on alumina, eluting with CH_2Cl_2/EtOAc (9:1) gave *N-(trans*-4-((6-(2-(difluoromethyl)imidazo[1,2-a]pyridin-3-yl)-2-morpholinopyrimidin-4-yl)oxy)cyclohexyl)-2-(dimethylamino)acetamide (**58**) (0.325 g, 83%): mp (*i*-Pr_2O) 188-190 °C; ^{1}H NMR ($CDCl_3$) δ=9.03 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.73 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.35 (ddd, *J* = 9.1, 6.7, 1.2 Hz, 1H), 7.10 (d, *J* = 8.42 Hz, 1H), 7.03 (t, J_{HF} = 54.0 Hz, 1H), 6.33 (s, 1H), 5.07-4.99 (m, 1H), 3.94-3.84 (m, 1H), 3.84-3.77 (m, 8H), 2.94 (s, 2H), 2.29 (s, 6H), 2.24-2.17 (m, 2H), 2.15-2.05 (m, 2H), 1.67 (dq, *J* = 12.9, 3.4 Hz, 2H), 1.47-1.36 ppm (m, 2H); ^{13}C NMR ($CDCl_3$) δ=170.3 (C), 170.0 (C), 161.8 (C), 160.6 (C), 155.8 (C), 146.0 (C), 139.4 (t, J_{CF} = 25.4 Hz, C), 126.93 (CH), 126.87 (CH), 122.3 (t, J_{CF} = 5.1 Hz, C), 118.8 (CH), 113.9 (CH), 111.2 (t, J_{CF} = 235.7 Hz, CH), 96.9 (CH), 73.7 (CH), 67.0 (CH_2), 63.4 (CH_2), 46.8 (CH), 46.1 (CH_3), 44.5 (CH_2), 30.8 (CH_2), 30.1 ppm (CH_2); HRMS (APCI): *m/z* calcd for $C_{26}H_{33}F_2N_7O_3$+H^+: 530.2697 [*M*+H^+]; found: 530.2701.

Enzyme assays

The biochemical activity of the drug compounds against the p110α, p110β, and p110δ isoforms of PI3K was determined using the PI3K (human) HTRF assay (Millipore) as previously described.[11]

Acknowledgements

The authors would like to thank Dr Adrian Blaser for NMR spectroscopy services; Wilson Sun, Sisira Kumara and Sree Sreebhavan for technical assistance; the Cancer Society Auckland / Northland and the Health Research Council of New Zealand for project funding.

Conflict of interest

The authors declare no conflict of interest.

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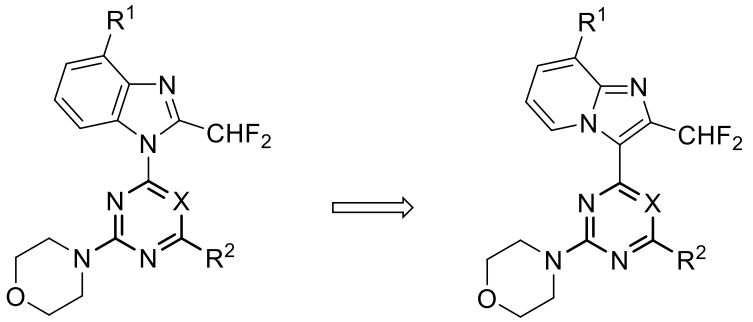

Benzimidazole PI3K Inhibitors **Imidazo[1,2-*a*]pyridine analogues**

Imidazo[1,2-*a*]pyridine analogues of the ZSTK474 (benzimidazole) class of phosphatidylinositol 3-kinase (PI3K) inhibitors were synthesized for biological evaluation using a heteroaryl Heck reaction procedure. The new compounds maintain the PI3K isoform selectivity of their benzimidazole analogues, but in general show less potency.