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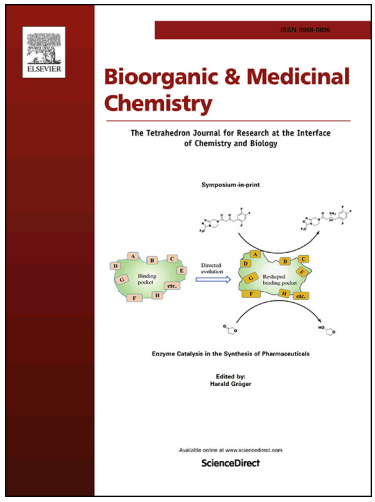

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Synthesis and biological evaluation of solubilized sulfonamide analogues of the phosphatidylinositol 3-kinase inhibitor ZSTK474

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Keywords: Phosphatidylinositol 3-kinase, PI3K, p110α, ZSTK474, SN32976

Abstract

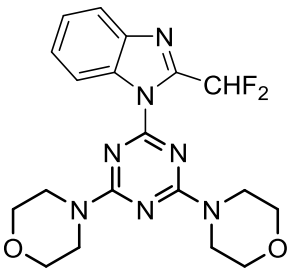
Replacing one of the morpholine groups of the phosphatidylinositol 3-kinase (PI3K) inhibitor ZSTK474 with a variety of sulfonamide-linked solubilizing substituents produced a new class of active and potent PI3Kα inhibitors, with several derivatives demonstrating high PI3Kα enzyme potency and good cellular potency in two human derived cell lines. The overall results suggest a preference for linear and somewhat flexible solubilizing functions. From this series, compound **16**, also known as SN32976, was selected for advanced preclinical evaluation.

1. Introduction

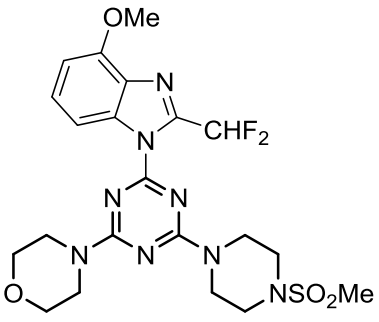
Phosphatidylinositol 3-kinases (PI3Ks) are a family of three distinct classes (I, II and

III) of lipid kinases that play key roles in cell and tissue physiology.[1-4] The three class-Ia PI3Ks (PI3Kα/β/δ) and the sole class-Ib PI3K (PI3Kγ) couple growth factor receptors and G-protein coupled receptors respectively to a wide range of downstream pathways.[5-6] These enzymes have different mechanisms of activation and different kinetic properties,[7] but all use phosphatidylinositol-4,5-bisphosphate (PIP2) to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3). The cellular levels of PIP3 are tightly controlled by phosphatases including PTEN which dephosphorylates PIP3 back to PIP2.[8,9] The importance of this pathway in cancer is highlighted by the fact that defects in both the kinase and phosphatase activities are commonly observed in tumours, and there is now increasing evidence that a high proportion of human cancers depend strongly on PI3Kα for their survival and resistance to therapy.[8-15] Selective PI3Kα inhibition also appears to be less immunosuppressive *in vivo* compared with PI3Kδ or pan-class I inhibition.[16] Therefore the targeting of PI3K, and more specifically the p110α isoform, with small molecule inhibitors has been widely explored and a number of programs to develop PI3K inhibitors are currently in progress,[5, 17-25] with two p110α-specific inhibitors in clinical trial.[26-28]

2-(Difluoromethyl)-1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]-1*H*-benzimidazole (ZSTK474) (**1**) (Fig. 1) is a potent ATP-competitive pan-class I PI3K inhibitor, with high selectivity over other classes of PI3K and protein kinases,[29-31] that demonstrated antitumour activity *in vivo* against human tumour xenografts.[29, 31] A crystal structure of ZSTK474 bound in the p110δ active site has shown that it binds in the same way as other morpholine-containing inhibitors,[32] with one of the morpholine oxygen atoms making a critical H-bond to the hinge region Val828 residue, and the benzimidazole N-3 making another H-bond to Lys779. The important CHF_2 group forms a hydrogen bond contact to Pro758 in the hydrophobic affinity pocket, while the second morpholino group adopts a somewhat twisted chair conformation and projects out of the ATP-binding pocket towards solvent. [32]



1: ZSTK474



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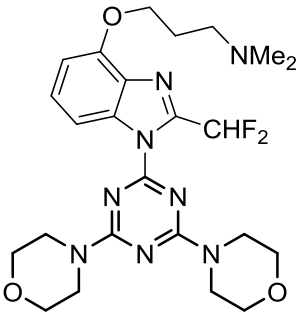


3

Fig. 1. Structures of compounds **1**-**3**.

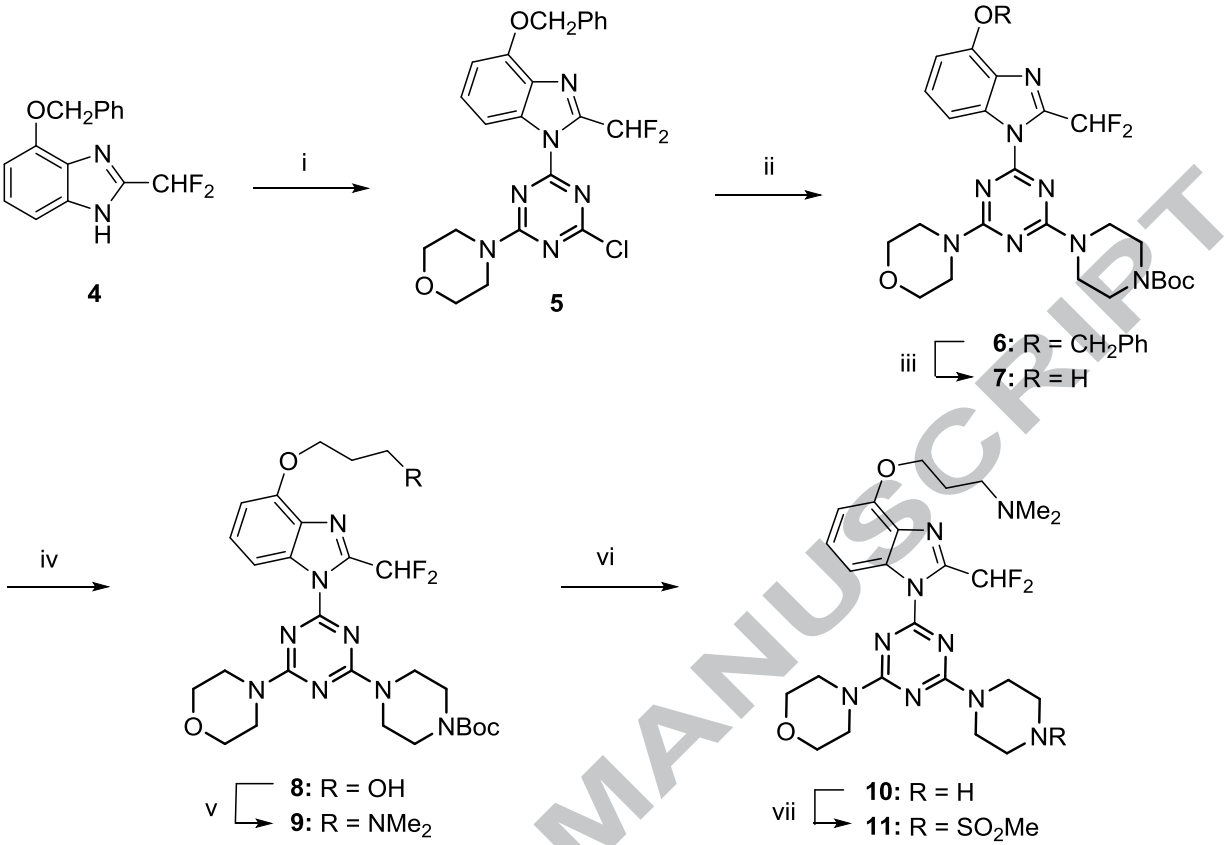
We performed a structure activity relationship (SAR) study of this compound, and showed that the addition of a methoxy group at the 4-position of the benzimidazole resulted in improved selectivity for the p110α isoform of PI3K over the other isoforms, relative to **1**.[33] Also, since only one of the morpholine substituents of **1** is involved in binding to the various p110 isoforms (Val828 in p110δ is equivalent to Val851 in p110α and Val854 in p110β), we found that the second (solvent-oriented) morpholine could be replaced by sulfonamide derivatives, such as the piperazine **2**.[34] This compound, and a number of related analogues, showed good potency against the p110α isoform of PI3K, and good selectivity over the p110β and p110δ isoforms, confirming piperazine-sulfonamide groups as good alternatives for the second morpholine of **1**.[34] It is noted that a piperazine-sulfonamide unit has also recently been incorporated in an example of a bifunctional MEK1/PI3K inhibitor that was derived from 1.[35] Unfortunately, compounds like **2** did not possess good bioavailability, due to limited aqueous solubility (similar to **1** itself), leading us to investigate more soluble derivatives.

Previously we had shown that derivatives of **1**, substituted by solubilizing groups at the 4-position of the benzimidazole, such as **3**, had good aqueous solubility, and displayed moderate *in vivo* activity in a U87MG xenograft model,[36] so we began by targeting compound **11** (Scheme 1), which represents a combination of **2** and **3**.

2. Results and discussion

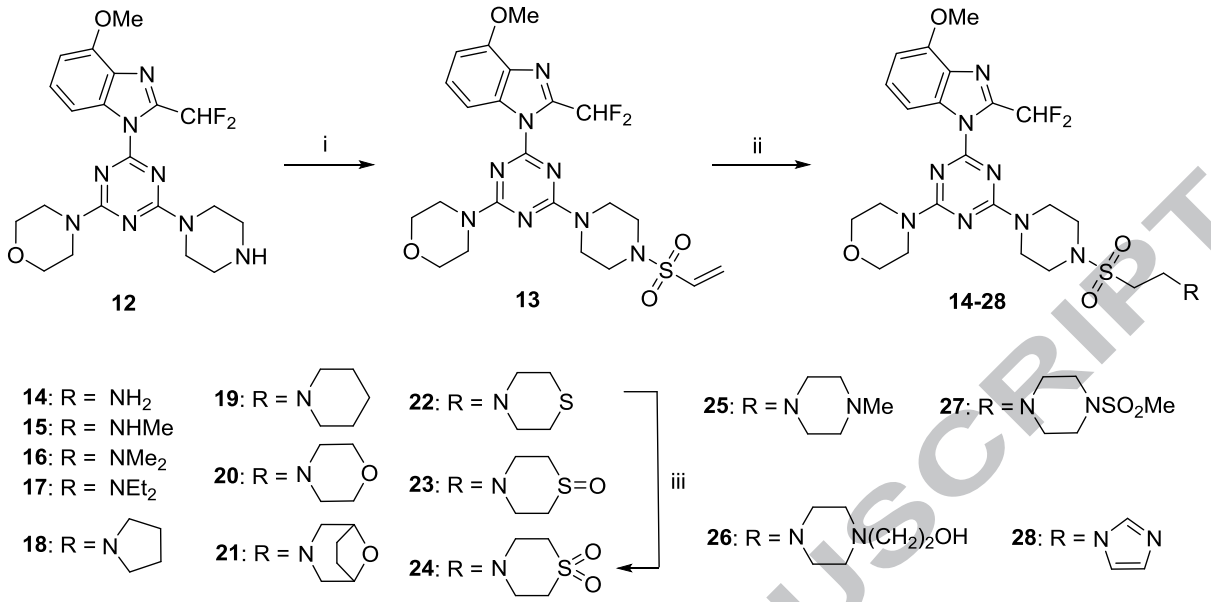
2.1. Chemistry

For the synthesis of **11** (Scheme 1), the use of a benzyl protecting group for the 4-oxygen atom of the benzimidazole was found to give superior results to the TBDMS or TIPS protecting groups that had been employed earlier.[33] Thus, reaction of **4**, readily prepared from known precursors,[37] with 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine gave **5**, which was combined with Boc-piperazine to give **6**, which was then converted to phenol **7** by hydrogenation over palladium on carbon. Successive reaction of **7** with 3-bromo-1-propanol, methanesulfonyl chloride, and aqueous dimethylamine then gave amine **9**, which was readily converted to sulfonamide **11**, by standard procedures.[34]

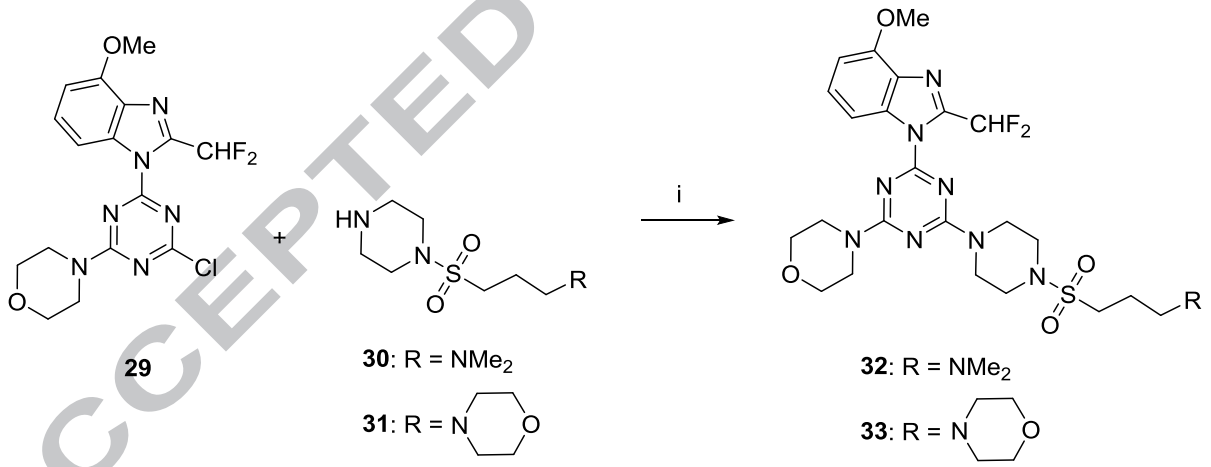


Scheme 1. Reagents and conditions: (i) 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine, K_2CO_3, acetone, rt; (ii) 4-Boc-piperazine, DIPEA, THF, rt; (iii) H_2, Pd/C, THF-MeOH; (iv) 3-bromo-1-propanol, K_2CO_3, DMF, rt; (v) MsCl, Et_3N, THF, 0 °C, then aq. Me_2NH, rt; (vi) TFA, CH_2Cl_2 rt, then aq. NH_3; (vii) MsCl, K_2CO_3, CH_2Cl_2, 0 °C then rt.

Compounds **14**-**28** (Scheme 2) and **32** and **33** (Scheme 3) represent derivatives of **2**, with the methyl group replaced by aminoalkyl substituents. Aminoethyl derivatives **14**-**28** were prepared via the vinyl sulfone **13**, prepared by reaction of piperazine **12**[34] with 2-chloroethanesulfonyl chloride. Michael addition of the appropriate amines to **13** then gave the compounds of Scheme 2, with the exception of sulfone **24**, which was prepared by $KMnO_4$ oxidation of sulfide **22**. Aminopropyl derivatives **32** and **33** were readily prepared by direct reaction of the preformed sulfonylpiperazines **30** and **31**[38] with chloride **29**[33] (Scheme 3).

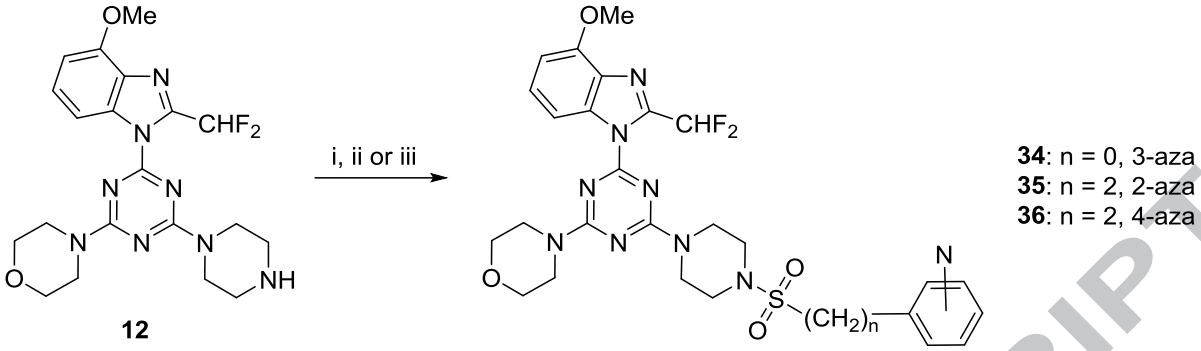


Scheme 2. Reagents and conditions: (i) $Cl(CH_2)_2SO_2Cl$, DIPEA, CH_2Cl_2, -15 °C, then 0 °C; (ii) (for **14**-**23** and **25**-**28)** RH, THF or dioxane, rt, or 80 °C, or 100 °C; (iii) (for **24**) aq. $KMnO_4$, acetone, AcOH, rt.

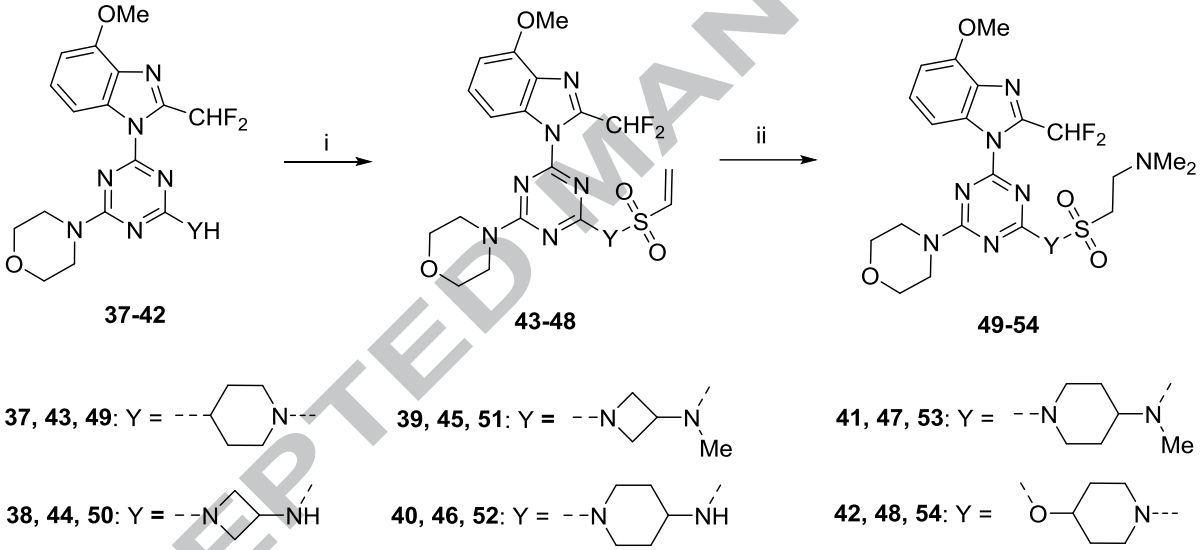


Scheme 3. Reagents and conditions: (i) DIPEA, THF or DMSO, rt.

Pyridyl-sulfonyl piperazine derivatives **34**-**36** (Scheme 4) were prepared by reaction of the appropriate sulfonyl chlorides with **12**, while heterocyclic ring variants **49**-**54** (Scheme 5) were prepared by reaction of the respective vinylsulfones with aqueous dimethylamine, using procedures similar to those of Scheme 2.



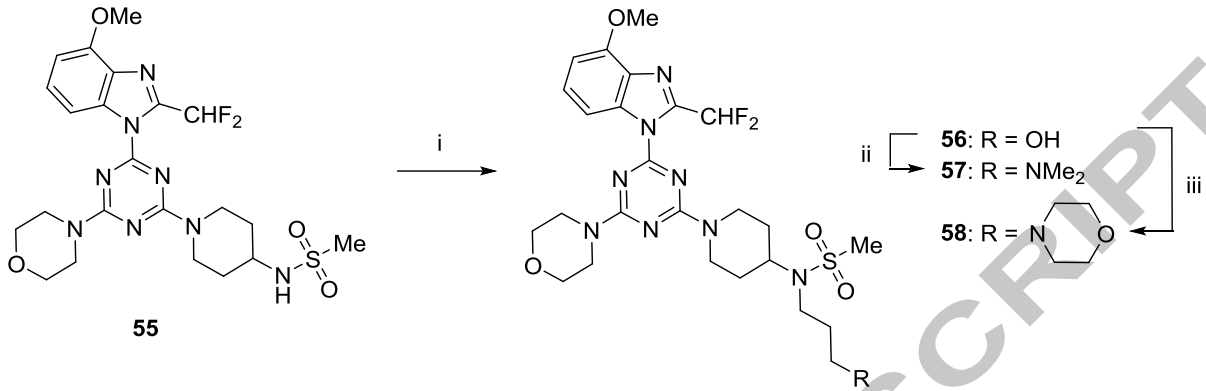
Scheme 4. Reagents and conditions: (i) (for **34**) 3-pyridinesufonyl chloride, DIPEA, CH_2Cl_2, rt; (ii) (for **35**) 2-[2-(chlorosulfonyl)ethyl]pyridine hydrochloride, DIPEA, CH_2Cl_2, rt; (iii) (for **36**) 4-[2-(chlorosulfonyl)ethyl]pyridine hydrochloride, DIPEA, CH_2Cl_2, rt.



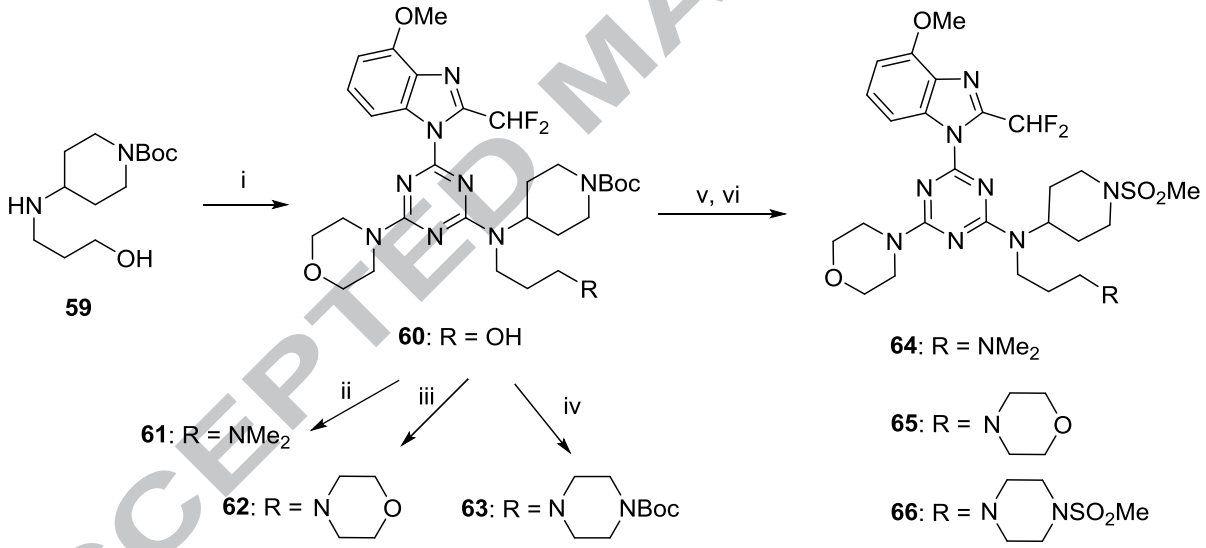
Scheme 5. Reagents and conditions: (i) $Cl(CH_2)_2SO_2Cl$, DIPEA, CH_2Cl_2, 0 °C; (ii) aq. Me_2NH, THF, rt.

The compounds of Schemes 6, 7, and 8 represent examples where a solubilizing aminopropyl substituent is attached to either the sulfonamide nitrogen (compounds **57** and **58**), or another nitrogen atom in the molecule (compounds **64**-**66**, **71** and **72**). Thus, alkylation of sulfonamide **55**[34] with 3-bromo-1-propanol gave alcohol **56**, which was then converted to products **57** and **58** via in situ reaction of a mesylate intermediate with the appropriate amines (Scheme 6). In the case of intermediates **60** and **68** (Schemes 7 and 8 respectively), the *N*-propanol substituents were introduced via preformed intermediates **59**[39] and **67**, by reaction with compound **29**. As with alcohol **56**, in situ reaction of mesylate intermediates gave amines **61**-**63**, **69** and **70**, which were then converted to the product sulfonamides **64**-**66**, **71** and **72** by

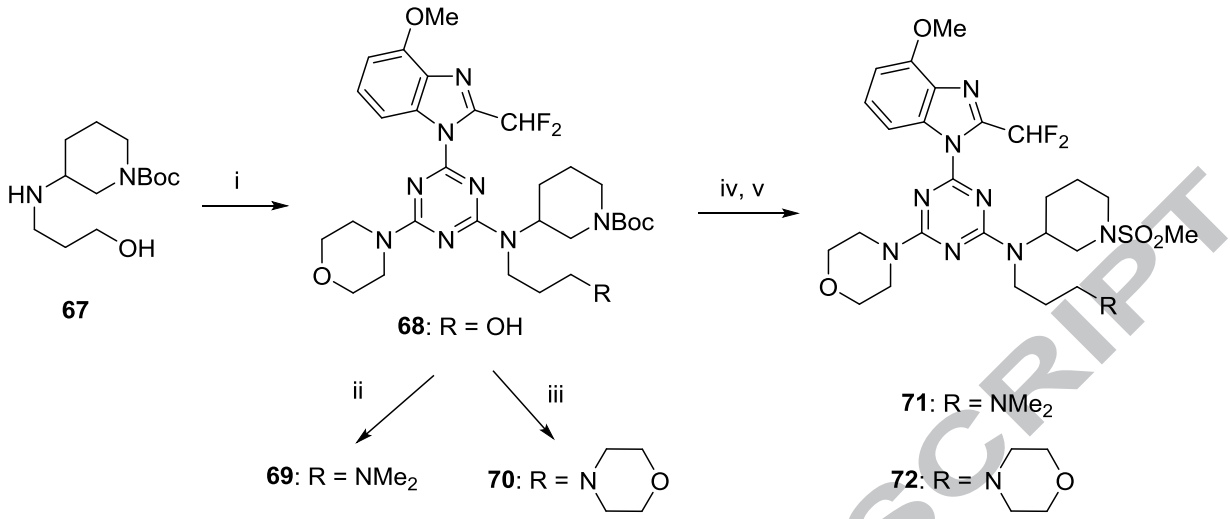
standard procedures.[34]



Scheme 6. Reagents and conditions: (i) 3-bromo-1-propanol, K_2CO_3, DMF, rt; (ii) MsCl, Et_3N, THF, 0 °C, then aq. Me_2NH, rt; (iii) MsCl, Et_3N, THF, 0 °C, then morpholine, rt.

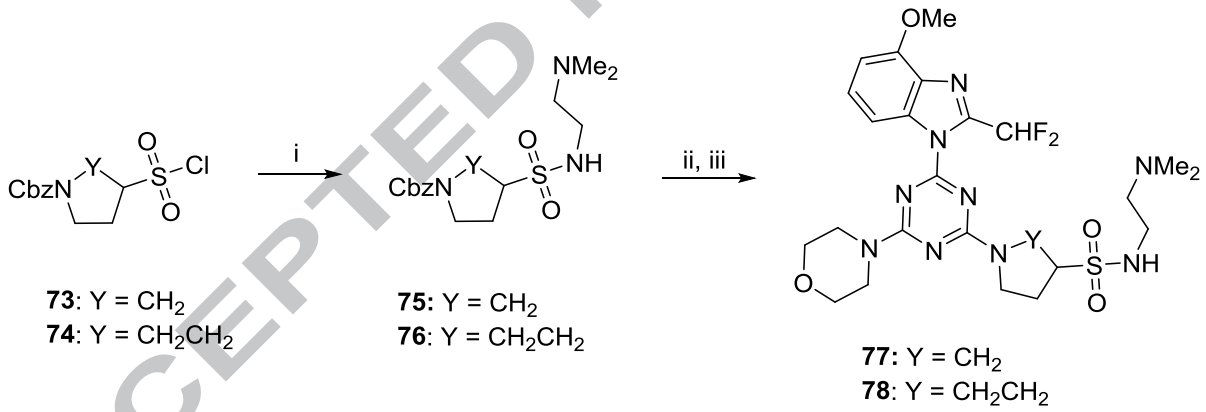


Scheme 7. Reagents and conditions: (i) **29**, DIPEA, DMF, rt; (ii) MsCl, Et_3N, THF, 0 °C, then aq. Me_2NH, rt; (iii) MsCl, Et_3N, THF, 0 °C, then morpholine, rt; (iv) MsCl, Et_3N, THF, 0 °C, then Boc-piperazine, rt. (v) TFA, CH_2Cl_2, rt, then aq NH_3; (vi) MsCl, DIPEA, CH_2Cl_2, 0 °C, then rt.



Scheme 8. Reagents and conditions: (i) **29**, DIPEA, DMF, rt; (ii) MsCl, Et_3N, THF, 0 °C, then aq. Me_2NH, rt; (iii) MsCl, Et_3N, THF, 0 °C, then morpholine, rt; (iv) TFA, CH_2Cl_2, rt, then aq NH_3; (v) MsCl, K_2CO_3, CH_2Cl_2, 0 °C, then rt.

Finally, the reversed sulfonamide derivatives **77** and **78** were prepared by reaction of preformed intermediates **75** and **76** with compound **29** (Scheme 9).



Scheme 9. Reagents and conditions: (i) $Me_2NCH_2CH_2NH_2$, CH_2Cl_2, 0 °C, then rt; (ii) H_2, Pd/C, MeOH; (iii) **29**, DIPEA, THF, rt.

For biological evaluation, the prepared compounds (Table 1) were normally converted to their hydrochloride or methanesulfonate salts, with the latter routinely displaying greater aqueous solubility. Hydrochlorides were usually sufficiently soluble with aliphatic amines, but with heterocyclic and heteroaromatic amines, methanesulfonates were preferred.

2.2 Enzyme Data

The compounds in Table 1 were tested for their inhibitory activity against the p110α,

p110β, and p110δ isoforms of PI3K using Homogeneous Time Resolved Fluorescence (HTRF) assays. Compounds were generally more selective for the p110α isoform over p110β and p110δ, and apart from compounds **11**, **51**, **53**, **57**, **71** and **72**, did not show a significant loss in p110α potency compared to the non-solubilized **2**. Since compound **11**, with the solubilizing substituent on the benzimidazole 4-position, did not show the desired p110α potency, we did not investigate this class of compound further, and all subsequent compounds contain a 4-methoxy substituent, with the solubilizing substituent being positioned elsewhere in the molecule.

Piperazine derivatives **14**-**28** and **32**-**33** showed that a variety of aliphatic amino substituents and chain lengths were acceptable, while compounds **28** and **34**-**36** showed that heteroaromatic amines were also acceptable. Compound **49** showed that removal of one of the piperazine nitrogen atoms from **16** was acceptable in terms of p110α activity, although selectivity over p110β and p110δ was significantly reduced. Compounds **50**-**54** showed that good results were achievable with heterocyclic substituents other than piperazine, although interestingly the *N*-methyl azetidine **51** and the *N*-methyl piperidine **53** were significantly less potent than the analogous des-methyl compounds **50** and **52** respectively, indicating either a favorable hydrogen bonding interaction of the sulfonamide NH for compounds **50** and **52**, or else an unfavorable conformational rigidity or steric interaction for compounds **51** and **53**.

Compounds **57** and **58** investigated moving the aminoalkyl substituent from the sulfonamide carbon to the sulfonamide nitrogen, while compounds **64**-**66**, and **71** and **72** investigated moving the aminoalkyl substituent even further, to a nitrogen atom separate from the sulfonamide group. All of these compounds were slightly less potent than the majority of the earlier compounds, with the 3-*N*-alkylated piperidines **71** and **72**, being even less potent than the isomeric 4-*N*-alkylated piperidines **57** and **58**. This is probably due to steric factors.

Finally, the pyrrolidine reversed sulfonamide **77** displayed good p110α potency while the piperidine analogue **78** was slightly less potent against p110α, but more potent against p110β and p110δ, especially when compared to the isomeric sulfonamide **52**. This is possibly due to a more favourable H-bonding arrangement for **78** in the p110β and p110δ binding sites.

2.3. Cellular Data

The compounds were evaluated in cellular assays against two early passage human cancer cell lines as described previously.[34] These were NZB5, a brain (medulloblastoma) cell

line which contains the wild-type gene for p110α, and NZOV9, a poorly differentiated ovarian (endometrioid) adenocarcinoma that is wild-type for expression of p53 protein but contains a mutant p110α enzyme with a single amino acid substitution (Y1021C) in the kinase domain leading to activation of the PI3K enzyme.

The compounds covered a broad range of IC50 values from 52 to 4,300 nM. The IC50 values for the two cell lines were highly correlated with each other ($p = 2 \times 10^{-6}$, Spearman rank test, SigmaPlot) but were nevertheless different; the IC50 ratios for the two cell lines covered a range from 0.23 to 7.2. These ratios were weakly correlated with the IC50 values for the NZB5 and NZOV9 lines ($r < 0.01$ in each case), suggesting that more potent compounds had greater selectivity for the mutant enzyme. Weak correlations were found between the IC50 values for the NZB5 and NZOV9 cell lines and that for PI3K p110δ ($p = 0.002$ and 0.005, respectively). The corresponding correlations for the p110α and p110β isoforms were not statistically significant. A striking result was the gain in potency, with both cell lines, in going from an amino substituent in compound **14**, to a methylamino substituent in compound **15**, to a dimethylamino substituent in compound **16**. This is probably related to lower hydrogen bonding for **16** leading to greater permeability into cells. Pyridyl compounds **34**–**36** displayed even better cellular potency, presumably as a result of their pKa allowing for a greater proportion of uncharged form at physiological pH, thus allowing for a faster diffusion rate into cells (greater membrane permeability), compared to the more highly charged aliphatic amines. Unfortunately this also comes at a cost of lower solubility at physiological pH.

2.4. In vivo Data

Based on the enzyme and cellular potency data, **16** (hydrochloride) was evaluated *in vivo* to investigate its anticancer efficacy in a U-87 xenograft model, alongside the equipotent but insoluble **2**, and the slightly less potent **20 (**hydrochloride), all tested at their maximum tolerated dose levels. Treatment with **16** resulted in a substantial reduction in tumor volume that was significantly different from all other treatments at the completion of dosing ($P<0.0001$ vs control and **2**, $P<0.05$ vs **20**; one-way ANOVA) (Fig. 2). **20** also significantly reduced tumor growth compared to control ($P<0.05$), while **2** had similar activity to control. All treatments were well tolerated with no greater than 2% bodyweight loss on average during the treatment period.

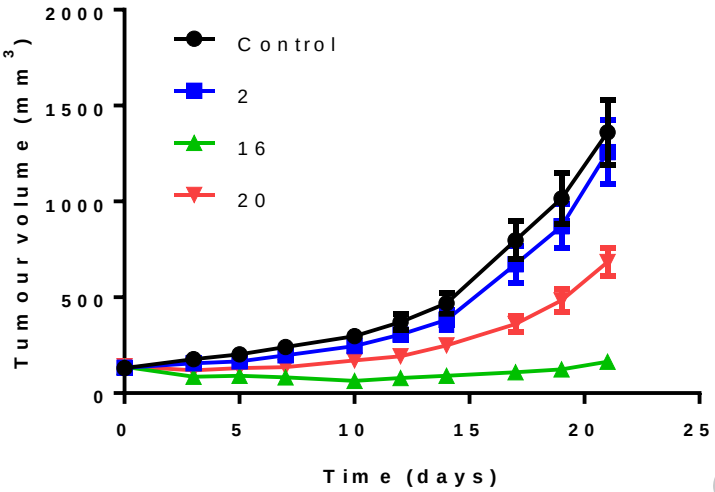


Fig. 2: *In vivo* antitumor efficacy of **2**, **16** and **20** following daily treatment at 80 mg/kg, 60 mg/kg and 80 mg/kg, respectively in a U-87 MG human glioblastoma xenograft model.

3. Conclusions

We have investigated a variety of different solubilizing positions for ZSTK474 (**1**) based sulfonamide derivatives, and identified amino substitution on the sulfonamide carbon portion of the molecule as being the most optimum. Dimethylamino substituents were superior to methylamino, or primary amino, and as an example of this type, compound **16** (SN32976) demonstrated potent biochemical, cellular and *in vivo* activity as the hydrochloride salt (aqueous solubility 24 μg/mL). On the basis of this data, **16** was selected for advanced evaluation as the more soluble methanesulfonate salt (aqueous solubility >59 μg/mL), the results of which are published elsewhere.[40] This work identified compound **15** as the major *in vivo* metabolite of **16**, while compounds **13** and **14** were also detected, although at much lower concentrations.[40]

4. Experimental

4.1. Chemistry

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. Proton NMR spectra were obtained on a Bruker Avance-400 spectrometer at 400 MHz and are referenced to Me_4Si. Low-resolution

atmospheric pressure chemical ionization (APCI) mass spectra were measured for organic solutions on a ThermoFinnigan Surveyor MSQ mass spectrometer, connected to a Gilson autosampler. High-resolution electron impact (HREIMS) and fast atom bombardment (HRFABMS) mass spectra were determined on a Varian VG-70SE mass spectrometer at nominal 5000 resolution. 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.

4.1.1. 3-[[2-(Difluoromethyl)-1-[4-[4-(methylsulfonyl)-1-piperazinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazol-4-yl]oxy]-N,N-dimethyl-1-propanamine ***(11)***

A solution of 2-benzyloxy-6-nitroaniline[37] (4.89 g, 20 mmol) in MeOH was hydrogenated over Pt on carbon at 50 psi. After filtration through celite, the methanol was removed under vacuum and the residue was dissolved in 2,2-difluoroacetic acid. The solution was heated at 70 °C for 4 h, and the solvent was removed under vacuum. The residue was treated with aq. K_2CO_3, extracted with EtOAc, and dried (Na_2SO_4). The solvent was removed, and the residue was dissolved in hot *i*-Pr_2O, decolourized with activated charcoal, and filtered through celite. Removal of the solvent gave 4-(benzyloxy)-2-(difluoromethyl)-1*H*-benzimidazole (**4**) (3.83 g, 70%): mp (*i*-Pr_2O/hexanes) 152-154 °C; ^{1}H NMR (DMSO-d_6) δ 13.42 (br s, 1H), 7.53 (br d, J = 7.3 Hz, 2H), 7.41 (br t, J = 7.3 Hz, 2H), 7.34 (br t, J = 7.3 Hz, 1H), 7.23 (t, J_{HF} = 54.2 Hz, 2H), 6.90 (br s, 1H), 5.32 (s, 2H), MS (APCI) *m/z*: 275.2 ($M+H^+$); Anal. Calcd. for $C_{15}H_{12}F_2N_2O$: C, 65.7; H, 4.4; N, 10.2; Found: C, 65.9; H, 4.4; N, 10.3%.

A mixture of **4** (1.05 g, 3.8 mmoL), 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine (0.90 g, 3.8 mmol), and powdered K_2CO_3 (2.1 g, 15 mmol.) in acetone (30 mL) was stirred at room temperature overnight. The mixture was diluted with water, and the solid was collected and washed successively with water and MeOH, to give 4-(benzyloxy)-1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1*H*-benzimidazole (**5)** (1.71 g, 95%): mp (MeOH) 233-234 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 1H), 7.51 (t, J_{HF} = 51.6 Hz, 1H), 7.50 (br d, J = 7.4 Hz, 2H), 7.37 (br t, J = 7.3 Hz, 2H), 7.33-7.28 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 5.43 (s, 2H), 4.00-3.94 (m, 4H), 3.84-3.78 (m, 4H); MS (APCI) *m/z*: 473.2 ($M+H^+$); Anal. Calcd. for $C_{22}H_{19}ClF_2N_6O_2$: C, 55.9; H, 4.05; N, 17.8; Found: C, 55.9; H, 4.0;

N, 17.8%.

Reaction of **5** (0.166 g, 0.35 mmol) with *tert*-butyl 1-piperazinecarboxylate (78 mg, 0.43 mmol) and DIPEA (68 mg, 0.53 mmol) in THF at room temperature for 2 h, followed by dilution with 1% aqueous acetic acid gave a quantitative yield of *tert*-butyl 4-[4-[4-(benzyloxy)-2-(difluoromethyl)-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]piperazine-1-carboxylate (**6),** as a white solid: mp (MeOH) 215-217 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.51 (br d, J = 7.0 Hz, 2H), 7.49 (t, J_{HF} = 53.5 Hz, 1H), 7.39-7.34(m, 5H), 6.80 (d, J = 8.0 Hz, 1H), 3.85 (m, 8H), 3.77 (m, 4H), 3.53 (m, 4H), 1.50 (s, 9H); MS (APCI) *m/z*: 623.0 ($M+H^+$); Anal. Calcd. for $C_{31}H_{36}F_2N_8O_4$: C, 59.8; H, 5.8; N, 18.0; Found: C, 59.7; H, 6.0; N, 18.0%.

Hydrogenation of **6** with 10% Pd on carbon in MeOH/THF gave a quantitative yield of *tert*-butyl 4-[4-[2-(difluoromethyl)-4-hydroxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]piperazine-1-carboxylate (**7**): mp (MeOH) 228-230 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H), 7.55 (t, J_{HF} = 53.6 Hz, 1H), 7.32 (t, J = 8.2 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.90 - 3.84 (m, 8H), 3.80 - 3.76 (m, 4H), 3.55 – 3.51 (m, 4H), 1.50 (s, 9H); MS (APCI) *m/z*: 533.3 ($M+H^+$); Anal. Calcd. for $C_{24}H_{30}F_2N_8O_4$: C, 54.1; H, 5.7; N, 21.0; Found: C, 54.15; H, 5.8; N, 21.3%.

A mixture of **7** (0.60 g, 1.1 mmol), 3-bromo-1-propanol (0.47 g, 3.3 mmol), and powdered K_2CO_3 (0.80 g, 5.5 mmol) in dry DMF (20 mL) was stirred at room temperature for 8 h. Dilution with water gave *tert*-butyl 4-[4-[2-(difluoromethyl)-4-(3-hydroxypropoxy)-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinecarboxylate (**8**) (0.66 g, 99% yield): ^{1}H NMR ($CDCl_3$) δ 7.94 (dd, J = 8.4. 0.7 Hz, 1H), 7.49 (t, J_{HF} = 53.4 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 6.92 (dd, J = 8.0, 0.6 Hz, 1H), 4.47 (t, J = 5.9 Hz, 2H), 3.98 (t, J = 5.4 Hz, 2H), 3.87 (m, 8H), 3.79 (m, 4H), 3.54 (m, 4H), 3.30 (m, exchangeable with D_2O, 1H), 2.14 (pentet, J = 5.8 Hz, 2H), 1.50 (s, 9H).

A mixture of **8** and Et_3N (0.34 g, 3.3 mmol) in THF (20 mL) was cooled to 0 °C and methanesulfonyl chloride (0.32 g, 2.8 mmol) was added dropwise. After 1 h, 40% aqueous Me_2NH (6 mL) was added, and the resulting mixture was stirred at room temperature for 36 h. The volatiles were removed under vacuum, and the residue was diluted with water, and extracted into CH_2Cl_2. Drying and removal of the solvent gave *tert*-butyl 4-[4-[2-(difluoromethyl)-4-[3-(dimethylamino)propoxy]-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinecarboxylate (**9**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.87 (dd, J = 8.4. 0.6 Hz, 1H), 7.48 (t, J_{HF} = 53.5 Hz, 1H), 7.33 (t, J = 8.2 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 4.31 (t, J = 6.7 Hz, 2H), 3.87 (m, 8H), 3.79 (m, 4H), 3.53 (m, 4H), 2.51 (t, J = 7.2 Hz,

2H), 2.26 (s, 6H), 2.13 (pentet, *J* = 7.0 Hz, 2H), 1.50 (s, 9H).

A solution of **9** in CH_2Cl_2 (10 mL) was treated with with TFA (5 mL) and the mixture was stirred at room temperature for 3 h. The solution was poured onto ice and the mixture was made basic with aq. NH_3. The organic layer was dried, and removed under vacuum to give *N*-[3-[[2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(1-piperazinyl)-1,3,5-triazin-2-yl]-1*H*-benzimidazol-4-yl]oxy)propyl]-*N*,*N*-dimethylamine (**10**) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.89 (dd, *J* = 8.4. 0.7 Hz, 1H), 7.50 (t, J_{HF} = 53.5 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.86 (m, 8H), 3.78 (m, 4H), 2.95 (m, 4H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 6H), 2.13 (pentet, *J* = 6.9 Hz, 2H).

A stirred mixture of **10 (**297 mg, 0.57 mmol) and powdered K_2CO_3 (1 g) in CH_2Cl_2 was cooled to 0 °C, and methanesulphonyl chloride (0.4 g) was added. The mixture was allowed to warm to room temperature and, after 2 h, it was diluted with water, and the organic layer was separated and dried. Chromatography on alumina, eluting first with CH_2Cl_2/EtOAc (1:1) and then with EtOAc gave **11** (200 mg, 59% yield): ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, *J* = 8.4. 0.6 Hz, 1H), 7.43 (t, J_{HF} = 53.5 Hz, 1H), 7.33 (t, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 4.02 (m, 4H), 3.88 (m, 4H), 3.78 (m, 4H), 3.33 (m, 4H), 2.81 (s, 3H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 6H), 2.14 (pentet, *J* = 7.0 Hz, 2H); MS (APCI) *m/z*: 596.0 ($M+H^+$).

Hydrochloride: mp (EtOH) 243-247 °C; ^{1}H NMR (DMSO-d_6) δ 10.26 (br s, 1H, exchangeable with D_2O), 7.92 (d, *J* = 8.3 Hz, 1H), 7.70 (t, J_{HF} = 52.8 Hz, 1H), 7.42 (t, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 4.33 (t, *J* = 6.1 Hz, 2H), 3.97-3.92 (m, 4H), 3.84-3.79 (m, 4H), 3.72-3.67 (m, 4H), 3.30-3.22 (m, 6H), 2.91 (s, 3H), 2.81 (s, 6H), 2.29-2.21 (tt, *J* = 12.2, 6.1 Hz, 2H); Anal. Calcd. for $C_{25}H_{36}ClF_2N_9O_4S{\cdot}1.5H_2O$: C, 45.6; H, 6.0; Cl, 5.4, N, 19.1; Found: C, 45.5; H, 6.1; Cl, 5.2; N, 19.2%.

*4.1.2. 2-[[4-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]sulfonyl]ethanamine (**14**)*

A mixture of 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1-piperazinyl)-1,3,5-triazin-2-yl]-1*H*-benzimidazole (**12**)[34] (1.0 g, 2.2 mmol) and DIPEA (0.72 g, 5.5 mmol) in CH_2Cl_2 (150 mL) was cooled to -15 °C and 2-chloroethanesulfonyl chloride (0.54 g, 3.3 mmol) was added dropwise over 5 min. The mixture was stirred at 0 °C for 2 h and water was added. The mixture was filtered to remove a white precipitate, and the CH_2Cl_2 solution was dried (Na_2SO_4), concentrated, and eluted on to a column of silica. Elution with CH_2Cl_2/EtOAc (9:1) gave 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-[4-

(vinylsulfonyl)-1-piperazinyl]-1,3,5-triazin-2-yl]-1*H*-benzimidazole (**13**) (0.84 g, 70% yield): mp (MeOH) 242-244 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, J = 8.4, 0.7 Hz, 1H), 7.43 (t, J_{HF} = 53.5 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.43 (dd, J = 16.6, 9.8 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 6.07 (d, J = 9.8 Hz, 1H), 4.05 (s, 3H), 4.01 (m, 4H), 3.87 (m, 4H), 3.78 (m, 4H), 3.26 (m, 4H); MS (APCI) *m/z*: 536.9 ($M+H^+$); Anal. Calcd. for $C_{22}H_{26}F_2N_8O_4S$: C, 49.25; H, 4.9; N, 20.9; Found: C, 49.1; H, 5.0; N, 20.4%.

A mixture of **13** (107 mg, 0.2 mmol) and conc. aqueous NH_3 (2 mL) in THF (20 mL) was heated at 100 °C in a sealed tube for 2 h. The solvents were removed under vacuum and the resulting residue was recrystallized from MeOH to give **14** (106 mg, 96%): mp 244-246 °C; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, J = 7.9 Hz, 1H), 7.69 (t, J_{HF} = 52.8 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 3.98 (s, 3H), 3.93-3.91 (m, 4H), 3.83-3.80 (m, 4H), 3.71-3.68 (m, 4H), 3.28-3.21 (m, 4H), 3.14 (t, J = 6.8 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H); MS (APCI) *m/z*: 553.9 ($M+H^+$); Anal. Calcd. for $C_{22}H_{29}F_2N_9O_4S.0.06CH_2Cl_2$: C, 47.4; H, 5.25; N, 22.6; Found: C, 47.3; H, 5.25; N, 22.7%.

*4.1.3. 2-[[4-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3, 5-triazin-2-yl]-1-piperazinyl]sulfonyl]-N-methylethanamine **(15)***

A mixture of compound **13** (272 mg, 0.51 mmol) and 40% aq. methylamine (5 mL) in THF (20 mL) was stirred at 20 °C for 20 h. The mixture was evaporated to dryness and the residue was chromatographed on SiO_2, eluting with CH_2Cl_2/EtOAc to give **15** (290 mg, 90%). Treatment of a methanolic solution of **15** with methanesulfonic acid gave the methanesulfonate: mp (MeOH/EtOAc) 236-239 °C; ^{1}H NMR (DMSO-d_6) δ 8.45 (br s, 2H), 7.89 (d, J = 8.04 Hz, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 3.95 (m, 4H), 3.83 (m, 4H), 3.70 (m, 4H), 3.49-3.45 (m, 2H), 3.53-3.17 (m, 5H), 2.62 (s, 3H), 2.31 (s, 3H); MS (APCI) *m/z*: 567.9 ($M+H^+$); Anal. Calcd. for $C_{24}H_{35}F_2N_9O_7S_2$: C, 43.4; H, 5.32; N, 19.0; Found: C, 43.3; H, 5.3; N, 19.3%.

*4.1.4. 2-[[4-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3, 5-triazin-2-yl]-1-piperazinyl]sulfonyl]-N,N-dimethylethanamine **(16)***

A mixture of **13** (0.536 g, 1 mmol) and 40 % aqueous dimethylamine (10 mL) in THF (200 mL) was warmed gently until a clear solution was obtained. After 15 min the THF was removed under vacuum, and the residue was diluted with water to give **16 (**0.51 g, 83 % yield): ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 8.4, 0.6 Hz, 1H), 7.45 (t, J_{HF} = 53.5 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.05 (s, 3H), 4.00 (m, 4H), 3.89 (m, 4H), 3.79 (m,

4H), 3.39 (m, 4H), 3.11 (dd, *J* = 8.1, 6.4 Hz, 2H), 2.78 (dd, *J* = 8.1, 6.4 Hz, 2H), 2.26 (s, 6H). MS (APCI) *m/z*: 582.0 ($M+H^+$).

Hydrochloride: mp (MeOH/EtOAc) 222-224 °C; Anal. Calcd. for $C_{24}H_{34}ClF_2N_9O_4S$: C, 46.6; H, 5.5; N, 20.4; Cl, 5.7; Found: C, 46.3; H, 5.7; N, 20.0; Cl, 5.7%.

Methanesulfonate: mp (MeOH/EtOAc) 211-213 °C; Anal. Calcd. for $C_{25}H_{37}F_2N_9O_7S_2$: C, 44.3; H, 5.5; N, 18.6; Found: C, 44.5; H, 5.5; N, 18.6%.

*4.1.5. 2-[[4-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]sulfonyl]-N,N-diethylethanamine (**17**)*

A mixture of **13** (107 mg, 0.2 mmol) and *N*,*N*-diethylamine (0.4 mL, 4 mmol) in THF (20 mL) was heated at 100 °C in a sealed tube for 2 h. The clear solution was cooled to room temperature and the solvent was removed under vacuum. The residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and concentrated under vacuum. Chromatography on silica, eluting with CH_2Cl_2/MeOH (100:0 to 98:2), gave **17** (54 mg, 53%).

Methanesulfonate: mp 148-151 °C; ^{1}H NMR (DMSO-d_6) δ 9.32 (br s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 3.98 (s, 3H), 3.98-3.95 (m, 4H), 3.84-3.81 (m, 4H), 3.70 (m, 4H), 3.59 (dd, *J* = 10.0, 5.5 Hz, 2H), 3.44 (m, 2H), 3.36 (m, 4H), 3.22-3.16 (m, 4H), 2.31 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 6H); MS (APCI) *m/z*: 610.0 ($M+H^+$); Anal. Calcd. for $C_{27}H_{41}F_2N_9O_7S_2 \cdot 0.4H_2O$: C, 45.5; H, 5.9; N, 17.7; Found: C, 45.5; H, 5.9; N, 17.6%.

*4.1.6. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(1-pyrrolidinyl)-ethyl]sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**18**)*

A mixture of **13** (150 mg, 0.280 mmol) and pyrrolidine (0.23 mL, 2.80 mmol) in dioxane (20 mL) was refluxed for 3 h, and the solvent was removed under vacuum. The residue was diluted with water, and the resulting precipitate was collected and dried. Chromatography on silica eluting with CH_2Cl_2/MeOH (98:2), followed by recrystallization from CH_2Cl_2/hexanes gave **18** (137 mg, 81%): mp 186-188 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.44 (t, J_{HF} = 53.5 Hz, 1H), 7.35 (t, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 4.05 (s, 3H), 3.99 (m, 4H), 3.88 (m, 4H), 3.80-3.77 (m, 4H), 3.39 (t, *J* = 5.0 Hz, 4H), 3.18-3.15 (m, 2H), 2.94-2.91 (m, 2H), 2.54-2.51 (m, 4H), 1.80-1.73 (m, 4H); MS (APCI) *m/z*: 607.9 ($M+H^+$); Anal. Calcd. for $C_{26}H_{35}F_2N_9O_4S$: C, 51.4; H, 5.8; N, 20.7; Found: C, 51.3; H, 5.9; N, 20.5%.

*4.1.7. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(1-piperidinyl)-ethyl]sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**19**)*

A mixture of **13** (150 mg, 0.280 mmol) and piperidine (0.14 mL, 1.42 mmol) in dioxane (20 mL) was refluxed for 18 h. After cooling to room temperature, the solvents were removed under vacuum. The residue was partitioned between CH_2Cl_2 and H_2O, and after drying (Na_2SO_4), the organic solvent was removed under vacuum. Chromatography on silica, eluting with CH_2Cl_2/MeOH (100:0 to 98:2) gave **19** (147 mg, 84%).

Methanesulfonate: mp 250-252 °C; ^{1}H NMR (DMSO-d_6) δ 9.21 (br s, 1H), 7.89 (d, J = 7.9, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.8, 1H), 3.98 (s, 3H), 3.96 (m, 4H), 3.84-3.81 (m, 4H), 3.70 (m, 4H), 3.59 (m, 2H), 3.51-3.43 (m, 4H), 3.35 (m, 4H), 2.97-2.89 (m, 2H), 2.31 (s, 3H), 1.84-1.81 (m, 2H), 1.70-1.54 (m, 3H), 1.38-1.29 (m, 1H); MS (APCI) *m/z*: 622.0 (M+H$^+$); Anal. Calcd. for $C_{28}H_{41}F_2N_9O_7S_2$: C, 46.85; H, 5.8; N, 17.6; Found: C, 46.85; H, 5.9; N, 17.3%.

*4.1.8. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(4-morpholinyl)-ethyl]sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**20**)*

A mixture of **13** (0.536 g, 1 mmol) and morpholine (10 mL) in THF (150 mL) was heated under reflux for 2 h. The solvent was removed under vacuum and the residue was diluted with water, to give a solid which was collected by filtration. Drying at 100 °C under vacuum gave **20 (**0.605 g, 97% yield): ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 7.9 Hz, 1H), 7.44 (t, J_{HF} = 53.5 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 4.05 (s, 3H), 4.00 (m, 4H), 3.89 (m, 4H), 3.79 (m, 4H), 3.37 (m, 4H) 3.39 (m, 4H), 3.14 (dd, J = 8.3, 6.4 Hz, 2H), 2.84 (dd, J = 8.3, 6.3 Hz, 2H), 2.48 (m, 4H); MS (APCI) *m/z*: 623.2 (M+H$^+$). Hydrochloride: mp (MeOH/EtOAc) 209-212 °C; ^{1}H NMR (DMSO-d_6) δ 11.49 (br, 1H), 7.89 (d, J = 8.08 Hz, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.88 Hz, 1H), 3.98 (s, 3H), 3.98-3.93 (m, 4H), 3.85-3.79 (m, 4H), 3.78-3.67 (m, 8H), 3.53-3.41 (m, 2H), 3.40-3.30 (m, 8H), 3.19-3.05 (m, 2H). Anal. Calcd. for $C_{26}H_{36}ClF_2N_9O_5S\cdot 1.2H_2O$: C, 45.8; H, 5.7; N, 18.5; Cl, 5.2; Found: C, 45.8; H, 5.7; N, 18.3; Cl, 5.2%.

*4.1.9. 3-[2-[[4-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]sulfonyl)ethyl]-8-oxa-3-azabicyclo[3.2.1]octane (**21**)*

A mixture of **13** (150 mg, 0.280 mmol), 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (293 mg, 1.96 mmol), and DIPEA (0.49 mL, 2.80 mmol) in dioxane was heated under reflux for 12 h. The solvent was removed under vacuum, and the residue was diluted with water.

The resulting precipitate was dissolved in CH_2Cl_2 and dried (Na_2SO_4). Chromatography on silica, eluting with CH_2Cl_2/MeOH (98:2), followed by recrystallization from CH_2Cl_2/hexanes to give **21** (118 mg, 87%): mp 219-221 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, J = 8.4, 0.5 Hz, 1H), 7.43 (t, J_{HF} = 53.5 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 4.27-4.26 (m, 2H), 4.05 (s, 3H), 4.01 (m, 4H), 3.88 (m, 4H), 3.80-3.77 (m, 4H), 3.38 (t, J = 5.0 Hz, 4H), 3.07 (dd, J = 8.1, 6.3 Hz, 2H), 2.79 (dd, J = 8.1, 6.3 Hz, 2H), 2.55 (d, J = 10.6 Hz, 2H), 2.38 (dd, J = 10.9, 2.0 Hz, 2H), 1.89-1.77 (m, 4H); MS (APCI) *m/z*: 650.0 ($M+H^+$); Anal. Calcd. for $C_{28}H_{37}F_2N_9O_5S$: C, 51.8; H, 5.7; N, 19.4; Found: C, 51.8; H, 5.9; N, 19.3%.

*4.1.10. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(4-thiomorpholin-yl)ethyl]sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**22**)*

A mixture of **13** (268 mg, 0.5 mmol), thiomorpholine (0.52 g, 5 mmol), and dioxane (30 mL) was heated under reflux for 2 h. The solvent was removed under vacuum and the residue was diluted with water. The resulting precipitate was collected, washed with water, and dried. Chromatography on silica, eluting with CH_2Cl_2/EtOAc (4:1), gave **22** (0.23 g, 72% yield): mp (CH_2Cl_2/hexanes) 210-212 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 8.3, 0.5 Hz, 1H), 7.43 (t, J_{HF} = 53.5 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 4.05 (s, 3H), 4.00 (br s, 4H), 3.89 (br s, 4H), 3.79 (m, 4H), 3.38 (t, J = 5.1 Hz, 4H), 3.11 (dd, J = 8.3, 6.1 Hz, 2H), 2.87 (dd, J = 8.3, 6.1 Hz, 2H), 2.73 (dd, J = 6.1, 3.8 Hz, 4H), 2.63 (m, 4H); MS (APCI) *m/z*: 640.3 ($M+H^+$); Anal. Calcd. for $C_{26}H_{35}F_2N_9O_4S_2 \cdot 0.5H_2O$: C, 48.1; H, 5.6; N, 19.4; Found: C, 48.2; H, 5.4; N, 19.3%.

*4.1.11. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(1-oxido-4-thiomorpholinyl)ethyl]sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**23**)*

A mixture of **13** (200 mg, 0.373 mmol), thiomorpholine 1-oxide trifluoroacetate[41] (403 mg, 1.87 mmol), and DIPEA (0.9 mL, 5.22 mmol) was refluxed in dioxane (60 mL) for 2 days. The solvent was removed under vacuum, the residue was diluted with water, and the resulting precipitate was collected and dried. Chromatography on silica, eluting with CH_2Cl_2/MeOH (95:5), followed by recrystallization from CH_2Cl_2/hexane gave **23** (138 mg, 56% yield): mp 229-231 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.43 (t, J_{HF} = 53.5 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 4.05 (s, 3H), 4.01 (m, 4H), 3.89 (m, 4H), 3.80-3.78 (m, 4H), 3.38 (t, J = 5.0 Hz, 4H), 3.19-3.10 (m, 4H), 2.99 (dd, J = 8.8, 5.4, 2H), 2.89-2.68 (m, 6H); MS (APCI) *m/z*: 655.9 ($M+H^+$); Anal. Calcd. for $C_{26}H_{35}F_2N_9O_5S_2 \cdot 0.2H_2O$: C, 47.4; H, 5.4; N, 19.1; Found: C, 47.3; H, 5.5; N, 18.7.

*4.1.12. 2-(Difluoromethyl)-1-[4-(4-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]sulfonyl]-1-piperazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-methoxy-1H-benzimidazole (**24**)*

A solution of $KMnO_4$ (88 mg, 0.559 mmol) in water (6 mL) was added dropwise to a stirred solution of **22** (170 mg, 0.266 mmol) in acetone (50 mL) and acetic acid (7.5 mL) at room temperature. After 2.5 h the reaction was diluted with water, decolourized with Na_2SO_3, and the acetone was removed under vacuum. The mixture was neutralized with conc. aq. NH_3 to give a precipitate, which was collected and dried. Chromatography on silica, eluting with CH_2Cl_2/MeOH (98.5:1.5) gave **24** (117 mg, 65% yield): mp 258-261 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 1H), 7.42 (t, J_{HF} = 53.5 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.05 (s, 3H), 4.01 (m, 4H), 3.88 (m, 4H), 3.80-3.78 (m, 4H), 3.37 (t, J = 5.0 Hz, 4H), 3.09-3.06 (m, 4H), 3.05 (s, 8H); HRMS Calcd. for $C_{26}H_{36}F_2N_9O_6S_2$: ($M+H^+$) *m/z* 672.2198; Found: *m/z* 672.2184.

*4.1.13. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-[[2-(4-methyl-1-piperazinyl)ethyl]sulfonyl]-1-piperazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**25**)*

A mixture of **13** (150 mg, 0.280 mmol) and 1-methylpiperazine (0.32 mL, 2.88 mmol) in dioxane (20 mL) was heated under reflux for 20 h. The solvent was removed under vacuum, and the residue was diluted with water, and extracted twice with CH_2Cl_2. Chromatography on silica eluting with CH_2Cl_2/MeOH (100:0 to 95:5) followed by recrystallization from CH_2Cl_2/hexanes gave **25** (116 mg, 65%).

Bismethanesulfonate: mp (MeOH/EtOAc) 198-201 °C; ^{1}H NMR (DMSO-d_6) δ 9.52 (br s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 3.98 (s, 3H), 3.94-3.92 (m, 4H), 3.83-3.81 (m, 4H), 3.70 (m, 4H), 3.44-3.18 (m, 12H), 3.05-2.97 (m, 4H), 2.79 (s, 3H), 2.35 (s, 6H); MS (APCI) *m/z*: 637.0 ($M+H^+$); Anal. Calcd. for $C_{29}H_{46}F_2N_{10}O_{10}S_3$: C, 42.0; H, 5.6; N, 16.9; Found: C, 42.3; H, 5.6; N, 16.6%.

*4.1.14. 2-[4-[2-[[4-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]sulfonyl]ethyl]-1-piperazinyl]-1-ethanol (**26**)*

A mixture of **13** (150 mg, 0.280 mmol) and *N*-(2-hydroxyethyl)piperazine (360 mg, 2.77 mmol) in 1,4-dioxane (15 mL) was refluxed for 3 h. The solvent was removed under vacuum and the residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was dried (Na_2SO_4), and the solvent was removed under vacuum. Recrystallization from CH_2Cl_2/hexanes gave **26** (134 mg, 72%).

Bismethanesulfonate: mp (MeOH/EtOAc) 236-238 °C; ^{1}H NMR (DMSO-d_6) δ 9.46 (br s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 3.98 (s, 3H), 3.95-3.92 (m, 4H), 3.83-3.81 (m, 4H), 3.73-3.70 (m 4H), 3.70-3.66 (m, 4H), 3.40-3.32 (m, 6H), 3.18 (t, J = 4.9 Hz, 4H), 3.08-2.99 (m, 4H), 2.67 (m, 2H), 2.34 (s, 6H); MS (APCI) *m/z*: 666.9 (M+H$^+$); Anal. Calcd. for $C_{30}H_{48}F_2N_{10}O_{11}S_3 \cdot 1.5H_2O$: C, 40.7; H, 5.8; N, 15.8; Found: C, 40.3; H, 5.6; N, 15.8%.

*4.1.15. 2-(Difluoromethyl)-4-methoxy-1-[4-[4-[[2-[4-(methylsulfonyl)-1-piperazinyl]ethyl]-sulfonyl]-1-piperazinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**27**)*

A mixture of **13** (0.20 g, 0.37 mmol) and 1-(methylsulfonyl)piperazine (0.31 g, 1.9 mmol) in THF (100 mL) was refluxed for 2 days. The solvent was removed under vacuum, and the residue was diluted with water to give a white solid, which was collected and dried. Chromatography on alumina eluting with CH_2Cl_2/EtOAc (9:1) gave **27 (**0.22 g, 84% yield): ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 8.4, 0.6 Hz, 1H), 7.43 (t, J_{HF} = 53.5 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 4.05 (s, 3H), 4.01 (m, 4H), 3.88 (m, 4H), 3.79 (m, 4H), 3.38 (m, 4H) 3.23 (m, 4H), 3.11 (dd, J = 8.5, 6.0 Hz, 2H), 2.92 (dd, J = 8.4, 6.0 Hz, 2H), 2.75 (s, 3H), 2.60 (m, 4H).

Methanesulfonate: mp (MeOH/EtOAc) 232-235 °C; ^{1}H NMR (DMSO-d_6) δ 9.88 (br, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.96 Hz, 1H), 3.98 (s, 3H), 3.98-3.94 (m, 4H), 3.84-3.89 (m, 4H), 3.73-3.67 (m, 4H), 3.62-3.41 (m, 12H), 3.39-3.33 (m, 4H), 2.99 (s, 3H), 2.34 (s, 3H). MS (APCI) *m/z*: 700.9 (M+H$^+$); Anal. Calcd. for $C_{28}H_{42}F_2N_{10}O_9S_3 \cdot 0.5H_2O$: C, 41.7; H, 5.4; N, 17.4; Found: C, 41.7; H, 5.3; N, 17.2%.

*4.1.16. 2-(Difluoromethyl)-1-[4-(4-[[2-(1H-imidazol-1-yl)ethyl]sulfonyl]-1-piperazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-methoxy-1H-benzimidazole (**28**)*

A mixture of **13** (150 mg, 0.280 mmol), imidazole (38 mg, 0.558 mmol), and pyridine (2 drops) in DMSO (5 mL) was heated at 135-140 °C for 5 days. The mixture was poured over ice and extracted with CH_2Cl_2. The organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. Chromatography on silica, eluting with CH_2Cl_2/MeOH (100:0 to 95:5), followed by recrystallization from CH_2Cl_2/hexanes gave **28** (45 mg, 27%): mp 188-191 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, J = 8.4, 0.6 Hz, 1H), 7.55 (s, 1H), 7.41 (t, J_{HF} = 53.5 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 7.10 (t, J = 1.0 Hz, 1H), 6.96 (t, J = 1.3 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 4.46 (t, J = 7.0 Hz, 2H), 4.05 (s, 3H), 3.94 (m, 4H), 3.87 (m, 4H), 3.79-3.77 (m,

4H), 3.35 (t, *J* = 7.1 Hz, 2H), 3.29 (m, 4H); MS (APCI) *m/z*: 604.9 ($M+H^+$); Anal. Calcd. for $C_{25}H_{30}F_2N_{10}O_4S$: C, 49.7; H, 5.0; N, 23.2; Found: C, 49.3; H, 4.9; N, 23.2%.

4.1.17. 3-[[4-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]sulfonyl]-N,N-dimethyl-1-propanamine ***(32)***

A mixture of 4-(4-chloro-6-(2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl)-1,3,5-triazin-2-yl)morpholine (**29**)[33] (150 mg, 0.378 mmol), *N*,*N*-dimethyl-3-(1-piperazinylsulfonyl)-1-propanamine dihydrochloride (**30**)[38] (151 mg, 0.491 mmol), and DIPEA (0.40 mL, 2.27 mmol) in DMSO was stirred at room temperature for 30 minutes. The reaction mixture was diluted with water; and the resulting precipitate was collected and dried. Chromatography on silica eluting with CH_2Cl_2/MeOH (95:5), followed by additional chromatography on silica eluting with CH_2Cl_2/MeOH (96:4) gave **32** (91 mg, 40%).

Hydrochloride: mp (MeOH/EtOAc) 209-211 °C; ^{1}H NMR (DMSO-d_6) δ 10.16 (br s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 3.98 (s, 3H), 3.94 (m, 4H), 3.82 (m, 4H), 3.70 (br s, 4H), 3.33 (m, 4H), 3.23 (dd, *J* = 9.3, 5.8 Hz, 2H), 3.12 (m, 2H), 2.75 (s, 6H), 2.08 (td, *J* = 15.4, 7.8 Hz, 2H); MS (APCI) *m/z*: 596.0 ($M+H^+$); Anal. Calcd. for $C_{25}H_{36}ClF_2N_9O_4S{\cdot}0.5H_2O$: C, 46.8; H, 5.8; N, 19.7; Found: C, 46.9; H, 5.8; N, 19.4%.

4.1.18. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[3-(4-morpholinyl)propyl]-sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole ***(33)***

A mixture of **29** (150 mg, 0.378 mmol), 4-[3-(1-piperazinylsulfonyl)propyl]morpholine dihydrochloride (**31**)[38] (172 mg, 0.491 mmol) and DIPEA (0.40 mL, 2.27 mmol) in THF was stirred at room temperature for 17 h. The solvent was removed under vacuum, and the residue was diluted with water and extracted with CH_2Cl_2. Chromatography on silica, eluting with CH_2Cl_2/MeOH (98:2) followed by recrystallization from CH_2Cl_2/hexanes gave **33** (188 mg, 78%).

Methanesulfonate: mp (MeOH/EtOAc) 216-218 °C; ^{1}H NMR (DMSO-d_6) δ 9.50 (br s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.01-3.93 (m, 6H), 3.98 (s, 3H), 3.82 (m, 4H), 3.70 (m, 4H), 3.63 (t, *J* = 12.1 Hz, 2H), 3.45 (d, *J* = 12.6 Hz, 2H), 3.32 (m, 4H), 3.21 (t, *J* = 7.1 Hz, 4H), 3.13-3.06 (m, 2H), 2.30 (s, 3H), 2.14-2.06 (m, 2H); MS (APCI) *m/z*: 638.0 ($M+H^+$); Anal. Calcd for $C_{28}H_{41}F_2N_9O_8S_2$: C, 45.8; H, 5.6; N, 17.2; Found: C, 45.7; H, 5.6; N, 17.2%.

*4.1.19. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-[4-(3-pyridinylsulfonyl)-1-piperazinyl]-1,3,5-triazin-2-yl]-1H-benzimidazole (**34**)*

DIPEA (0.78 mL, 4.48 mmol) was added to a mixture of **12** (200 mg, 0.449 mmol) and 3-pyridinesulfonyl chloride (159 mg, 0.859 mmol) in CH_2Cl_2 (12 mL), and the reaction mixture was stirred at room temperature overnight under nitrogen. Water was added, and the organic phase was separated and dried (Na_2SO_4). Chromatography on silica, eluting with CH_2Cl_2/MeOH (99:1) gave **34** (227 mg, 86%).

Methanesulfonate: mp (MeOH/EtOAc) 243-246 °C; ^{1}H NMR (DMSO-d_6) δ 8.94 (dd, J = 2.2, 0.5 Hz, 1H), 8.88 (dd, J = 4.8, 1.6 Hz, 1H), 8.19 (ddd, J = 8.1, 2.3, 1.7 Hz, 1H), 7.84 (dd, J = 8.4, 0.4 Hz, 1H), 7.68 (ddd, J = 8.1, 4.8, 0.7 Hz, 1H), 7.63 (t, J_{HF} = 52.8 Hz, 1H), 7.39 (t, J = 8.2 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 3.96 (s, 3H), 3.94-3.92 (m, 4H), 3.78-3.76 (m, 4H), 3.66 (m, 4H), 3.11 (m, 4H), 2.33 (s, 3H); MS (APCI) *m/z*: 587.9 ($M+H^+$); Anal. Calcd, for $C_{26}H_{31}F_2N_9O_7S_2$: C, 45.7; H, 4.6; N, 18.4; Found: C, 45.6; H, 4.6; N, 18.3%.

*4.1.20. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(2-pyridinyl)ethyl]-sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**35**)*

DIPEA (0.29 mL, 1.66 mmol) was added to a suspension of **12** (150 mg, 0.336 mmol) and 2-[2-(chlorosulfonyl)ethyl]pyridine hydrochloride (165 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) at room temperature under nitrogen, and the mixture was stirred for 24 h. Water was added and the and the organic phase was separated and dried (Na_2SO_4). Chromatography on silica, eluting with CH_2Cl_2/MeOH (100:0 to 98.5:1.5), gave **35** (148 mg, 71%).

Methanesulfonate: mp (MeOH/EtOAc) 154-157°C; ^{1}H NMR (DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 1H), 8.07 (t, J = 6.9 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.67-7.52 (m, 2H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 3.98 (s, 3H), 3.92-3.90 (m, 4H), 3.83-3.80 (m, 4H), 3.70 (m, 4H), 3.59 (dd, J = 9.0, 6.7 Hz, 2H), 3.30-3.27 (m, 6H), 2.31 (s, 3H); MS (APCI) *m/z*: 615.9 ($M+H^+$); Anal. Calcd. for $C_{28}H_{35}F_2N_9O_7S_2 \cdot 0.7H_2O$: C, 46.4; H, 5.1; N, 17.4; Found: C, 46.4; H, 5.2; N, 17.6%.

*4.1.21. 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-[[2-(4-pyridinyl)ethyl]-sulfonyl]-1-piperazinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (**36**)*

DIPEA (0.29 mL, 1.66 mmol) was added to a suspension of **12** (150 mg, 0.336 mmol) and 4-[2-(chlorosulfonyl)ethyl]pyridine hydrochloride (165 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) at room temperature under nitrogen, and the mixture was stirred for 24 h. Water was added, and the organic phase was separated and dried (Na_2SO_4). Chromatography on silica

eluting with CH_2Cl_2/MeOH (100:0 to 98:2) followed by recrystallization from CH_2Cl_2/MeOH gave **36** (134 mg, 65%).

Methanesulfonate: mp (MeOH/EtOAc) 290-293 °C; ^{1}H NMR (DMSO-d_6) δ 8.76 (dd, J = 5.4, 1.1 Hz, 2H), 7.89-7.87 (m, 3H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 3.98 (s, 3H), 3.94-3.91 (m, 4H), 3.83-3.81 (m, 4H), 3.70 (m, 4H), 3.59 (dd, J = 8.8, 6.8 Hz, 2H), 3.30-3.23 (m, 6H), 2.31 (s, 3H); MS (APCI) *m/z*: 615.9 ($M+H^+$); Anal. Calcd. for $C_{28}H_{35}F_2N_9O_7S_2$: C, 47.25; H, 5.0; N, 17.7; Found: C, 47.1; H, 5.0; N, 17.6%.

*4.1.22. 2-[[4-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1, 3,5-triazin-2-yl]-1-piperidinyl]sulfonyl]-N,N-dimethylethanamine (**49**)*

To a mixture of 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-piperidinyl)-1,3,5-triazin-2-yl]-1*H*-benzimidazole (**37**)[34] (0.891 mg, 2 mmol) and DIPEA (0.77 g, 6 mmol) in CH_2Cl_2 (100 mL) was added dropwise 2-chloroethanesulfonyl chloride (0.49 g, 3 mmol) at 0 °C, and the reaction mixture was stirred at that temperature for an additional 2 h. The reaction mixture was quenched with water (100 mL), and the organic layer was washed successively with aq. HOAc (1%, 100 mL) and aqueous NH_3, and dried. Chromatography on silica eluting with CH_2Cl_2/EtOAc (9:1) gave 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-[1-(vinylsulfonyl)-4-piperidinyl]-1,3,5-triazin-2-yl]-1*H*-benzimidazole (**43**) (0.589 g, 55% yield): mp (MeOH) 229-232 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (dd, J = 8.4, 0.7 Hz, 1H), 7.54 (t, J_{HF} = 53.6 Hz, 1H), 7.39 (t, J = 8.3 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.47 (dd, J = 16.6, 9.9 Hz, 1H), 6.27 (d, J = 16.6 Hz, 1H), 6.05 (d, J = 9.9 Hz, 1H), 4.06 (s, 3H), 4.00-3.97 (m, 4H), 3.89-3.79 (m, 6H), 2.78 (m, 3H), 2.17 (br dd, J = 13.6, 3.0 Hz, 2H), 2.01 (ddd, J = 25.2, 11.7, 4.1 Hz, 2H); MS (APCI) *m/z*: 536.2 ($M+H^+$); Anal. Calcd. for $C_{23}H_{27}F_2N_7O_4S$: C, 51.6; H, 5.1; N, 18.3; Found: C, 51.7; H, 5.2; N, 18.25%.

A mixture of **43** (59 mg, 0.11 mmol) and 40% aqueous dimethylamine (5 mL) in THF (25 mL) was stirred at room temperature for 15 min. The solvent was removed under vacuum and the residue was diluted with water, to give **49 (**63 mg, 99% yield): ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 7.9 Hz, 1H), 7.55 (t, J_{HF} = 53.6 Hz, 1H), 7.39 (t, J = 8.3 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 4.06 (s, 3H), 4.02 - 3.89 (m, 6H), 3.85 - 3.78 (m, 4H), 3.14-3.11 (m, 2H), 2.97 (dt, J = 12.2, 2.6 Hz, 2H), 2.84-2.77 (m, 3H), 2.28 (s, 6H), 2.17 (br dd, J = 13.2, 2.6 Hz, 2H), 2.00 (ddd, J = 25.1, 11.8, 4.1 Hz, 2H).

Hydrochloride: mp (MeOH/EtOAc) 243-245 °C; MS (APCI) *m/z*: 580.9 ($M+H^+$); Anal. Calcd. for $C_{25}H_{35}ClF_2N_8O_4S$: C, 48.7; H, 5.7; N, 18.2; Cl, 5.7; Found: C, 48.7; H,5.7; N,

18.0; Cl, 5.7%.

*4.1.23. N-[1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinyl]-2-(dimethylamino)ethanesulfonamide (**50**)*

To a solution of 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinamine (**38**)[34] (1.04 g, 2.42 mmol) and DIPEA (0.85 mL, 9.7 mmol) in CH_2Cl_2 (30 mL) at -10 °C was added 2-chloroethanesulfonyl chloride (0.5 mL, excess). The stirred mixture was allowed to warm to 20 °C and then diluted with water. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic fractions were washed with aq. HOAc and then with aq. K_2CO_3, and dried (Na_2SO_4). Evaporation of the solvents and the chromatography of the residue on SiO_2, eluting with CH_2Cl_2/EtOAc (0-30%) gave *N*-[1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinyl]ethenesulfonamide (**44**) (123 mg, 9.7% yield): mp (CH_2Cl_2/MeOH) 250-252 °C; ^{1}H NMR (DMSO-d_6) δ 8.20 (br, 1H), 7.96 (dd, J = 7.9, 0.6 Hz, 1H), 7.72 (t, J_{HF} = 53.0 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.82 (dd, J = 16.5, 10.0 Hz, 1H), 6.08 (dd, J = 26.8, 13.2 Hz, 2H), 4.47 (t, J = 7.6 Hz, 1H), 4.37 (t, J = 8.1 Hz, 1H), 4.26-4.20 (m, 1H), 4.04-3.97 (m, 2H), 3.97 (s, 3H), 3.80-3.77 (m, 4H), 3.68 (m, 4H); MS (APCI) *m/z*: 523.2 ($M+H^+$); Anal. Calcd. for $C_{21}H_{24}F_2N_8O_4S$; C, 48.3; H, 4.6; N, 21.4; Found: C, 48.4; H, 4.7; N, 21.6%.

A mixture of **44** (110 mg, 0.21 mmol) and 40% aqueous dimethylamine (3 mL) in THF (15 mL) was stirred overnight at 20 °C. The reaction mixture was evaporated to dryness and the residue was triturated with water to give **50 (**112 mg, 93% yield).

Hydrochloride: mp (MeOH) 214-216 °C; ^{1}H NMR (DMSO-d_6) δ 10.25 (br s, 1H, exchangeable with D_2O), 8.45 (d, J = 7.40 Hz, 1H), 7.98 (d, J = 8.41 Hz, 1H), 7.74 (t, J_{HF} = 53.0 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 4.55-4.36 (m, 3H), 4.15-4.00 (m, 2H), 3.97 (s, 3H), 3.97-3.98 (m, 4H), 3.69 (m, 4H), 3.62-3.59 (m, 2H), 3.41-3.38 (m, 2H), 2.80 (s, 6H); MS (APCI) *m/z*: 568.0 ($M+H^+$); Anal. Calcd. for $C_{23}H_{32}ClF_2N_9O_4S\cdot 0.25H_2O$: C, 45.4; H, 5.4; Cl, 6.2; N, 20.7; Found: C, 45.4; H, 5.2; Cl; 6.0; N, 20.8%.

*4.1.24. N-[1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinyl]-2-(dimethylamino)-N-methylethanesulfonamide (**51**)*

To a solution of of *tert*-butyl 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-

1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinylcarbamate[34] (842 mg, 1.58 mmol) in DMF (5 mL) at 0 °C was added NaH (76 mg, 3.17 mmol), and the mixture was stirred for 30 min. MeI (0.5 mL, excess) was added and the mixture was stirred for an additional 1h, before being diluted with water. The resulting precipitate was collected by filtration, washed with water and dried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-15%) gave *tert*-butyl 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinyl(methyl)carbamate (823 mg, 95%): mp (CH_2Cl_2/MeOH) 186-188 °C; ^{1}H NMR (DMSO-d_6) δ 8.00 (d, J = 8.3 Hz, 1H), 7.75 (t, J_{HF} = 53.0 Hz, 1H), 7.39 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.88 (br, 1H), 4.40-4.15 (m, 4H), 3.97 (s, 3H), 3.80-3.78 (m, 4H), 3.69 (m, 4H), 2.89 (s, 3H), 1.41 (s, 9H); Anal. Calcd. for $C_{25}H_{32}F_2N_8O_4$: C, 54.9; H, 5.9; N, 20.5; Found: C, 55.1; H, 5.9; N, 20.6%.

A solution of the above carbamate (760 mg, 1.39 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (10 mL) and stirred at 20 °C for 1h. The solvent and excess TFA were remoced under vacuum, and the resulting residue was stirred with aq NH_3. The solid was collected by filtration, washed with water, and dried, to give 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-*N*-methyl-3-azetidinamine (**39**) in 96% yield: mp (CH_2Cl_2/hexanes) 199-201°C; ^{1}H NMR (DMSO-d_6) δ 7.99 (dd, J = 8.4, 0.5 Hz, 1H), 7.75 (t, J_{HF} = 53.1Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.30-4.20 (m, 2H), 3.97 (s, 3H), 3.89-3.85 (m, 1H), 3.80-3.77 (m, 5H), 3.70-3.68 (m, 4H), 3.64-3.58 (m, 1H), 2.26 (s, 3H).

To a solution of **39** (580 mg, 1.3 mmol) and DIPEA (0.8 mL) in CH_2Cl_2 (10 mL) at -10 °C was added 2-chloroethanesulfonyl chloride (0.6 mL, excess) and the reaction mixture was stirred for an additional 1h, with warming to 20 °C. Dilution with water, and removal of the CH_2Cl_2 gave a soild which was collected by filtration, washed with water, and died. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-12.5%) gave *N*-[1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-azetidinyl]-*N*-methylethenesulfonamide (**45**) (305 mg, 44%): mp (CH_2Cl_2/MeOH) 244-246 °C; ^{1}H NMR (DMSO-d_6) δ 7.98 (d, J = 8.4 Hz, 1H), 7.74 (t, J_{HF} = 53.0 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.86 (dd, J = 16.5, 10.0 Hz, 1H), 6.17 (dd, J = 13.2, 7.7 Hz, 2H), 4.74-4.67 (m, 1H), 4,22-4.20 (m, 4H), 3.98 (s, 3H), 3.80-3.78 (m, 4H), 3.68 (m, 4H), 2.86 (s, 3H); MS (APCI) *m/z*: 537.2 ($M+H^+$); Anal. Calcd. for $C_{22}H_{26}F_2N_8O_4S$: C, 49.3; H, 4.9; N, 20.9; Found: C, 49.3; H, 4.9; 20.9%.

To a suspension of **45** (280 mg, 0.52 mmol) in THF (20 mL) was added 40% aqueous dimethylamine (5 mL) and the mixture was heated at 70 °C for 1h, and cooled to 20 °C. The

volatiles were removed, and the residue was diluted with water. The resulting precipitate was collected by filtration, washed with water and dried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-20%) gave **51** (309 mg, 88%).

Methanesulfonate: mp (CH_2Cl_2/MeOH/EtOAc) 239-242°C; ^{1}H NMR (DMSO-d_6) δ 9.44 (br, 1H, exchangeable with D_2O), 7.99 (dd, J = 8.4, 0.5 Hz, 1H), 7.75 (t, J_{HF} = 53.0 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 7.7 Hz, 1H), 4.88-4.81 (m, 1H), 4.49-4.29 (m, 4H), 3.98 (s, 3H), 3.82-3.79 (m, 4H), 3.69 (m, 4H), 3.60-3.56 (m, 2H), 3.46-3.43 (m, 2H), 3.01 (s, 3H), 2.86 (s, 6H), 2.30 (s, 3H); MS (APCI) *m/z*: 581.9 ($M+H^+$); Anal. Calcd. for $C_{25}H_{37}F_2N_9O_7S_2 \cdot 0.75H_2O$: C, 43.4; H, 5.6; N, 18.2; Found: C, 43.4; H, 5.5; N, 17.9%.

*4.1.25. N-[1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]-2-(dimethylamino)ethanesulfonamide (**52**)*

Reaction of 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinamine (**40**)[34] with 2-chloroethanesulfonyl chloride, as in previous examples, gave *N*-[1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]ethenesulfonamide (**46**) in 42% yield: mp (CH_2Cl_2/MeOH) 221-224 °C; ^{1}H NMR (DMSO-d_6) δ 7.87 (dd, J = 7.9, 0.6 Hz, 1H), 7.68 (t, J_{HF} = 52.9 Hz, 1H), 7.45 (br s, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.79 (dd, J = 16.5, 9.9 Hz, 1H), 6.07 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.46 (t, J = 17.0 Hz, 1H), 9.98 (s, 3H), 3.81-3.78 (m, 4H), 3.70-3.69 (m, 4H), 3.41-3.32 (m, 4H), 1.92 (br s, 2H), 1.44-1.42 (m, 2H); MS (APCI) *m/z*: 551.2 ($M+H^+$); Anal. Calcd. for $C_{23}H_{28}F_2N_8O_4S$: C, 50.2; H, 5.1; N, 20.3; Found: C, 50.3; H, 5.1; N, 20.5%.

A solution of **46** (251 mg, 0.46 mmol) in THF (15 mL) was treated with 40% aqueous dimethylamine (5 mL, excess) and the mixture was stirred at 20 °C for 1 h. After dilution with water the volatiles were removed, and the resulting precipitate was collected, washed with water, and dried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-20%), then CH_2Cl_2/MeOH (3%) gave **52** (188 mg, 65%).

Hydrochloride: mp (MeOH) 236-239 °C; ^{1}H NMR (DMSO-d_6) δ 10.31 (br s, 1H), 7.88 (dd, J = 8.4, 0.4 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.52 (t, J = 16.8 Hz, 2H), 3.98 (s, 3H), 3.82-3.79 (m, 4H), 3.71-3.69 (m, 4H), 3.62-3.49 (m, 3H), 3.40-3.36 (m, 2H), 3.25-3.24 (m, 2H), 2.81 (s, 6H), 2.00 (br, 2H), 1.50-1.45 (m, 2H); MS (APCI) *m/z*: 596.0 ($M+H^+$); Anal. Calcd. for $C_{21}H_{36}ClF_2N_9O_4S$: C, 47.5; H, 5.7; N. 19.9; Cl, 5.6; Found: C, 47.6; H, 5.8; N, 20.1; Cl, 5.9%.

*4.1.26. N-[1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]-2-(dimethylamino)-N-methylethanesulfonamide (**53**)*

A mixture of **29** (873 mg, 2.2 mmol), *tert*-butyl methyl(4-piperidinyl)carbamate (566 mg, 2.64 mmol), and DIPEA (1.1 mL, 4.2 mmol) in THF (25 mL) was stirred at 20 °C for 20 h. The solvent was removed under vacuum and the residue was stirred in aq. HOAc, resulting in a precipitate which was collected, washed with water, and dried. Recrystallization from CH_2Cl_2/MeOH gave *tert*-butyl 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl(methyl)carbamate (1.18 g, 93%): mp (CH_2Cl_2/MeOH) 182-184 °C; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, J = 7.9 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.83-4.72 (m, 2H), 4.09 (br, 1H), 3,98 (s, 3H), 3.81-3.79 (m, 4H), 3,70-3.69 (m, 4H), 3.07-2.93 (m, 2H), 2.66 (s, 3H), 1.66 (m, 4H), 1.41 (s, 9H); Anal. Calcd. for $C_{27}H_{36}F_2N_8O_4$: C, 56.4; H, 6.3; N, 19.7; Found: C, 56.6; H, 6.3; N, 19.8%.

A solution of the above carbamate (1.1 g, 1.91 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (10 mL) and stirred for 2 h. The reaction mixture was carefully poured into a mixture of ice/aq NH_3, and stirred for 10 min. The organic layer was separated, washed with water, and dried (Na_2SO_4), to give 1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-*N*-methyl-4-piperidinamine (**41**) (677 mg, 65%) in 96% yield: ^{1}H NMR (DMSO-d_6) δ 7.89 (dd, J = 8.3, 0.5 Hz, 1H), 7.68 (t, J_{HF} = 52.9 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 4.42 (t, J = 14.2 Hz, 1H), 3.98 (s, 3H), 3.80-3.78 (m, 4H), 3.70-3.69 (m, 4H), 3.36-3.18 (m, 2H), 2.62-2.54 (m, 1H), 2.30 (s, 3H),1.89 (br, 2H), 1.64 (br, 1H), 1.24 (br, 2H).

A solution of **41** (875 mg, 1.84 mmol) and DIPEA (0.64 mL, 3.68 mmol) in CH_2Cl_2 (30 mL) at -10°C was treated with chloroethanesulfonyl chloride (1 mL, excess). The reaction mixture was stirred for 1h, and allowed to warm to 20 °C. After dilution with water (50 mL), the organic layer was seperated, and the aq layer was futher extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4), and the solvent was removed. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-10%) gave *N*-[1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]-*N*-methylethenesulfonamide (**47**) (677 mg, 65%): mp (CH_2Cl_2/MeOH) 223-225 °C; ^{1}H NMR (DMSO-d_6) δ 7.88 (d, J = 8.0 Hz, 1H), 7.68 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.85 (dd, J = 16.4, 10.0 Hz, 1H), 6.07 (dd, J = 15.2, 13.2 Hz, 2H), 4.82-4.70 (m, 2H), 3.98 (s, 3H), 3.95-3.88 (m, 1H), 3.81-3.79 (m, 4H), 3.70-3.69 (m, 4H), 3.10-2.97 (m, 2H), 2.62 (s, 3H), 1.72 (m, 4H); MS

(APCI) *m/z*: 565.2 ($M+H^+$); Anal. Calcd. for $C_{24}H_{30}F_2N_8O_4S$: C, 51.1; H, 5.4; N, 19.9; Found: C, 50.8; H, 5.3; N, 19.9%.

A solution of **47** (336 mg, 0.59 mmol) in THF (15 mL) was treated with 40% aqueous dimethylamine (5 mL, excess) and the reaction mixture was stirred for 2h at 20 °C. The volatiles were removed, and the resulting precipitate was collected, washed with water, and diried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-20%), followed by CH_2Cl_2/MeOH (3%) gave **53** (356 mg, 93%).

Hydrochloride: mp (MeOH) 242-245 °C; ^{1}H NMR (DMSO-d_6) δ 10.47 (br, 1H, N^+H), 7.89 (d, J = 8.0 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.84-4.74 (m, 2H), 3.98 (s, 3H), 3.98-3.91 (m, 1H), 3.82-3.80 (m, 4H), 3.70-3.63 (m, 6H), 3.40-3.36 (m, 2H), 3.14-3.00 (m, 2H), 2.81(s. 6H), 2.75 (s, 3H), 1.78 (m, 4H); MS (APCI) *m/z*: 610.0 ($M+H^+$); Anal. Calcd. for $C_{26}H_{38}ClF_2N_9O_4S{\cdot}0.25H_2O$: C, 48.0; H, 6.0; Cl, 5.5; N, 19.4; Found: C; 48.0; H, 6.1; Cl. 5.7; N, 19.5%.

*4.1.27. 2-[[4-[[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]oxy]-1-piperidinyl]sulfonyl]-N,N-dimethylethanamine (**54**)*

To a solution of 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(4-piperidinyloxy)-1,3,5-triazin-2-yl]-1*H*-benzimidazole (**42**)[34] (1.52 g, 3.29 mmol) and DIPEA (2.3 ml, 4 eq.) in CH_2Cl_2 (30 mL) at 0 °C was added 2-chloroethanesulfonyl chloride (1 mL, excess). The reaction mixture was stirred at 20 °C for 20 h and diluted with water (50 mL). The organic fraction was washed successively with aq. HOAc, aq. K_2CO_3, and water, and dried ($MgSO_4$). Chromatography on silica, eluting with CH_2Cl_2/EtOAc (9:1) gave 2-(difluoromethyl)-4-methoxy-1-(4-(4-morpholinyl)-6-[[1-(vinylsulfonyl)-4-piperidinyl]oxy]-1,3,5-triazin-2-yl)-1*H*-benzimidazole (**48**) (1.17 g, 65% yield): mp (CH_2Cl_2/MeOH) 266-269 °C; ^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 7.9 Hz, 1H), 7.70 (t, J_{HF} = 52.8 Hz, 1H), 7.44 (t, J = 8.2 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.88 (dd, J = 16.5, 10.0 Hz, 1H), 6.19 (d, J = 10.0 Hz, 1H), 6.15 (d, J = 16.5 Hz, 1H), 5.26-5.20 (m, 1H), 3.98 (s, 3H), 3.84 (m, 4H), 3.74-3.32 (m, 4H), 3.39-3.32 (m, 2H), 3.14-3.08 (m, 2H), 2.14-2.09 (m, 2H), 1.90-1.18 (m, 2H); Anal. Calcd. for $C_{23}H_{27}F_2N_7O_5S{\cdot}0.5CH_2Cl_2$: C, 47.7; H, 4.7; N, 16.5; Found: C, 47.8; H, 4.7; N, 16.8%.

To a suspension of **48** (207 mg, 0.38 mmol) in THF (25 mL) was added 40% aq. dimethylamine (5 mL, excess) and the reaction mixture was stirred at 20 °C for 20 h. The solvent was evaporated and the residue was diluted with H_2O (50 mL), to give a precipitate which was collected and dried. Chromatography on silica, eluting with CH_2Cl_2/MeOH (97:3)

gave **54** (210 mg, 97% yield).

Hydrochloride: mp (MeOH), 264-268 °C; ^{1}H NMR (DMSO-d_6) δ 10.20 (br s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.72 (t, J_{HF} = 52.8 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 5.30-5.24 (m, 1H), 3.90 (s, 3H), 3.86-3.83 (m, 4H), 3.74-3.71 (m, 4H), 3.64-3.60 (m, 2H), 3.54-3.49 (m, 2H), 3.42-3.39 (m, 2H), 3.32-3.24 (m, 2H), 2.80 (s, 6H), 2.16-2.09 (m. 2H), 1.92-1.84 (m, 2H); MS (APCI) *m/z*: 597.0 ($M+H^+$); Anal. Calcd. for $C_{25}H_{35}ClF_2N_8O_5S$: C, 47.3; H, 5.6; N, 17.7; Cl, 5.6; Found: C, 47.4; H, 5.7; N, 17.8; Cl, 5.7%.

*4.1.28. N-[1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]-N-[3-(dimethylamino)propyl]methanesulfonamide (**57**)*

To a mixture of *N*-[1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]methanesulfonamide (**55**)[34] (1.95 g, 3.62 mmol) and K_2CO_3 (6 g, excess) in DMF (20 mL) was added 3-bromo-1-propanol (4 mL, excess). The reaction mixture was stirred at 20 °C for 7 days and diluted with water. The resulting sticky material was extracted into CH_2Cl_2 and dried (Na_2SO_4). Chromatography on silica, eluting with a gradient of CH_2Cl_2/EtOAc (0-20%) followed by CH_2Cl_2/MeOH (97:3) gave *N*-[1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]-*N*-(3-hydroxypropyl)methanesulfonamide (**56**) (1.04 g, 49%): mp (CH_2Cl_2/MeOH) 219-221 °C; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, J = 8.2 Hz, 1H), 7.69 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 4.73 (d, J = 12.8 Hz, 1H), 4.82 (d, J = 12.3 Hz, 1H), 4.44 (t, J = 5.1 Hz, 1H), 3.97 (S, 3H), 3.92-3.83 (m, 1H), 3.80-3.79 (m, 4H), 3.69 (m, 4H), 3.40-3.32 (m, 2H), 3.14-2.96 (m, 4H), 3.96 (s, 3H), 1.87-1.80 (m, 2H), 1.74-1.64 (m, 4H); MS (APCI) *m/z*: 597.3 ($M+H^+$); Anal Calcd. for $C_{25}H_{34}F_2N_8O_5S$:C, 50.33; H, 5.74; N, 18.78; Found: C, 50.2; H, 5.9; N, 18.5%.

A solution of **56** (305 mg, 0.51 mmol) and Et_3N (0.3 mL) in CH_2Cl_2 (15 mL) at 0 °C was treated with methanesulfonyl chloride (0.2 mL, 2.5 mmol). The reaction mixture was stirred at 0 °C for 45 min and a solution of 40% aqueous dimethylamine (5 mL) was then added. Stirring was continued for 2 days at 20 °C, and the CH_2Cl_2 was evaporated. The residue was diluted with water, and the resulting precipitate was collected and dried. Chromatography on neutral alumina, eluting with CH_2Cl_2/MeOH (98:2), followed by chromatography on silica, eluting with CH_2Cl_2/MeOH/aq. NH_3 (96:3:1) gave **57** (200 mg, 63%).

Hydrochloride: mp (MeOH/*i*-PrOH) 187-191 °C; ^{1}H NMR (DMSO-d_6) δ 9.83 (br s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 6.95 (d, J

= 7.9 Hz, 1H), 4.84-4.73 (m, 2H), 3.98 (s, 3H), 3.92-3.85 (m, 1H), 3.80 (m, 4H), 3.70 (m, 4H), 3.16 (t, *J* = 7.4 Hz, 2H), 3.11-2.96 (m, 7H), 2.71 (s, 6H), 1.91-1.83 (m, 4H), 1.73-1.68 (m, 2H); MS (APCI) *m/z*: 623.9 ($M+H^+$); Anal. Calcd. for $C_{27}H_{40}ClF_2N_9O_4S.H_2O$: C, 47.8; H, 6.2; N, 18.6; Cl, 5.2; Found: C, 47.9; H, 6.2; N, 18.6; Cl, 5.0%.

*4.1.29. N-[1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-piperidinyl]-N-[3-(4-morpholinyl)propyl]methanesulfonamide (**58**)*

A solution of **56** (307 mg, 0.51 mmol) and Et_3N in CH_2Cl (20 mL) at 0 °C was treated with methanesulphonyl chloride (0.2 mL) and stirred for 45 min. The reaction mixture was treated with morpholine (2 ml, excess), and stirred at 20 °C for 10 days. After dilution with water, the CH_2Cl was removed under vacuum, and the resulting precipitate was collected by filtration, washed with water and dried. Chromatography on SiO_2 eluting with CH_2Cl/EtOAc (7:3) gave **58** (212 mg, 58%).

Hydrochloride: mp (MeOH) 229-231 °C; ^{1}H NMR (DMSO-d_6) δ 10.23 (br s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.70 (t, J_{HF} = 52.9 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 4.84-4.74 (m, 2H), 3.98 (s, 3H), 3.95-3.85 (m, 3H), 3.80 (m, 4H), 3.73-3.67 (m, 6H), 3.39-3.29 (m, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 3.11-2.99 (m, 9H), 1.94-1.84 (m, 4H), 1.72-1.70 (m, 2H); MS (APCI) *m/z*: 666.0 ($M+H^+$); Anal. Calcd. for $C_{29}H_{42}ClF_2N_9O_5S{\cdot}0.75H_2O$: C, 48.7; H, 6.1; N, 17.6; Cl, 5.0; Found: C, 48.7; H, 6.2; N, 17.6; Cl, 4.9%.

4.1.30. N^1-[4-[2-(Difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N^3,N^3-dimethyl-N^1-[1-(methylsulfonyl)-4-piperidinyl]-1,3-propanediamine (**64**)

A mixture of **29** (1.54 g, 3.88 mmol), DIPEA (3.0 mL excess) and *tert*-butyl 4-[(3-hydroxypropyl)amino]-piperidine-1-carboxylate (**59**)[39] (1.3 g, 5.0 mmol) in DMF (30 mL) was stirred at 20 °C for 48 h, and diluted with water. The resulting precipitate was collected, washed with water, and dried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-75%) gave *tert*-butyl 4-((4-(2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl)-6-morpholino-1,3,5-triazin-2-yl)(3-hydroxypropyl)amino)piperidine-1-carboxylate (**60**) (2.35 g, 97%): mp 212-214 °C; ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.99 and 7.90 (2d, *J* = 8.4, 8.5 Hz, 1H), 7.78 and 7.70 (2t, J_{HF} = 52.9, 52.3 Hz, 1H), 7.42 and 7.37 (2t, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 4.71-4.64 and 4.58-4.47 (2m, 2H), 4.13-4.04 (m, 2H), 3.98 and 3.97 (2s, 3H), 3.79 and 3.69 (2br m, 8H), 3.60-3.46 (m, 4H), 2.82-2.79 (m, 2H), 1.79-1.62 (m, 6H), 1.42 (br s, 9H);

MS (APCI) *m/z*: 619.3 ($M+H^+$); Anal. Calcd. for $C_{24}H_{40}F_2N_8O_5$: C, 56.3; H, 6.5; N, 18.1; Found: C, 56.4; H, 6.7; N, 18.0%.

A solution of **60** (637mg, 1.03 mmol) and Et_3N (0.2 mL, 1.44 mmol) in CH_2Cl_2 (12 mL) at -10°C was treated with methanesulfonyl chloride. The reaction mixture was stirred for 30 min and allowed to warm to 20 °C. Aqueous 40% dimethylamine (5 mL, excess) was added and the mixture was stirred for 48 h. The volatiles were removed and the residue was diluted with water. The resulting precipitate was collected, washed with water, and dried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc (0-20%), followed by CH_2Cl_2/MeOH/1% aq. NH_3 gave *tert*-butyl 4-[[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl][3-(dimethylamino)propyl]amino]-1-piperidine-carboxylate (**61**) (550 mg, 83%): ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.96 and 7.90 (2d, J = 8.3 Hz, 1H), 7.77 and 7.70 (2t, J_{HF} = 53.1, 53.0 Hz, 1H), 7.42 and 7.38 (t, J = 8.3, 8.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 4.71-4.64 and 4.55-4.45 (2m, 1H), 4.13-4.02 (m, 2H), 3.98 (s, 3H), 3.81-3.77 (m, 4H), 3.66 (br, 4H), 3.54-3.44 (m, 2H), 2.82 (br, 2H), 2.27 (t, J = 6.8 Hz, 2H), 2.14 and 2.12 (2s, 6H), 1.73-1.62 (m, 6H), 1.42 (s, 9H).

A solution of **61** (530 mg, 0.82 mmol) in CH_2Cl_2 (20 ml) was treated with TFA (5 mL, excess) and stirred at 20 °C for 2 h. The reaction mixture was carefully poured in to a mixtue of aq. NH_3 and ice, and stirred for 10 min. The organic layer was separated, washed with water, and dried (Na_2SO_4). The solvents were evaporated and the residue was recrystallized from CH_2Cl_2/EtOAc to give N^1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N^3,N^3-dimethyl-N^1-(4-piperidinyl)-1,3-propanediamine in 99% yield: ^{1} H NMR (DMSO-d_6) (rotamers) δ 7.96 and 7.93 (d, J = 8.3 Hz, 1H), 7.77 and 7.70 (t, J_{HF} = 53.1, 53.0 Hz, 1H), 7.40-7.35 (m, 1H), 6.95 (d, J = 8.1 Hz, 1H), 4.63-4.56 and 4.50-4.43 (2m, 1H), 3.98 (s, 3H), 3.82-3.77 (m, 4H), 3.70 (br, 4H), 3.55-3.45 (m, 2H), 3.08-3.05 (m, 2H), 2.59-2.52 (m, 3H), 2.28 (t, J = 6.8 Hz, 2H), 2.14 and 2.12 (2s, 6H), 1.76-1.61 (m, 6H).

A solution of the above amine (202 mg, 0.31 mmol) and K_2CO_3 (2.0 g, excess) in CH_2Cl_2 (12 mL) was cooled to 0 °C, and treated with excess methanesulfonyl chloride. After being stirred for 2 h, the mixture was diluted with water, and the CH_2Cl_2 was removed under vacuum. The resulting precipitate was collected, washed with water and dried. Chromatography on neutral alumina, eluting with CH_2Cl_2/MeOH (0-1%) gave **64** (192 mg, 99%). Hydrochloride: mp (CH_2Cl_2/MeOH) 241-243 °C; ^{1}H NMR (DMSO-d_6) (rotamers) δ 9.95 (br, 1H), 7.90 and 7.89 (2d, J = 8.2, 8.3 Hz, 1H), 7.71 and 7.70 (2t, J_{HF} = 52.9, 53.0 Hz, 1H), 7.45 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 4,69-4.55 (m, 1H), 3.98 (s, 3H), 3.82-

3.70 (m, 10H), 3.60-3.52 (m, 2H), 3.12-3.05 (m, 2H), 2.94 and 2.92 (2s, 3H), 2.90-2.79 (m, 2H), 2.74 and 2.70 (2s, 6H), 2.02-1.80 (m, 6H); MS (APCI) *m/z*: 624.0 ($M+H^+$); Anal Calcd. for $C_{27}H_{39}F_2N_9O_4S{\cdot}1.25HCl{\cdot}0.5H_2O$: C, 47.8; H, 6.1; Cl, 6.5; N, 18.6; Found: C, 47.9; H, 6.0; Cl, 6.4; N, 18.6%.

*4.1.31. 4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[1-(methylsulfonyl)-4-piperidinyl]-6-(4-morpholinyl)-N-[3-(4-morpholinyl)propyl]-1,3,5-triazin-2-amine (**65**)*

A solution of **60** (825 mg, 1.33 mmol) and Et_3N (0.4 mmol, 2.66 mmol) in CH_2Cl_2 (20 mL) was treated with methanesulphonyl chloride (0.13 mL, 0.17 mmol) at 0 °C and the reaction mixture was stirred for 30 min, while being allowed to warm to 20 °C. Morpholine (1 mL, excess) was added and stirring was continued for 7 days. The reaction mixture was diluted with water and the CH_2Cl_2 was removed under vacuum, to give an oil. The aqueous layer was decanted off, and oily layer was washed several times with water, and dried. Chromatography on SiO_2 eluting with CH_2Cl_2/EtOAc (0-20%) followed by CH_2Cl_2/MeOH (0-2%) gave *tert*-butyl 4-[[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl][3-(4-morpholinyl)propyl]amino]-1-piperidinecarboxylate (**62**) as an oil: ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.94 and 7.90 (2d, J = 8.3, 8.2 Hz, 1H), 7.73 and 7.70 (2t, J_{HF} = 53.0 Hz, 1H), 7.42 and 7.38 (2t, J = 8.2 Hz, 1H), 6.95 (dd, J = 8.0, 2.7 Hz, 1H), 4.72-4.59 and 4.58-4.82 (2m, 1H), 4.17-4.06 (m, 2H), 3.98 (s, 3H), 3.80-3.77 (m, 4H), 3.69 (br, 4H), 3.59-3.45 (m, 6H), 2.82 (br, 2H), 2.35-2.33 (m, 6H), 1.80-1.64 (m, 6H), 1.42 (s, 9H).

The above compound was dissolved in CH_2Cl_2 (30 mL), treated with TFA (5 mL), and stirred for 1 hr. The reaction mixture was carefully poured into ice/aq.NH_3, and stirred for 10 mins. The organic layer was separated, washed with more water, and dried (Na_2SO_4). Evaporation of the solvent gave 4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-*N*-[3-(4-morpholinyl)propyl]-*N*-(4-piperidinyl)-1,3,5-triazin-2-amine (75% yield over two steps): ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.94 (t, J = 7.6 Hz, 1H), 7.73 and 7.70 (2t, J_{HF} = 53.1, 53.0 Hz, 1H), 7.42-7.36 (m, 1H), 6.95 (d, J = 8.1 Hz, 1H), 4.63-4.55 and 4.50-4.42 (2m, 1H), 3.98 (s, 3H), 3.80-3.77 (m, 4H), 3.70 (br, 4H), 3.59-3.47 (m, 6H), 3.08-3.03 (m, 2H), 2.60-2.53 (m, 2H), 2.36-2.33 (m, 6H), 1.85-1.59 (m, 6H).

A mixture of the above amine (257 mg, 0.44 mmol) and powdered K_2CO_3 (2g, excess) in CH_2Cl_2 (10 mL) at 0 °C was treated with methanesulphonyl chloride (0.5 mL), and the

mixture was allowed to warm to 20 °C with stirring. The reaction mixture was diluted with water and the CH_2Cl_2 was removed under vacuum. The solid was collected by filtation, washed with water, and dried. Chromatography on SiO_2 eluting with CH_2Cl_2/MeOH (0-2%) gave **65**, which was directly converted to the HCl salt by dissolving in CH_2Cl_2 and adding 1.25 M methanolic HCl (1.0 mL). Removal of the solvent and recrystallization from methanol gave **65** hydrochloride (276 mg, 90%): mp 268-271°C, ^{1}H NMR (DMSO-d_6) (rotamers) δ 10.82 and 10.48 (2br, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.71 and 7.70 (2t, J_{HF} = 52.9 Hz, 1H), 7.48-7.43 (m, 1H), 6.96 (dd, J = 8.0, 2.3 Hz, 1H), 4.69-4.55 (m, 1H), 3.98 (s, 3H), 3.98-3.54 (m, 16H), 3.41-3.33 (m, 2H), 3.19-3.12 (m, 2H), 3.08-2.98 (m, 2H), 2.94 and 2.93 (2s, 3H), 2.89-2.80 (m, 2H), 2.09-1.85 (m, 6H); MS (APCI) *m/z*: 666.0 ($M+H^+$); Anal. Calcd. for $C_{29}H_{42}ClF_2N_9O_5S.0.5H_2O$: C, 49.0; H, 6.1; Cl, 5.0; N, 17.7; Found: C, 48.5; H, 6.0; Cl, 5.1; N; 17.5%.

*4.1.32. 4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[3-[4-(methylsulfonyl)-1-piperazinyl]propyl]-N-[1-(methylsulfonyl)-4-piperidinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine (**66**)*

To a solution of **60** (554 mg, 0.9 mmol) and Et_3N (0.23 mL, 1.8 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added methanesulphonyl chloride (0.09 mL, 1.17 mmol), and the mixture was stirred for 30 min. *tert*-Butyl 1-piperazinecarboxylate (2.0 g, excess) was added, and stirring was continued for 12 days at 20 °C. The reaction mixture was diluted with water, extracted with CH_2Cl_2, and dried (Na_2SO_4). Chromatography on SiO_2, eluting with CH_2Cl_2/MeOH (0-4% gave *tert*-butyl 4-(3-[[1-(*tert*-butoxycarbonyl)-4-piperidinyl][4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]amino]propyl)-1-piperazinecarboxylate (**63**), as an oil; ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.94 and 7.90 (2d, J = 8.4, 8.3 Hz, 1H), 7.72 and 7.70 (2t, J_{HF} = 53.1 53.0 Hz, 1H), 7.42 and 7.38 (2t, J = 8.2 Hz, 1H) 6.95 (d, J = 8.1 Hz, 1H), 4.75-4.64 and 4.58-4.50 (2m, 1H), 4.14-4.05 (m, 2H), 3.98 and 3.96 (2s, 3H), 3.80-3.77 (m, 4H), 3.69 (br m, 4H), 3.55-3.45 (m, 2H), 2.55-2.50 (m, 4), 2.37-2.28 (m, 9H), 1.67 (br, 5H), 1.42 (s, 9H), 1.39 (s, 9H).

A solution of the above compound in CH_2Cl_2 (10 mL) and TFA (5 mL) was stirred for 3h at 0 °C. The reaction mixture was diluted with ice water and carefully basified with aq NH_3. The organic layer was separated, washed with water, and dried (Na_2SO_4), to give 4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-*N*-[3-(1-piperazinyl)propyl]-*N*-(4-piperidinyl)-1,3,5-triazin-2-amine (375 mg, 71%): ^{1}H NMR

(DMSO-d_6) (rotamers) δ 7.95-7.91 (m, 1H), 7.73 and 7.70 (t, J_{HF} = 53.0 Hz, 1H), 7.42-7.36 (m, 1H), 6.95 (d, J = 8.08 Hz, 1H), 4.70-4.45 (m, 2H), 3.98 (s, 3H), 3.80-3.79 (m, 4H), 3.70 (br m, 4H), 3.56-3.46 (m, 2), 3.13-3.10 (m, 2H), 2.77-2.56 (m, 4H), 2.38-2.29 (m, 8H), 1.78-1.69 (m, 7H).

A mixture of the above amine (375 mg, 0.64 mmol) and K_2CO_3 (2.0 g, excess) in CH_2Cl_2 (15 mL) was treated with methanesulfonyl chloride (1.0 mL excess) at 0 °C, and the mixture was stirred for 20 h. After dilution with water, the CH_2Cl_2 was removed under vacuum, and the resulting precipitate was collected by filtration, and dried. Chromatography on SiO_2, eluting with CH_2Cl_2/EtOAc followed by CH_2Cl_2/MeOH gave partially clean product, which was further chromatographed on Al_2O_3, eluting with CH_2Cl_2/EtOAc (0-20%) to give **66** (170 mg, 36%): mp (CH_2Cl_2/MeOH) 246-250 °C; ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.94 and 7.89 (2d, J = 8.3 Hz, 1H), 7.73 and 7.70 (2t, J_{HF} = 53.0, 52.9 Hz, 1H), 7.44 and 7.40 (2t, J = 8.4, 8.2 Hz, 1H), 6.97 (dd, J = 8.0, 3.3 Hz, 1H), 4.68-4.51 (m, 1H), 3.98 (s, 3H), 3.81-3.69 (m, 10H), 3.59-3.48 (m, 2H), 3.12-3.10 (m, 2H), 3.06-3.02 (m, 2H), 2.94 and 2,92 (2s, 3H), 2.90-2.78 (m, 2H), 2.87 and 2.83 (2s, 3H), 2.55-2.39 (m, 6H), 1.92-1.75 (m, 6H); MS (APCI) *m/z*: 742.9 ($M+H^+$); Anal. Calcd. for $C_{30}H_{44}F_2N_{10}O_6S_2.0.25H_2O$: C, 48.2;H, 6.0; N, 18.7; Found: C, 48.1; H, 6.0; N, 18.7%.

*4.1.33. N^1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N^3-N^3-dimethyl-N^1-[1-(methylsulfonyl)-3-piperidinyl]-1,3-propanediamine (**71**)*

A mixture of *tert*-butyl 3-oxo-1-piperidinecarboxylate (5.0 g, 25.1 mmol) and 3-amino-1-propanol (5.66 mL, 73.8 mmol) in MeOH (75 mL) was hydrogenated over 10% Pd on C (200 mg) for 1 day at 50 psi, to give *tert*-butyl 3-[(3-hydroxypropyl)amino]-1-piperidinecarboxylate (**67**) as an oil: ^{1}H NMR ($CDCl_3$) (rotamers) δ 3.80 (t, J = 5.1 Hz, 2H), 3,80 (br, 1H), 3.65 and 3.67 (2t, J = 4.7 Hz, 1H), 3.06-2.86 (m, 4H), 2.62-2.56 (m, 1H), 1.90-1.86 (m, 1H), 1.72-1.62 (m, 3H), 1.50-1.30 (m, 2H), 1.46 (s, 9H).

A mixture of **67** (516 mg, 2.00 mmol), **29** (610 mg, 1.54 mmol), and DIPEA (1.5 mL, excess) in DMF (20 mL) was stirred at room temperature for 2 days. The reaction mixture was diluted with water, extracted with CH_2Cl_2 and dried (Na_2SO_4). Chromatography of the residue on silica eluting with a gradient of CH_2Cl_2/EtOAc (0-40%) gave *tert*-butyl 3-[[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl](3-hydroxypropyl)-amino]-1-piperidinecarboxylate (**68**) **(**854 mg, 90%): mp (CH_2Cl_2/hexanes) 109-191 °C; ^{1}H NMR (DMSO-d_6) (rotamers) δ 8.00 and 7.88 (2d, J = 8.3, 8.4 Hz, 1H), 7.79 and 7.63 (2t, J_{HF} = 53.0 Hz, 1H), 7.40-7.33 (m, 1H), 6.94 (dd, J = 8.0, 4.13 Hz, 1H), 4.60-

4.48 and 4.29 (m, 2H), 3.98 and 3.97 (2s, 3H), 3.97-3.48 (m, 16H), 2.93-2.88 and 2.66-2.64 (2 m, 2H), 1.99-1.69 (m, 3H), 1.52-1.17 (m, 10H); MS (APCI) *m/z*: 619.3 ($M+H^+$); Anal. Calcd. for $C_{29}H_{40}F_2N_8O_5$: C, 56.3; H, 6.5; N, 18.1; Found: C, 56.4; H, 6.4; N, 18.1%.

To a solution of **68** (420 mg, 0.72 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added Et_3N (0.2 mL, 1.4 mmol) and methanesulfonyl chloride (0.1 mL, 1.08 mmol). The reaction mixture was stirred at 0 °C for 30 min, and a solution of 40% aqueous dimethylamine (5 mL) was then added. The reaction mixture was stirred at room temperature for 2 days and the solvent was removed under vacuum. The residue was diluted with water and the precipitate was collected by filtration and dried. Chromatography on silica eluting first with CH_2Cl_2/EtOAc (4:1), and then with CH_2Cl_2/MeOH (95:5) containing 1% aq. NH_3, gave *tert*-butyl 3-[[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl][3-(dimethylamino)propyl]amino]-1-piperidinecarboxylate (**69**) (465 mg; 100%) as a white solid: mp (CH_2Cl_2/MeOH) 133-136°C; ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.96 and 7.88 (2d, J = 8.3 Hz, 1H), 7.77 and 7.68 (2t, J_{HF} = 53.0, 52.9 Hz, 1H), 7.40-7.34 (m, 1H), 6.96-6.93 (m, 1H), 4.56-4.88 and 4.30-4.27 (2 m, 1H), 3.98 and 3.97 (2s, 3H), 3.97-3.49 (m, 13H), 2.93-2.88 and 2.77-2.63 (2m, 2H), 2.35-2.27 (m, 2H), 2.15 and 2.13 (2s, 6H), 1.93-1.71 (m, 4H), 1.48-1.16 (m, 1H), 1.40 (s, 9H); MS (APCI) *m/z*: 646.3 ($M+H^+$); Anal. Calcd. for $C_{31}H_{45}F_2N_9O_4$ C, 57.7; H, 7.0; N, 19.5; Found: C, 57.7; H, 7.1; N, 19.7%.

To a solution of **69** (430 mg, 0.67 mmol) in CH_2Cl_2 (10 mL), was added TFA (5 mL), and the resulting mixture was stirred at room temperature for 30 min. The solvent and excess TFA were removed under vacuum, and the residue was diluted with water and aq. NH_3. The resulting precipitate was collected by filtration and dried, to give N^1-[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N^3,N^3-dimethyl-N^1-(3-piperidinyl)-1,3-propanediamine (323 mg, 88%): ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.95 and 7.93 (2d, J = 9.5, 8.8 Hz, 1H), 7.77 and 7.71 (2t, J_{HF} = 53.1 Hz, 1H), 7.42-7.36 (m, 1H), 6.95 (d, J = 1 Hz, 1H), 4.55-4.48 and 4.46-4.39 (2m, 1H), 3.98 (s, 3H), 3.81-3.80 (m, 4H), 3.72-3.70 (m, 4H), 3.55-3.45 (m, 2H), 2.99-2.96 (m, 1H), 2.92-2.89 (m, 1H), 2.77-2.66 (m, 1H), 2.45-2.40 (m, 1H), 2.27 (t, J = 6.9 Hz, 2H), 2.16 and 2.12 (2s, 6H), 1.80-1.48 (m, 6H).

To a solution of the above amine (155 mg, 0.28 mmol) and DIPEA (1 mL) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (0.5 mL) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. After dilution with water, the organic layer was separated, and dried (Na_2SO_4). Chromatography on alumina eluting with CH_2Cl_2/MeOH (97:3) to give partially pure material, which was further purified by chromatography on silica eluting with CH_2Cl_2/MeOH (97:3) to give **71** (125 mg, 72% yield).

Hydrochloride: mp (MeOH/EtOAc/hexanes) 189 °C (dec.); ^{1}H NMR (DMSO-d_6) (rotamers) δ 10.11 and 9.98 (2br, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.71 and 7.65 (2t, J_{HF} = 52.8, 52.9 Hz, 1H), 7.45 and 7.38 (2t, J = 8.2, 1H), 6.97 and 6.95 (2d, J = 5.7, 5.8 Hz, 1H), 4.73-4.65 and 4.51-4.44 (2m, 1H), 3.97 and 3.96 (2s, 3H), 3.91-3.57 (m, 12H), 3.11-3.03 (m, 2H), 2.93 and 2.92 (2s, 6H), 2.95-2.82 (m, 1H), 2.76-2.66 (m, 6H), 2.05-1.85 (m, 4H); MS (APCI) *m/z*: 624.0 ($M+H^+$); Anal. Calcd. for $C_{27}H_{38}N_9O_4 \cdot 1.25HCl \cdot 0.5H_2O$: C, 47.8; H, 6.1; Cl, 6.5; N, 18.6; Found: C, 47.6; H, 6.1; Cl, 6.6%; N, 17.8%.

*4.1.34. 4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[1-(methylsulfonyl)-3-piperidinyl]-6-(4-morpholinyl)-N-[3-(4-morpholinyl)propyl]-1,3,5-triazin-2-amine (**72**)*

A solution of **68** (401 mg, 0.65 mmol) and Et_3N (0.2 mL) in CH_2Cl_2 (12 mL) was treated with methanesulphonyl chloride (0.08 mL) at 0 °C, and the mixture was stirred for 30 min. Morpholine (1 mL, excess) was added and he mixture was stirred for 9 days at 20 °C., before being diluted with water. The mixture was extracted with CH_2Cl_2, and dried (Na_2SO_4). Removal of the solvent and chromatography on SiO_2, eluting with CH_2Cl_2 followed by CH_2Cl_2/MeOH (5%) gave *tert*-butyl 3-[[4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl][3-(4-morpholinyl)propyl]amino]-1-piperidinecarboxylate (**70**) as a sticky oil; ^{1}H NMR (DMSO-d_6) (rotamers) δ 7.94 and 7.88 (2d, J = 8.3 ,8.5 Hz, 1H), 7.62 and 7.73 (2t, J_{HF} = 52.9, 53.5 Hz, 1H) 7.39 and 7.36 (2t, J = 8.2 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 4.53 and 4.27 (2br, 1H), 4.02-3.93 (m, 2H), 3.98 and 3.98 (2s, 3H), 3.80 and 3.70 (2br, 8H), 3.55-3.53 (m, 4H), 2,94-2,62 (br m, 2H), 2,62-2.55 (m, 3H), 2.41-2.34 (m, 5H), 1.94-1.72 (m, 5H), 1.47-1.40 (m, 1H), 1.40 (s, 9H).

The above crude oil (519 mg, 0.75 mmol)) in CH_2Cl_2 (8.0 mL) was treated with TFA (5 mL, excess) and the mixture was stirred for 30 min. The solvent and excess TFA was removed under vacuum, and the residue was diluted with water, and basified with aq NH_3. After stirring for 30 min, the resulting recipitate was collected by filtration, washed with water and dried to give 4-[2-(difluoromethyl)-4-methoxy-1*H*-benzimidazol-1-yl]-6-(4-morpholinyl)-*N*-[3-(4-morpholinyl)propyl]-*N*-(3-piperidinyl)-1,3,5-triazin-2-amine (256 mg 58%).

A stirred mixture of the above amine (128 mg, 0.22 mmol) and powdered K_2CO_3 (2.0 g, excess) in CH_2Cl_2 (30 mL), was cooled to 0 °C, and methanesulfonyl chloride (0.2 mL) was added. After 2 h, the mixture was diluted with water, and the CH_2Cl_2 was removed under vacuum. The residual precipitate was collected by fitration, and driied.

Chromatography on SiO_2, eluting with CH_2Cl_2/MeOH (2%) gave **72** (119 mg,78%).

Hydrochloride: mp (MeOH) 186-190 °C**;** ^{1}H NMR (DMSO-d_6) (rotamers) δ 10.65 and 10.43 (2br, 1H), 7.90 and 7.89 (2d, J = 8.2, 8.1, Hz, 1H), 7.70 and 7.65 (2t, J_{HF} = 52.9, Hz, 1H), 7.46 and 7.39 (2t, J = 8.3, 8.2 Hz, 1H), 6.96 (m, 1H), 4.75-4.66 and 4.51-4.44 (2m, 1H), 3.98 and 3.97 (2s, 3H), 3.98-3.59 (m, 16H), 3.46-3.24 (m, 2H), 3.18-2.85 (m, 5H), 2.92 (s, 3H), 2.73-2.67 (m, 1H), 2.09-1.89 (m, 6H); MS (APCI) *m/z*: 666.0 ($M+H^+$); Anal. Calcd. for $C_{29}H_{42}ClF_2N_9O_5S.1.25H_2O$: C, 48.1; H, 6.2; N, 17.4; Cl, 4.9; Found: C, 47.9; H, 6.2; N, 17.3; Cl, 5.2%.

4.1.35. 1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N-[2-(dimethylamino)ethyl]-3-pyrrolidinesulfonamide (77)

A solution of benzyl 3-(chlorosulfonyl)pyrrolidine-1-carboxylate (**73**) (110 mg, 0.362 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of *N*,*N*-dimethylethylenediamine (0.20 mL, 1.83 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. Water was added, and the organic phase was dried (Na_2SO_4), to give benzyl 3-[[[2-(dimethylamino)ethyl]amino]sulfonyl]-1-pyrrolidinecarboxylate (**75**) (102 mg, 88%), which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.36-7.29 (m, 5H), 5.14 (d, J = 1.8 Hz, 2H), 3.80-3.72 (m, 4H), 3.53-3.47 (m, 1H), 3.16 (m, 2H), 2.42 (t, J = 5.7 Hz, 2H), 2.38-2.26 (m, 2H), 2.21 (s, 6H).

A mixture of **75** (171 mg, 0.481 mmol) and 10% Pd on carbon in MeOH (15 mL) was hydrogenated at 50 psi for 29 h. The reaction mixture was filtered through celite, the celite pad was washed with MeOH, and the solvent was removed under vacuum to give *N*-[2-(dimethylamino)ethyl]-3-pyrrolidinesulfonamide (94 mg, 89%), which was used in the next step without further purification: ^{1}H NMR (DMSO-d_6) δ 6.93 (br s, 1H), 3.66-3.57 (m, 1H), 3.04-2.99 (m 4H), 2.86-2.79 (m, 1H), 2.75-2.68 (m, 1H), 2.31 (t, J = 6.8 Hz, 2H), 2.14 (s, 6H), 1.97-1.87 (m, 2H).

DIPEA (0.11 mL, 0.632 mmol) was added to a stirred suspension of **29** (127 mg, 0.320 mmol) and the above amine (92 mg, 0.416 mmol) in THF (10 mL) at room temperature and the resulting mixture was stirred for 2.5 days. The solvent was removed under vacuum, and the residue was partitioned between H_2O and CH_2Cl_2, and the organic phase was dried (Na_2SO_4). Recrystallization from CH_2Cl_2/hexanes, followed by chromatography on silica, eluting with CH_2Cl_2/MeOH (100:0 to 95:5), gave **77** (92 mg, 49%).

Methanesulfonate: mp (MeOH/EtOAc) 196-199 °C; ^{1}H NMR (DMSO-d_6) δ 9.34 (br s, 1H), 8.00 (dd, J = 8.2, 5.4 Hz, 1H), 7.80-7.73 (m, 1H), 7.77 (t, J_{HF} = 53.1 Hz, 1H), 7.41 (t,

J = 8.2 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.20-4.12 (m, 1H), 3.95-3.40 (m, 1H), 3.98 (s, 3H), 3.91 (d, *J* = 6.6 Hz, 1H), 3.87-3.66 (m, 10H), 3.38 (q, *J* = 6.1 Hz, 2H), 3.19 (t, *J* = 6.3 Hz, 2H), 2.82 (d, *J* = 1.8 Hz, 6H), 2.45-2.34 (m, 2H), 2.31 (s, 3H); MS (APCI) *m/z*: 582.0 ($M+H^+$); Anal. Calcd. for $C_{25}H_{37}F_2N_9O_7S_2 \cdot 0.6H_2O$: C, 43.6; H, 5.6; N, 18.3; Found: C, 43.4; H, 5.6; N, 18.3%.

*4.1.36. 1-[4-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N-[2-(dimethylamino)ethyl]-4-piperidinesulfonamide (**78**)*

A solution of benzyl 4-(chlorosulfonyl)-1-piperidinecarboxylate (**74**) (430 mg, 1.35 mmol) in THF (10 mL) was treated with an excess of *N*,*N*-dimethylethylenediamine (0.594 g, 6.75 mmol) and the mixture was stirred at room temperature for 2 h. The THF was removed under vacuum and the residue was diluted with water, and extracted with CH_2Cl_2. Chromatography on alumina, eluting with EtOAc, gave benzyl 4-[[[2-(dimethylamino)ethyl]amino]sulfonyl]-1-piperidinecarboxylate (**76**) (450 mg, 90% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.40-7.30 (m, 5H), 5.13 (s, 2H), 4.33 (m, exchangeable with D_2O, 1H), 3.16 (m, 2H), 3.04 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.81(br t, *J* = 11.9 Hz, 1H), 2.43 (m, 2H), 2.22 (s, 6H), 2.12 (br d, *J* = 12.8 Hz, 2H), 1.74 (ddd, *J* = 25.0, 12.6, 4.5 Hz, 2H).

Carbamate **76** was hydrogenated over 5% Pd on carbon in MeOH at 50 psi, and after filtration, and removal of the solvent, the residue was combined with **29 (**0.48 g, 1.2 mmol) and DIPEA (0.35 g, 2.7 mmol) in THF (10 mL). The mixture was heated under reflux for 1 h and the solvent was concentrated. After dilution with water, the resulting solid was collected, and dried. Chromatography on alumina, eluting with EtOAc, gave **78**: mp (MeOH) 231-234 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.47 (t, J_{HF} = 53.5 Hz, 1H), 7.35 (t, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.91 (br d, *J* = 13.3 Hz, 2H), 4.04 (s, 3H), 3.88 (m, 4H), 3.78 (m, 4H), 3.25-3.17 (m, 3H), 3.00 (m, 2H), 2.45 (br t, *J* = 5.7 Hz, 2H), 2.27 (m, 2H), 2.23 (s, 6H), 1.83 (dq, *J* = 12.5, 4.4 Hz, 2H); MS (APCI) *m/z*: 596.0 ($M+H^+$); Anal. Calcd. for $C_{25}H_{35}F_2N_9O_4S$: C, 50.4; H, 5.9; N, 21.2; Found: C, 50.2; H, 5.7; N, 21.3%.

4.2. 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.[40,42]

The PI3Ks were produced by co-expressing the catalytic subunits with the p85α

regulatory subunit. Human clones for p110α, p110β, p110δ and p85α were isolated using PCR with an *N*-terminal His-tag being added to the p110 isoforms to facilitate purification. The catalytic subunits were cloned together with p85 in a baculoviral expression vector containing an IRES sequence and then co-expressed in Sf9 insect cells. The PI3Ks were purified using nickel-nitrilotriacetic acid (Ni-NTA) superflow (Qiagen) affinity column. The purity of the PI3K preparations was verified by coomassie staining of SDS-PAGE gels and the titers of baculovirus were adjusted such that the ratio of p85:p110 was approximately 1:1. The functional equivalence of multiple preparations of the recombinant PI3K was verified by western blotting and also by sensitivity to previously described isoform selective PI3K inhibitors. Nine inhibitor concentrations were used to determine the IC_{50}. Values reported are means of two experiments, variation between experiments is no more than ±20%, unless otherwise stated.

4.3. Cellular assays

The compounds were also evaluated in a cellular assay measuring inhibition of proliferation of two early passage human cancer cell lines, using ^{3}H-labelled thymidine incorporation as an index of proliferation, as previously described.[43] The NZB5 cell line was a medulloblastoma chosen because it contains the wild-type gene for p110α. The NZOV9 cell line was developed from a patient with a poorly differentiated ovarian (endometrioid) adenocarcinoma that was wild-type for expression of p53 protein but contained a mutant p110α enzyme with a single amino acid substitution (Y1021C) in the kinase domain leading to activation of the PI3K enzyme.[44]

Cell lines were grown in a-modified minimal essential growth medium supplemented with insulin, transferrin, selenite and 5% foetal bovine serum. Individual wells of 96-well tissue culture plates contained 1000 cells in a volume of 150 µL. Compounds were added at 10-fold concentration steps to a maximum of 20 µM and plates were incubated under an atmosphere of 5% O_2, 5% CO_2 and 90% N_2 for five days, with ^{3}H-thymidine (0.04 µCi per well) being added over the last 6 h. Cells were harvested and the incorporated radioactivity was measured. Duplicate samples were analyzed for each drug dose with multiple control samples and data were fitted to a least-squares regression of the form $y = y_0 + ae^{-bx}$, where y is the incorporated radioactivity, x is the drug concentration and y_0, a and b are variables. The IC_{50} value was

defined as the drug concentration reducing ^{3}H-thymidine incorporation by 50%.

4.4. In vivo assays

5 x 10^6 U-87 MG cells in PBS were subcutaneously inoculated on the right flank of 6-8 week old female Rag1$^{-/-}$ mice. Once tumors reached approx. 150 mm^3 in volume, the mice were treated with control vehicle, 80 mg/kg **2**, 60 mg/kg **16** or 80 mg/kg **20** at a qdx21 schedule by ip administration. Dosing was stopped 7 days early for **2** due to lack of effect. The vehicle for controls, **16** and **20** was 8% DMSO in a 20% 2-hydroxypropyl-β-cyclodextrin solution, and for **2** was 1% carboxymethylcellulose, 0.2% tween-80, 98.8% sterilized water for injection. Tumor volume was assessed by caliper measurement of tumor diameter and calculated as π/6 x length x width^2, where width represents the shorter diameter. Animal experiments followed protocols approved by the University of Auckland Animal Ethics Committee. U-87 MG cells were obtained from ATCC and were authenticated by short tandem repeat profiling of extracted DNA at DNA Diagnostics Ltd.

4.5 Aqueous solubility determinations.

The solid compound sample was mixed with water (enough to make a 2 mM solution) in an Eppendorf tube, and the suspension was sonicated for 15 min and then centrifuged at 13000 rpm for 6 min. An aliquot of the clear supernatant was diluted 2-fold with water, and then then centrifuged again at 13000 rpm for 6 min. A 100 μL aliquot of the clear supernatant was injected into the HPLC and the peak area measured. The solubility was calculated by comparing the peak area obtained with that from a standard solution of the compound in DMSO (after allowing for varying dilution factors and injection volumes). HPLC was conducted on an Agilent 1260 Infinity system using an Altima C8 column with a gradient elution from an organic phase of 80% v/v acetonitrile and water (40%), and an aqueous mobile phase of 45 mM ammonium formate solution (pH 3.5) (60%), to 100% organic phase.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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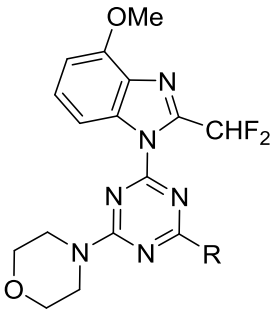
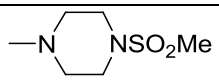
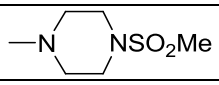
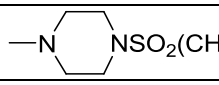
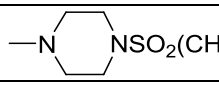
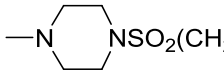
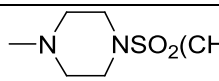
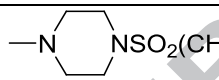
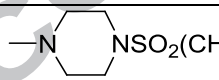
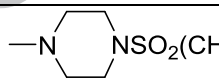
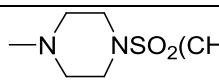
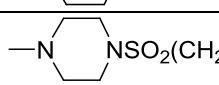
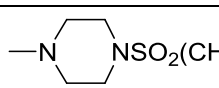
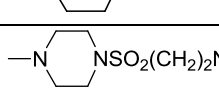
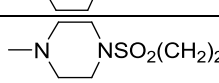
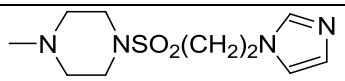
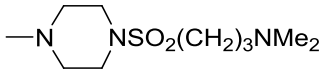
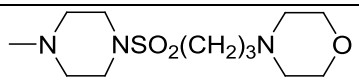
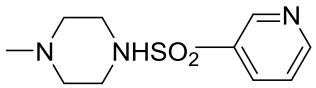
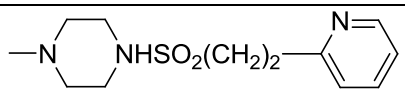
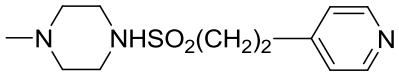
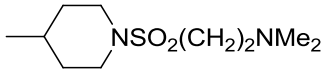
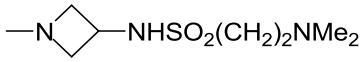
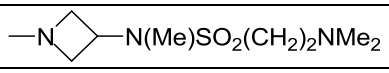
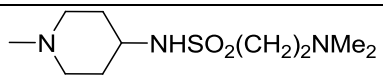
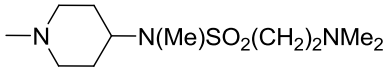
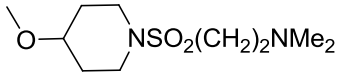
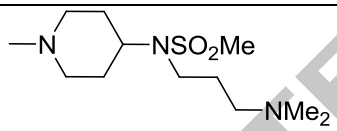
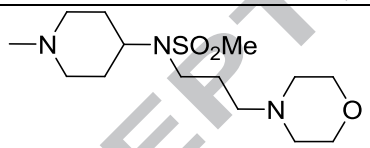
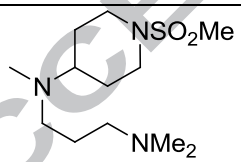
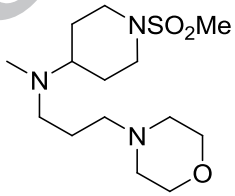
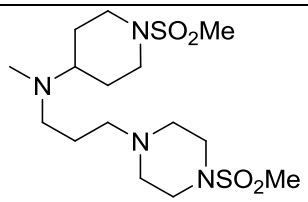
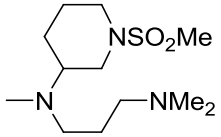
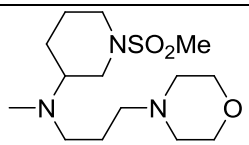
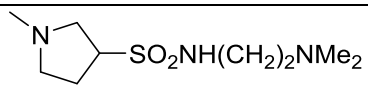
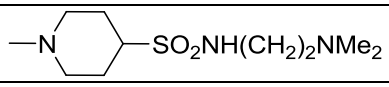
Table 1

Structural and biological data for solubilized sulfonamide analogues of ZSTK474 (**1**).



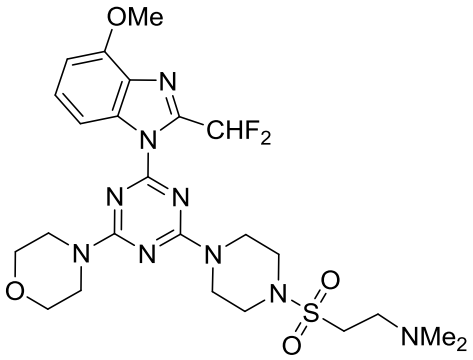
No.	R	Enzyme IC_{50} (nM)[a]			Cell IC_{50} (nM)[a]	
		p110α	p110β	p110δ	NZB5[b]	NZOV9[c]
2[d]		6	1,500	41	220	260
11[e]		83	2,201	307	680	620
14		5.4	153	44	4,150	1,210
15		6.5	95	63	220	960
16		5.3	743	206	140	75
17		5.9	382	63	250	80
18		14	99	102	370	130
19		6	184	28	190	110
20		18	2019	203	240	150
21		12	5610	185	360	130
22		5	714	83	200	221
23		8.9	5230	172	880	250
24		7.5	>1,250	62	370	120
25		13	3300	125	380	110
26		2.3	4620	173	470	140
27		7.8	$>10^4$	77	170	150

28		5.8	>1,250	62	230	53
32		7.9	1165	157	370	100
33		5.4	2590	89	450	110
34		3.8	>1,250	32	55	30
35		2.7	>1,250	38	110	53
36		5.3	>1,250	60	52	38
49		2.4	111	53	260	36
50		13	715	219	530	440
51		46	634	128	2,270	670
52		7.3	286	94	1,840	650
53		68	910	72	1,600	600
54		7.3	>1,250	207	720	350
57		55	>1,250	214	1,180	330
58		24	>1,250	151	210	79
64		29	225	84	650	200
65		20	139	20	150	50
66		23	319	11	250	50

71		70	>1,250	241	410	600
72		72	>1,250	19	86	91
77		9.1	350	71	4,300	1,290
78		27	21	65	210	100

[a] IC_{50} values are the mean of duplicate or triplicate measurements as described in Sections 4.2 and 4.3. [b] NZB5: early-passage human brain (medulloblastoma) cell line. [c] NZOV9: early-passage human ovarian cancer line. [d] Ref. 34. [e] Contains 4-$O(CH_2)_3NMe_2$ substituent instead of 4-OMe.

Graphical Abstract



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