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Discovery of Novel 6,6-Heterocycles as Transient Receptor Potential Vanilloid (TRPV1) Antagonists

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The transient receptor potential cation channel, subfamily V, member 1 (TRPV1) is a nonselective cation channel that can be activated by a wide range of noxious stimuli, including capsaicin, acid, and heat. Blockade of TRPV1 activation by selective antagonists is under investigation in an attempt to identify novel agents for pain treatment. The design and synthesis of a series of novel TRPV1 antagonists with a variety of different 6,6-heterocyclic cores is described, and an extensive evaluation of the pharmacological and pharmacokinetic properties of a number of these compounds is reported. For example, the 1,8-naphthyridine **52** was characterized as an orally bioavailable and brain penetrant TRPV1 antagonist. In vivo, **52** fully reversed carrageenan-induced thermal hyperalgesia (CITH) in rats and dose-dependently potently reduced complete Freund's adjuvant (CFA) induced chronic inflammatory pain after oral administration.

Introduction

The cloning of TRPV1[a] (transient receptor potential cation channel, subfamily V, member 1) by Julius and colleagues in 1997 represented a landmark in the understanding of the molecular mechanisms that underpin the transduction of noxious thermal and chemical stimuli by sensory neurons.[1] TRPV1 is a nonselective cation channel, predominantly expressed by peripheral nociceptors, that is activated by a diverse range of stimuli including protons (pH < 6.0), heat (> 43 °C), and noxious chemicals such as capsaicin, the ingredient responsible for the pungency of chili peppers, and resiniferatoxin, isolated from the latex of the cactus-like perennial *Euphorbia resinifera*. TRPV1 is also activated or potentiated by anandamide,[2] other endovanilloids, notably *N*-arachidonyldopamine and *N*-oleoyldopamine,[3] lipoxygenase products such as 12-hydroperoxyeicosatetraenoic acid,[4] and toxins from spiders[5] and jellyfish.[6] These diverse stimuli not only directly activate TRPV1 but also sensitize and reduce the activation thresholds of the channel to other stimuli, which leads to an influx of calcium and sodium ions through the channel, causing depolarization of the cell and the transmission of painful stimuli. TRPV1 knockout mice have shown reduced thermal hyperalgesia in several models of inflammatory pain[8] and also exhibited no change in physiological heat sensation in the hot-plate test at 50 °C.[7] However, TRPV1−/− mice did exhibit significantly longer (1.7- to 2.5-fold) response latencies than wild-type mice at hot-plate temperatures greater than 50 °C.[7] In addition to the treatment of inflammatory pain, evidence suggests that a number of other disorders, including urinary urge incontinence, cough, and irritable bowel syndrome, may be treatable through modulation of TRPV1 signaling.[9]

The identification of selective and potent antagonists of TRPV1 has become a focus of attention within the pharmaceutical industry,[10] and prominent examples of extensively characterized TRPV1 antagonists are depicted in Figure 1. The urea **1** (SB-705498) and pyrimidine **2** (AMG 517) were among the first TRPV1 antagonists reported to have reached clinical trials. The potent and selective pyrrolidine urea **1**[11] was discovered following optimization of the activity and pharmacokinetics of a simple 1,3-disubstituted arylurea series identified from screening of the GSK library.[12] In healthy human volunteers, **1** was reported to significantly reduce both (i) capsaicin-evoked flare and heat-evoked pain on nonsensitized skin and (ii) heat-evoked pain after ultraviolet B-evoked inflammation.[13] The pyrimidine **2** was identified by Amgen scientists following a sequence of modifications from a simple cinnamide lead.[14] In rats, **2** blocked capsaicin-induced flinching and reversed thermal hyperalgesia in the complete Freund's adjuvant (CFA) induced pain model. In humans, **2** has a long half-life although other analogues with improved physicochemical and pharmacokinetic properties have been reported by the same group.[14d] In addition to a long half-life, **2** was reported to elicit marked but reversible hyperthermia in humans in a plasma concentration-dependent manner.[15] Recently, researchers at Abbott have described the discovery[16] and characterization[17] of the clinical candidate ABT-102 (**3**), identified following optimization of an original 7-hydroxynaphthalene urea lead. Compound **3** exhibited potent oral analgesic efficacy in a number of rodent pain models including

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[a]Abbreviations: TRPV1, transient receptor potential vanilloid 1; CFA, complete Freund's adjuvant; CITH, carrageenan-induced thermal hyperalgesia; TFMA, 4-trifluoromethylaniline.

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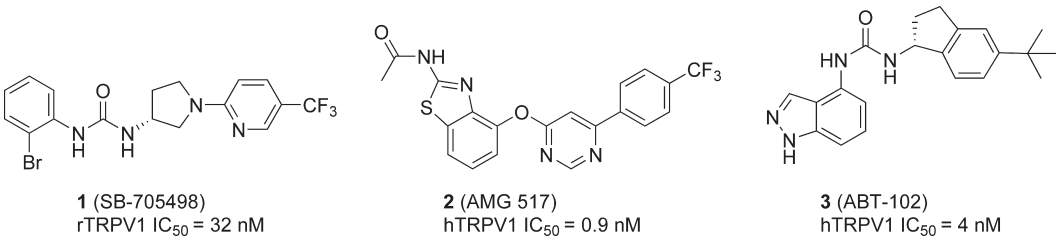


Figure 1. Examples of extensively characterized TRPV1 antagonists.

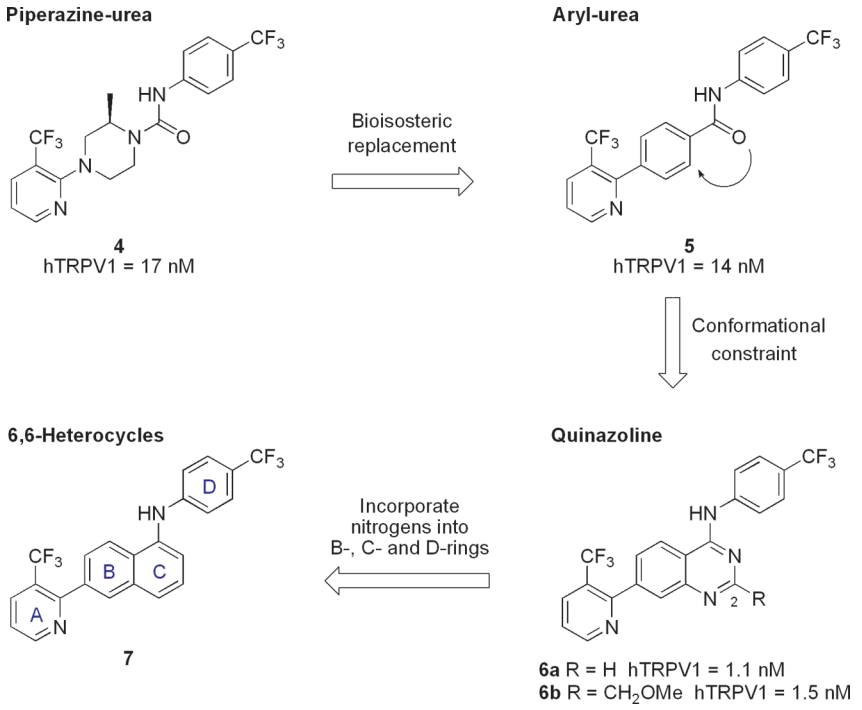
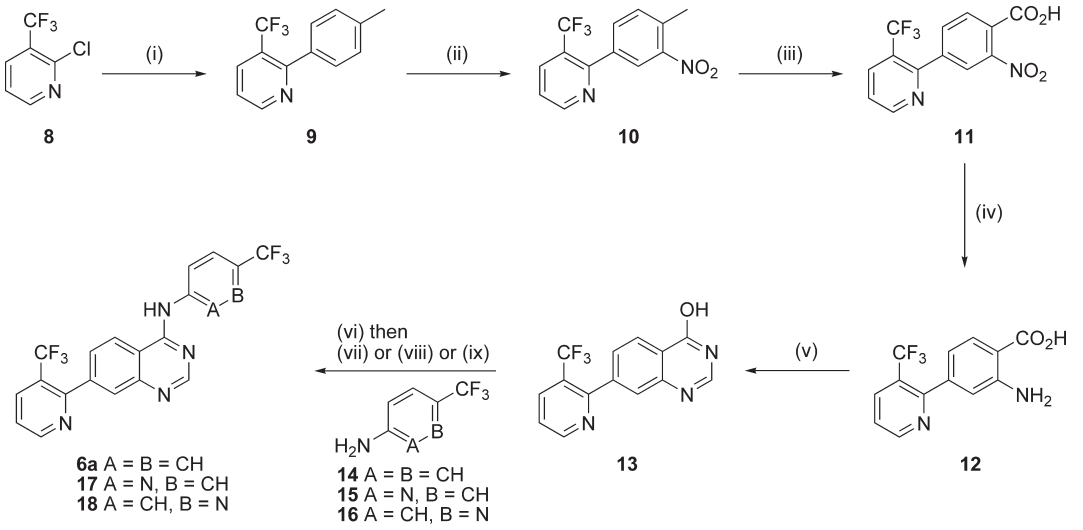


Figure 2. Evolution of TRPV1 antagonists.

carrageenan-induced thermal hyperalgesia (CITH). In addition to these prominent examples, a number of other TRPV1 antagonists with undisclosed structures are thought to be currently in various stages of clinical study. In addition to efficacy in pain trials the effects of other TRPV1 antagonists on body temperature in humans are awaited.

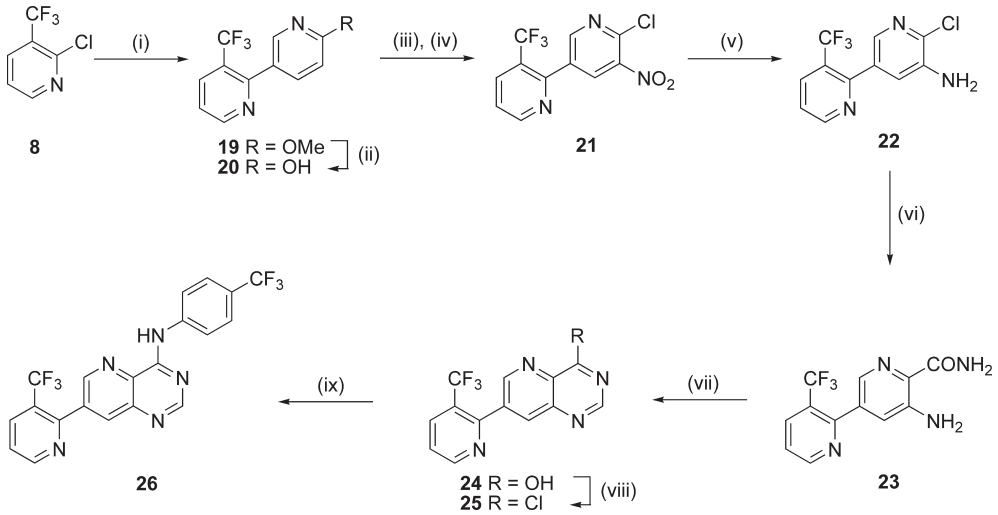
In a previous communication we described the discovery of a novel TRPV1 antagonist, the 4-aminoquinazoline **6a** (R = H), which was derived from the conformational restriction of the biarylamide **5**.[18] The biarylamide **5** in turn resulted from replacement of the piperazine in the original arylurea lead **4** with a phenyl ring (Figure 2).[19,20] The prototypical compound **6a** was superior to its forerunners in a number of respects, most notably in vitro potency. Furthermore, excellent oral exposure of **6a** was achieved using a dosing vehicle supplemented with vitamin E TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate). Under these conditions, **6a** demonstrated good in vivo efficacy, fully reversing CITH in rats (MED of 0.1 mg/kg). Plasma levels of **6a**, however, were significantly diminished upon dosing as a standard methylcellulose (MC) suspension. Efforts to improve the solubility and oral bioavailability of the series initially focused on the introduction of polar substituents at the C-2 position.[21] From this effort the 2-methoxymethyl analogue **6b** (R = CH_2OMe) exhibited good in vitro and in vivo potency (MED of 0.3 mg/kg in CITH) and was well absorbed following oral dosing as an MC homogeneous suspension. Unfortunately, significant hERG inhibition with **6b** (44% at 3 μM)[22] was deemed undesirable, as it could translate into cardiac QT interval prolongation in vivo. A second concern with compounds such as **6a** and **6b** was the presence of the 4-trifluoromethylaniline (TFMA) group at the 4-position of the quinazoline. TFMA is known to be mutagenic in the Ames assay and clastogenic in the in vitro assay for chromosome aberrations in Chinese hamster ovary cells.[23] Although TFMA is not clastogenic in the in vivo mouse micronucleus assay or in the in vivo cytogenetic test in Chinese hamster bone marrow cells, its potential release in vivo was considered a liability.[23] Third, the 4-aminoquinazoline skeleton has an extensive history of use in the pharmaceutical industry;[24] therefore, enhancing the structural novelty of this class was another important factor. Finally, improving aqueous solubility while maintaining potency and oral exposure remained critical considerations. With these concerns in mind, we initially chose to probe the effects of incorporating a nitrogen atom into the D-ring of the general structure **7** in an attempt to increase aqueous solubility and to lower the potential for oxidation to possibly toxic metabolites. Second, we investigated the importance of the location of the nitrogen atoms in the B- and C-rings of the general structure **7** on activity and "druglike" properties. For comparison, the 3-trifluoromethylpyridyl A-ring was kept constant throughout, since an earlier study had identified it

Scheme 1. Synthesis of Quinazolines **6a**, **17**, and **18**[a]



[a] Reaction conditions: (i) 4-MePhB(OH)$_2$, 2 M Na_2CO_3, $Pd(PPh_3)_4$, DME, 85 °C (83%); (ii) H_2SO_4, HNO_3, 0 °C (100%); (iii) $KMnO_4$, pyridine, H_2O, 110 °C (63%); (iv) 10% Pd/C, H_2, EtOH (92%); (v) $HCONH_2$, 145 °C (63%); (vi) $OPCl_3$, 2,6-lutidine, $CHCl_3$, 90 °C; (vii) **14**, IPA, 80 °C (68% over two steps); (viii) **15**, DMA, 125 °C, (21% over two steps); (ix) **16**, CH_3CN, 80 °C (81% over two steps).

Scheme 2. Synthesis of Pyrido[3,2-*d*]pyrimidine **26**[a]



[a] Reaction conditions: (i) 2-methoxypyridine-5-boronic acid, 2 M Na_2CO_3, $Pd(PPh_3)_4$, PhMe, 90 °C (95%); (ii) HBr, AcOH, reflux (93%); (iii) HNO_3, H_2SO_4, 0 °C, then 70 °C; (iv) $SOCl_2$, DMF (cat.), reflux (86% over two steps); (v) Fe, $CaCl_2$, EtOH, H_2O, reflux (85%); (vi) $Zn(CN)_2$, Pd_2dba_3, DPPF, DMF, H_2O, 120 °C (90%); (vii) $HC(OEt)_3$, 130 °C (91%); (viii) $SOCl_2$, DMF (cat.), reflux (87%); (ix) **14**, IPA, 80 °C (88%).

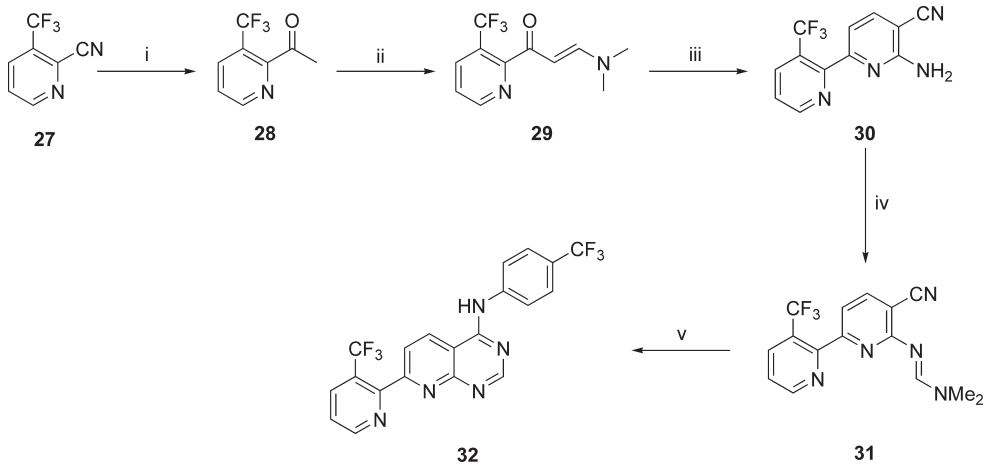
as a preferred substituent.[18] Herein we describe the synthesis, in vitro SAR, and in vivo characterization of a series of 6,6-heterocycles as replacements for the original quinazoline core.

Chemistry

The synthesis of the 4-aminoquinazolines **6a**, **17**, and **18** is outlined in Scheme 1. Suzuki coupling of the commercially available 2-chloro-3-(trifluoromethyl)pyridine (**8**) with *p*-tolylboronic acid gave the biaryl **9**. Subsequent nitration and benzylic oxidation with permanganate gave the acid **11** in good overall yield. Hydrogenation of the nitro group of **11** provided the aniline **12**, which was cyclized with formamide to the quinazoline **13**. Conversion of the quinazoline **13** to the corresponding chloride was achieved with phosphorus oxychloride and 2,6-lutidine. Since the product was sensitive to hydrolysis, it was used immediately in the final step to yield the desired targets **6a**, **17**, and **18**.

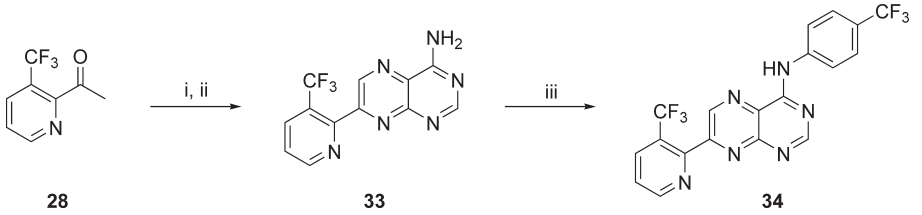
The synthesis of the pyrido[3,2-*d*]pyrimidine **26** is outlined in Scheme 2. Suzuki coupling of **8** and 2-methoxypyridine-5-boronic acid produced **19** which was demethylated with HBr in refluxing acetic acid to give the pyridone **20**. Nitration of **20** and chlorination of the product afforded 2-chloro-4-nitropyridine **21** in excellent yield over the two steps. The selective reduction of the nitro group of **21** in the presence of the 2-chloro group was achieved with iron and calcium chloride in refluxing ethanol, affording the 3-aminopyridine **22**. Cyanation of **22** was achieved using conditions described by Maligres;[25] however, analysis of an aliquot of the reaction mixture indicated that partial hydrolysis of the cyano group to the corresponding amide had occurred. Therefore, with additional water and further heating, the nitrile hydrolysis was brought to completion, providing an excellent yield of the amide **23**. Cyclization of **23** with triethyl orthoformate followed by chlorination with thionyl chloride and thermal

Scheme 3. Synthesis of Pyrido[2,3-*d*]pyrimidine **32**[a]



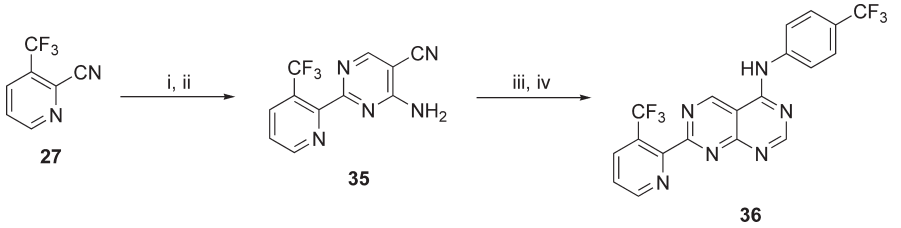
[a] Reaction conditions: (i) MeMgI, THF, 0 °C, 83%; (ii) $Me_2NCH(OMe)_2$, 105 °C, 100%; (iii) 3-amino-3-methoxyacrylonitrile, NH_4OAc, EtOH, 80 °C, 41%; (iv) $Me_2NCH(OMe)_2$, 110 °C, 100%; (v) **14**, AcOH, H_2O, reflux, 57%.

Scheme 4. Synthesis of Pteridine **34**[a]



[a] Reaction conditions: (i) AcOH, HBr, Br_2, 0 °C, 100%; (ii) 4,5,6-triaminopyrimidine, $NaHCO_3$, H_2O, 100 °C, air-oxidation, 23%; (iii) 4-trifluoromethylbromobenzene, Pd_2dba_3, Cs_2CO_3, xantphos, dioxane, 100 °C (39%).

Scheme 5. Synthesis of Pyrimido[4,5-*d*]pyrimidine **36**[a]



[a] Reaction conditions: (i) $LiN(SiMe_3)_2$, Et_2O, 0 °C, then AcOH, H_2O, room temp (66%); (ii) Et_3N, MeOH, $EtOCHC(CN)_2$, reflux (69%); (iii) $(MeO)_2CHNMe_2$, 110 °C (100%); (iv) **14**, AcOH, H_2O, reflux (49%).

displacement of the chloride with TFMA gave the pyrido-[3,2-*d*]pyrimidine **26**.

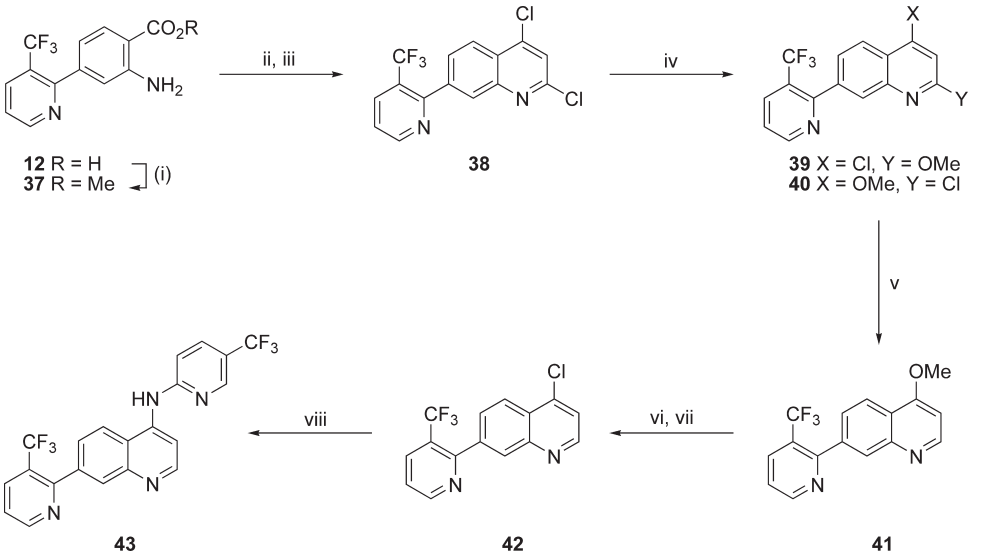
The synthesis of the pyrido[2,3-*d*]pyrimidine **32** is depicted in Scheme 3. Addition of methyl Grignard reagent to 2-cyano-3-trifluoromethylpyridine (**27**) gave the ketone **28** which was condensed with DMF dimethylacetal to yield the dimethylaminopropenone **29** quantitatively. Cyclization of **29** with 3-amino-3-methoxyacrylonitrile produced the 2-amino-3-cyanopyridine **30** in 41% yield. Condensation of the 2-aminopyridine **30** with DMF dimethylacetal afforded the formamidine **31** which was treated with TFMA in acetic acid at 100 °C to provide the desired pyrido[2,3-*d*]pyrimidine **32**.

The concise, albeit low yielding synthesis of the pteridine **34** is illustrated in Scheme 4. The methyl ketone **28** was treated with bromine and HBr in acetic acid. The resulting α-bromoketone was condensed with 4,5,6-triaminopyrimidine, then air-oxidized and purified to give the 4-aminopteridine **33** in moderate yield. Introduction of TFMA to the pteridine core was achieved by a palladium-coupling reaction and using xantphos as the catalyst[26] to afford the target **34**.

The synthesis of the pyrimido[4,5-*d*]pyrimidine **36** is shown in Scheme 5. 2-Cyano-3-trifluoromethylpyridine (**27**) was converted to the corresponding amidine which was thermally cyclized with (ethoxymethylene)malononitrile to give the suitably functionalized pyrimidine **35**. Condensation of the aminopyrimidine **35** with DMF dimethylacetal gave the corresponding formamidine which was treated with TFMA in acetic acid at 100 °C to afford the desired target compound **36**.

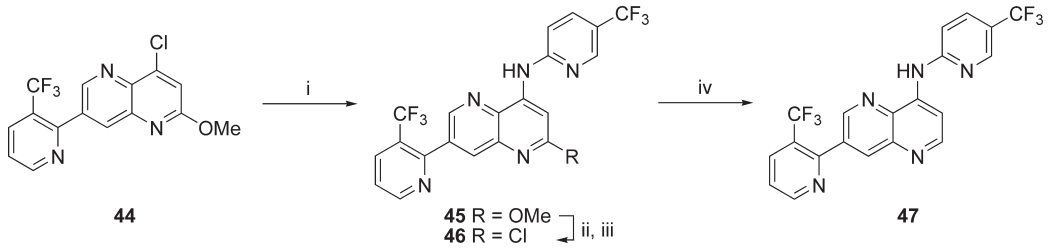
The route to the quinoline **43** is outlined in Scheme 6. The previously described acid **12** was converted to the methyl ester **37**, and by use of conditions similar to those described by Cai,[27] cyclization followed by chlorination gave the 2,4-dichloroquinoline **38**. Treatment of **38** with sodium methoxide produced a mixture of the 2-methoxyquinoline **39** and the 4-methoxyquinoline **40** which were separated by chromatography. Dechlorination of **40** using phase-transfer hydrogenation conditions[28]

Scheme 6. Synthesis of Quinoline **43**[a]



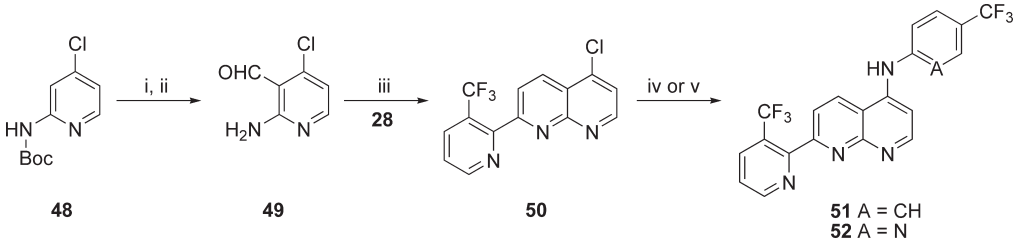
[a] Reaction conditions: (i) MeOH, HCl(g), reflux (92%); (ii) AcOH, dioxane, 60 °C, then $KN(SiMe_3)_2$, THF, PhMe, −78 °C to room temp; (iii) $OPCl_3$, reflux (77% over two steps); (iv) NaOMe, THF, room temp (59% for **39** and 30% for **40**); (v) **40**, CO_2NH_4, 10% Pd/C, MeOH, room temp (96%); (vi) 33% HBr in AcOH, 100 °C (100%); (vii) $OPCl_3$, reflux (89%); (viii) **15**, Pd_2dba_3, Cs_2CO_3, xantphos, dioxane, 100 °C (68%).

Scheme 7. Synthesis of [1,5]Naphthyridine **47**[a]



[a] Reaction conditions: (i) **15**, Pd_2dba_3, Cs_2CO_3, xantphos, dioxane, 100 °C (85%); (ii) 33% HBr in AcOH, 100 °C; (iii) $OPCl_3$, reflux (63% over two steps); (iv) HCO_2NH_4, 10% Pd/C, MeOH, 50 °C (71%).

Scheme 8. Synthesis of [1,8]Naphthyridines **51** and **52**[a]



[a] Reaction conditions: (i) ^{n}BuLi, THF, −78 °C, then DMF (73%); (ii) TFA, CH_2Cl_2, room temp (94%); (iii) ^{t}BuOK, THF, −20 °C (87%); (iv) **14**, 2 M HCl, ^{i}PrOH, 80 °C (78%); (v) **15**, 180 °C (62%).

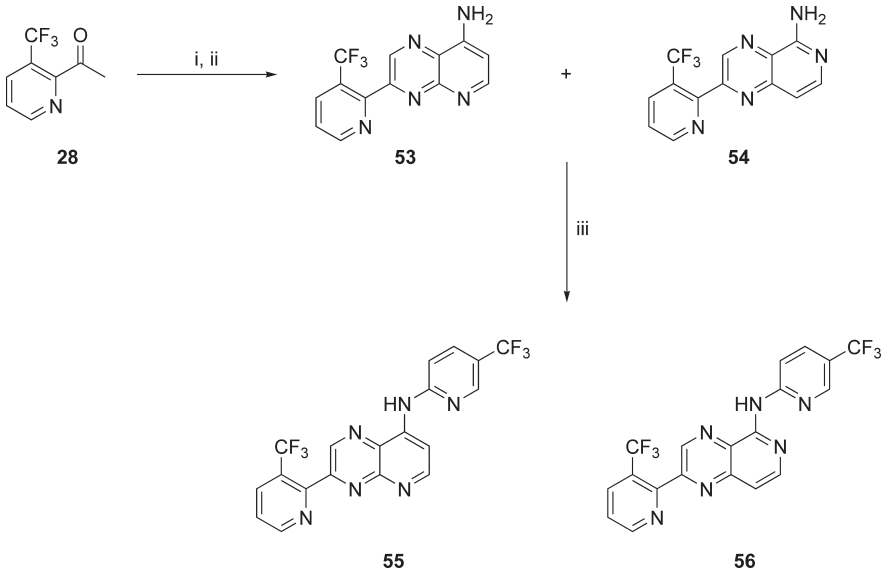
gave **41** in excellent yield. Subsequent demethylation and chlorination furnished the 4-chloroquinoline **42**. The 2-amino-5-trifluoromethyl pyridine D-ring was introduced in good yield using a xantphos-mediated palladium-catalyzed coupling[26] reaction with **42** to yield the quinoline **43**.

In a fashion analogous to the synthesis of the quinoline **41**, the 1,5-naphthyridine **44** was prepared from the previously described pyridine **23**. The 2-amino-5-trifluoromethylpyridyl group was introduced using the previously described xantphos/Pd_2dba_3 system[26] to provide **45**. The 2-methoxy substituent was removed following a three-step demethylation, chlorination, and hydrogenation sequence to afford the 1,5-naphthyridine **47** (Scheme 7).

The preparation of the [1,8]naphthyridines **51** and **52** is illustrated in Scheme 8. Ortho-lithiation of the commercially available 2-BOC-amino-4-chloropyridine (**48**), quenching of the aryllithium with DMF, and cleavage of the BOC group gave the functionalized pyridine **49**. Friedlander[29] reaction between the aldehyde **49** and the ketone **28** directly gave the 5-chloro-1,8-naphthyridine **50** in excellent yield. Introduction of the TFMA moiety under standard conditions gave **51**. A melt between **50** and 2-amino-5-trifluoromethylpyridine furnished **52**.

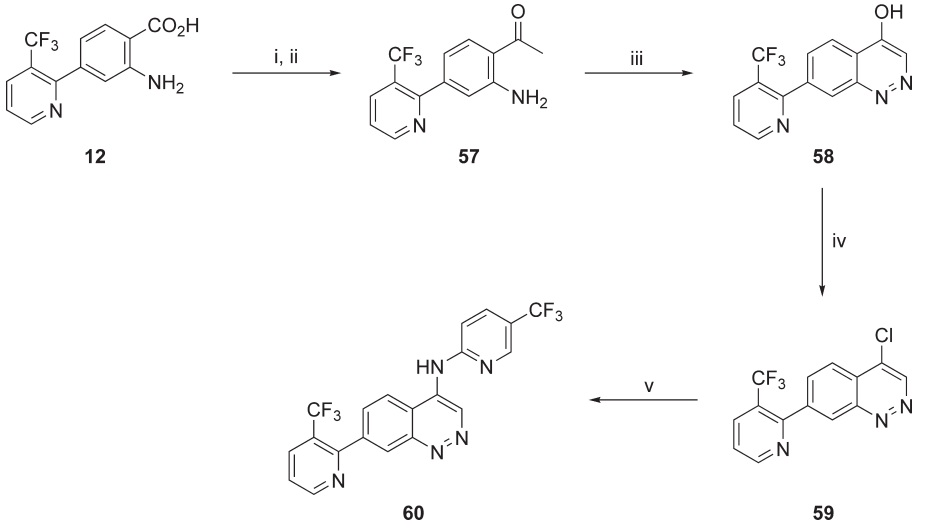
The route employed for the synthesis of the pyrido[2,3-*b*]-pyrazine **55** and the pyrido[3,4-*b*]pyrazine **56** is shown in Scheme 9. The methyl ketone **28** was brominated as described

Scheme 9. Synthesis of Pyrido[2,3-*b*]pyrazine **55** and Pyrido[3,4-*b*]pyrazine **56**[a]



[a] Reaction conditions: (i) AcOH, HBr, Br_2, 0 °C, 100%; (ii) 2,3,4-triaminopyridine, $NaHCO_3$, H_2O, 100 °C (32% yield of a mixture of **53** and **54**); (iii) 2-chloro-5-trifluoromethylpyridine, Pd_2dba_3, Cs_2CO_3, xantphos, dioxane, 100 °C (28% yield of **55** and 23% yield of **56**).

Scheme 10. Synthesis of Cinnoline **60**[a]



[a] Reaction conditions: (i) HN(OMe)Me·HCl, EDCI, Hünig's base, CH_2Cl_2, room temp (34%); (ii) MeMgI, THF, 0 °C (43%); (iii) $NaNO_2$, HCl, H_2O, 0 °C (62%); (iv) $OPCl_3$, reflux (87%); (v) **15**, Pd_2dba_3, Cs_2CO_3, xantphos, dioxane, 100 °C (76%).

previously and treated with 2,3,4-triaminopyridine to afford an inseparable mixture of the two regioisomers, the pyrido-[2,3-*b*]pyrazin-8-amine **53** and the pyrido[3,4-*b*]pyrazin-5-amine **54**. Palladium-catalyzed coupling[26] was carried out on this mixture, using 2-chloro-5-trifluoromethylpyridine to give **55** and **56** which were successfully separated in moderate yield by flash chromatography.

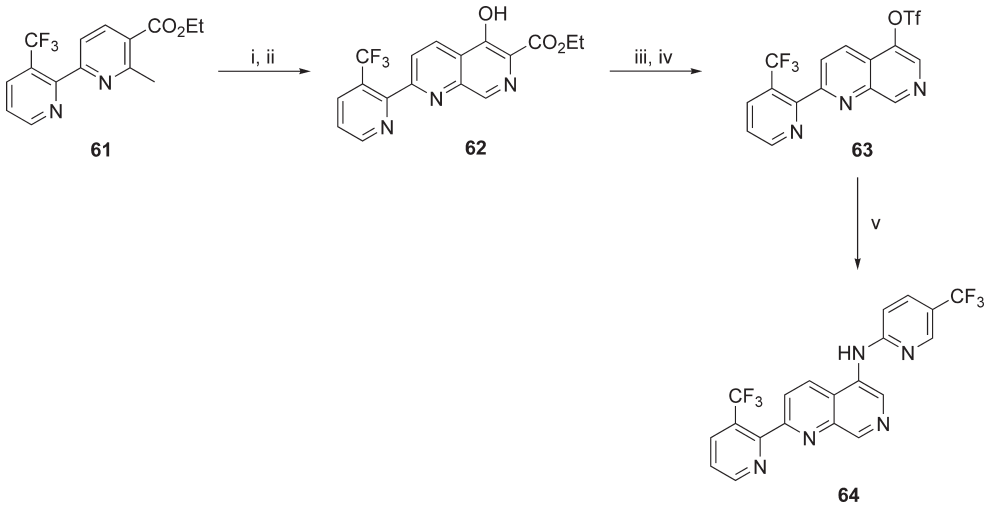
The synthesis of the cinnoline **60** is depicted in Scheme 10. The acid **12** described previously was converted, via the Weinreb amide, to the ketone **57** in moderate overall yield. Diazotization of the 2-aminoacetophenone **57** and ensuing cyclization[30] furnished the 4-cinnoline **58** in moderated yield. The cinnoline **58** was converted to the chloride **59** with phosphorus oxychloride, and then palladium-catalyzed coupling of **59** with the aminopyridine **15** gave the desired cinnoline **60**.

The synthesis of the [1,7]naphthyridine analogue **64** is outlined in Scheme 11. Bromination of the methylpyridine **61** and subsequent cyclization with methyl 2-(4-methylphenylsulfonamido)acetate and sodium ethoxide in refluxing ethanol gave the [1,7]naphthyridine **62** in 61% yield over the two steps. Hydrolysis and decarboxylation of the ester **62** was followed by conversion to the triflate to afford the final intermediate **63**. Palladium-catalyzed coupling of **63** with the aminopyridine **15** gave the desired [1,7]naphthyridine **64**.

Results and Discussion

The compounds were evaluated for their ability to block capsaicin activation of human TRPV1 channels using fluorometric imaging plate reader (FLIPR) technology, and the results are shown in Table 1.[31] In the first three compounds **6a**, **17**, and **18**, the aminoquinazoline core was kept constant and the three *p*-trifluoromethylaryl D-rings were compared. The potency of **17** (2-amino-5-trifluoromethylpyridine) was

Scheme 11. Synthesis of [1,7]Naphthyridine **64**[a]



[a] Reaction conditions: (i) AIBN, NBS, CH_2Cl_2, H_2O; (ii) $TosNHCH_2CO_2Et$, NaOEt, EtOH, (61% over two steps); (iii) 6 M HCl, 95 °C; (iv) Tf_2O, Hünig's base, CH_2Cl_2, (59% over two steps); (v) **15**, Pd_2dba_3, Cs_2CO_3, xantphos, dioxane, 110 °C (61%).

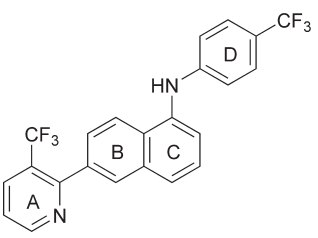
similar to the benchmark **6a** (TFMA), while that of **18** (3-amino-6-trifluoromethylpyridine) was slightly lower. Because of the poor solubility of **6a** (below the limit of detection at pH 7.4)[21] and to allow comparisons following modification, the solubility of compounds was measured in 0.1 N HCl. The solubility of **6a** was measurable under these conditions (16 μg/mL), and the addition of a nitrogen atom into the D-ring essentially doubled the solubility when measured in 0.1 N HCl.

The effect of the introduction of nitrogen atoms into the B-ring was investigated next, while the TFMA D-ring was retained for each of the four analogues **26**, **32**, **34**, and **36**. Introduction of a nitrogen at the 5-position of the quinazoline (pyrido[3,2-*d*]pyrimidine **26**) or at the 8-position (pyrido[2,3-*d*]pyrimidine **32**) gave compounds that were of similar activity to **6a**. Incorporation of nitrogen at both the 5- and 8-positions gave the pteridine **34** (IC_{50} = 0.21 nM) which was the most active compound prepared in the series. The compound derived from introduction of a single nitrogen atom at the 6-position of the aminoquinazoline was not prepared in this series; however, introduction of nitrogen at both the 6- and 8-positions, as in the pyrimido[4,5-*d*]pyrimidine **36**, resulted in a dramatic loss in activity (IC_{50} = 665 nM). This result was in accord with the introduction of nitrogen at positions equivalent to the 6-position in other templates which also resulted in a significant loss in activity.[18] In terms of solubility, the addition of nitrogen atoms into the B-ring had a detrimental effect and all four analogues had very poor solubility in 0.1 N HCl (< 10 μg/mL).

The effect on TRPV1 activity of the nitrogen atoms in the C-ring was investigated next, with the 2-amino-5-trifluoromethylpyridine D-ring kept constant. Removal of the nitrogen at the 3-position of the quinazoline core gave quinoline **43** and only a small loss in the ability of the compound to block activation of TVRP1 (compare **43** IC_{50} = 1.65 nM vs **17** IC_{50} = 0.85 nM). Surprisingly, introduction of nitrogen at the 5-position, a change that had given a boost in activity in the quinazoline series (**26** IC_{50} = 0.63 nM), gave a significant loss in activity for the corresponding [1,5]naphthyridine **47** (IC_{50} = 308 ± 190 nM); it is unclear why this led to such a loss in activity. Addition of nitrogen at the 8-position in the quinazoline series had given an increase in activity. However, in the quinoline series, this modification, exemplified with [1,8]naphthyridine **52**, resulted in a minor loss in activity (compare **32** IC_{50} = 0.83 nM vs **52** IC_{50} = 2.2 nM). The TFMA analogue **51** was also made with the [1,8]naphthyridine core, and consistent with the activity observed for D-rings in the quinazoline series, the activity was slightly reduced. The introduction of nitrogen at both the 5- and 8-positions in the quinazoline template gave the most active compound in the study, pteridine **34** (IC_{50} = 0.21 nM), and the same modification in the quinoline series afforded the similarly potent pyrido[2,3-*b*]pyrazine **55** (IC_{50} = 0.23 nM). The importance of the nitrogen at the 1-position of the C-ring was established by the loss in activity observed for pyrido-[3,4-*b*]pyrazine **56** in which the nitrogen at the 1-position had been deleted (compare **34** IC_{50} = 0.21 nM vs **56** IC_{50} = 79 nM). The effect of the introduction of a nitrogen atom at the 2-position was investigated with the cinnoline **60** and the [1,7]naphthyridine **64** analogues. In both examples, the inhibitory potency was greatly diminished (compare **60** IC_{50} = 29 nM vs **43** IC_{50} = 1.65 nM and **64** IC_{50} = 460 nM vs **52** IC_{50} = 2.2 nM). In terms of solubility the quinoline **43** and aza-quinoline analogues **47**, **51**, **52**, and **64** had measurable solubility in 0.1 N HCl, but the addition of a third nitrogen atom into the core (e.g., **55** and **56**) resulted in a significant loss in solubility.

The aminoquinazolines **6a**, **17**, and **18** and the [1,8]naphthyridine **52** demonstrated acceptable potency, solubility in 0.1 N HCl, and stability in rat liver microsomes. They were advanced into rat pharmacokinetic experiments (Table 2). Upon oral dosing as an MC suspension, the bioavailabilty of **6a** (TFMA D-ring) was very low (F = 8%). To determine if the low bioavailability of **6a** was related to poor permeability, the rate of basolateral to apical (B to A) movement and the rate of apical to basolateral (A to B) movement across a monolayer of MDR1-transfected LLC-PK1 cells were determined for **6a**.[32] Adequate permeability (P_{app} = 11.0 × 10^{-6} cm/s) and a Pgp efflux ratio (B to A)/(A to B) of close to unity (1.1) implied that **6a** was not a Pgp substrate, and the excellent stability in rat liver microsomes[33] suggested that the poor oral exposure was more likely due to low solubility rather than poor permeability or metabolic stability. Indeed, the levels of **6a** were below the limits of quantification (BLQ) when

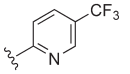
Table 1. In Vitro Ability of Compounds To Inhibit Activation of hTRPV1 Receptors[a] and Solubility in 0.1 N HCl[b]



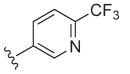
D-Ring:

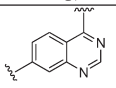
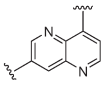
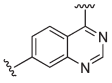
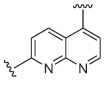
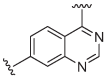
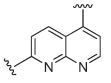
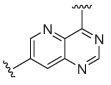
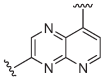
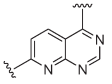
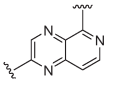
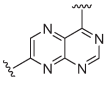
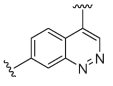
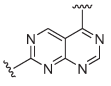
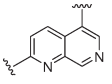
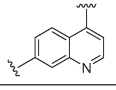
D1

D2



D3



Cmpd	CORE (B/C-Ring)	D-ring	hTRPVl[a] IC_{50} (nM)	Solubility 0.1N HCl (μg/ml)[b]	Cmpd	CORE (B/C-Ring)	D-ring	hTRPVl[a] IC_{50} (nM)	Solubility 0.1N HCl (μg/ml)[b]
6a		D1	1.1 ± 0.8	16	**47**		D2	308 ± 190	38
17		D2	0.85±0.6	33	**51**		D1	6.1 ± 2	24
18		D3	7.1 ± 2	35	**52**		D2	2.2 ± 1	40
26		D1	0.63±0.4	6	**55**		D2	0.23 ± 0.1	8
32		D1	0.83±0.7	9	**56**		D2	79 ± 28	12
34		D1	0.21±0.1	1	**60**		D2	29 ± 9	ND[c]
36		D1	665 ±220	4	**64**		D2	460 ± 290	20
43		D2	1.65±0.8	34					

[a] Human TRPV1 receptor activated by capsaicin. Unless otherwise stated, all values are the mean ± SEM of at least three separate experiments. [b] Determined by HPLC/MS analysis after 4 h in 0.1 N HCl. [c] ND = not determined.

Table 2. Rat Pharmacokinetic Data for Selected Compounds[a]

	iv/po dose (mg/kg)	T_{max} (h)	$T_{1/2}$ (h)	CL ((mL/min)/kg)	Vd (L/kg)	F (%)	solubility, 0.1 N HCl (μg/mL)[b]	solubility, pH 7.4 (μg/mL)[c]	rat liver microsomes, % remaining[d]
6a	2.7/2	3.0	8	23	13	8	16	0	93
17	1.5/2	5.7	38	4.2	12	89	33	0	91
18	1.5/10	4.7	4	22	5.5	65	35	0	100
52	1/1	1.1	1.4	34	3.9	52	40	2	100

[a] Compounds dosed in 50% PEG-400/water (iv) and 0.5% methylcellulose, 0.1% triacetin (po). [b] Determined in 0.1 N HCl. [c] Equilibrium solubility determined at pH 7.4. [d] Percentage of compound remaining after 10 min in rat liver microsomes.[33]

assessed at pH 7.4 in an equilibrium solubility study. Replacement of the TFMA with the 2-amino-5-trifluoromethylpyridine group, as in compound **17**, resulted in higher solubility than **6a** in 0.1 N HCl but not at pH 7.4. Nevertheless, when dosed in the same vehicle, **17** achieved a remarkably higher oral bioavailability (F = 89%) than **6a** (F = 8%). The very low clearance (4.2 (mL/min)/kg) and large volume of distribution (12 L/kg) exhibited by **17** accounted for its very long half-life (38 h). In fact, a significant improvement in pharmacokinetic properties upon replacing a TFMA group by 2-amino-5-trifluoromethylpyridine had previously been described by Carruthers in the arylurea series **4** of TRPV1 antagonists.[20c] The 3-amino-6-trifluoromethylpyridine analogue **18**, which displayed a similar solubility profile to **17**, also had good oral bioavailability (F = 65%) but a greatly reduced half-life (4 h) and volume of distribution (5.5 L/kg) compared to **17** and consequently a higher but still moderate clearance. The [1,8]naphthyridine **52** was rapidly absorbed compared to

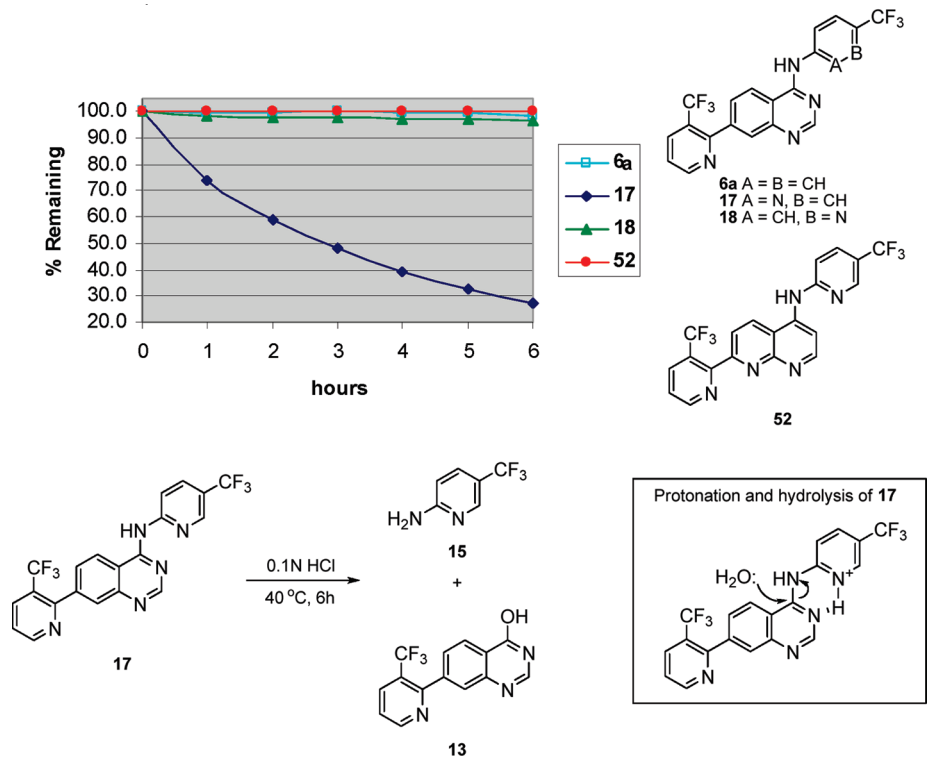


Figure 3. Stability of selected compounds in 0.1 N HCl at 40 °C.

the three quinazolines (T_{max} = 1.1 h) and had good oral bioavailability (F = 52%). Compound **52** had a relatively high clearance (~45% liver blood flow) and lower volume of distribution than **6a**, **17**, and **18**, resulting in a shorter observed half-life (1.4 h).

Because of concerns about the stability of the compounds during transit through the stomach (pH between 1 and 2), the acid stability of the three quinazolines **6a**, **17**, and **18** and the [1,8]naphthyridine **52** was studied in 0.1 N HCl at 40 °C over 6 h. Aliquots were removed and assayed at 1 h intervals (Figure 3). Compound **6a** (TFMA D-ring) degraded by 3% after 6 h, while **18** (3-aminopyridine D-ring) was more stable and had degraded by only 1% over 6 h. In contrast, the 2-amino-5-trifluoromethylpyridine D-ring analogue **17** was hydrolytically labile and rapidly degraded by ~60% after 4 h (approximate stomach transit time in humans) and by ~73% after 6 h. In principle, hydrolysis could have occurred to produce quinazoline **13** or 5-trifluoromethylpyridin-2-one. However, analysis was highly selective, yielding quinazoline **13** and 2-amino-5-trifluoromethylpyridine (**15**) exclusively. The lability of **17** was disappointing, since 2-amino-5-trifluoromethylpyridine (**15**) was inactive in an in-house Ames mutagenicity assay and had emerged as a preferred D-ring and TFMA alternative in this series. Presumably, protonation of the activated pyridinylaminoquinazoline rendered it susceptible to the hydrolysis. Accordingly, retention of the 2-aminopyridine D-ring but deletion of one of the activating nitrogen's from the core, as in the [1,8]naphthyridine **52**, afforded a hydrolytically stable compound (0.06% degradation after 6 h).

On the basis of a number of factors including hTRPV1 potency, solubility, oral bioavailability, and acid stability, the [1,8]naphthyridine **52** was profiled further. Key in vitro and in vivo parameters obtained for **52** are compiled in Table 3. The ability of **52** to inhibit the rat TRPV1 receptor upon activation at low pH (5.0−5.5) was consistent with the activity at the human receptor (capsaicin activation), demonstrating the effectiveness of **52** to block the TRPV1 channel irrespective of the species or the mode of activation. Measurement of the plasma protein binding in fresh rat and human plasma indicated relatively high free-fractions for **52**: 10.7% free in rat plasma and 6.5% free in human plasma. The high permeability (P_{app} = 29.8 × 10^{-6} cm/s) and Pgp efflux ratio of 1.7 indicated that **52** was not a Pgp substrate, although an in vivo brain to plasma ratio of less than unity (B/P = 0.3) indicated that there was resistance to crossing the blood−brain barrier. hERG inhibition had been identified as a potential liability for some analogues in the quinazoline series.[21] SAR suggested that a substituent at the 2-position contributed to this undesirable activity (compare **6a** R = H, 8% inhibition at 3 μM but **6b** R = CH_2OMe, 44% inhibition at 3 μM in a whole cell

Table 3. Key in Vitro and in Vivo Data for Compound **52**

parameter	
hTRPV1-cap IC_{50} (nM)[a]	2.2
rTRPV1-pH IC_{50} (nM)[b]	3.25
plasma protein binding, rat (%)[c]	89.3
plasma protein binding, human (%)[c]	93.5
Pgp efflux ratio[d]	1.7
P_{app} (10^{-6} cm/s)[e]	29.8
brain/plasma ratio[f]	0.3
hERG, % inhibition at 10 μM[g]	47
hERK1, IC_{50} (μM)[h]	0.98

[a] Human TRPV1 receptor activated by capsaicin. [b] Rat TRPV1 receptor activated by low pH (5.0−5.5). [c] Percentage plasma protein bound to fresh rat or human plasma (centrifugation method using ^{14}C radiolabeled **52**). [d] MDR1 directional transport ratio (B to A)/(A to B). [e] Passive permeability (10^{-6} cm/s). [f] Brain to plasma ratio at 1 h following a 3 mg/kg oral dose in rats (0.5% methylcellulose, 0.1% triacetin vehicle). [g] Blockade of hERG potassium channel in whole cell (Cos7) electrophysiological assay. [h] Human protein serine/threonine kinase, ERK1.

Table 4. Pharmacokinetic Data for Ascending Doses of **52** in Rat[a]

species	po dose (mg/kg)	AUC_{0-24h} (μM·h)	C_{max} (μM)	T_{max} (μM)
rat	1	0.6	0.24	1.1
rat	10	22.6	2.87	3.33
rat	100	203.9	12.87	6.00

[a] Compounds dosed in 0.5% methylcellulose, 0.1% triacetin (po).

(Cos7) electrophysiological assay). We were therefore gratified to observe a moderate but acceptable level of hERG inhibition for **52** (47% at 10 μM) which lacks a C-2 substituent. Compound **52** was highly selective and showed few effects at 10 μM against a panel of more than 160 receptors, ion channels, transporters, and kinases (MDS Pharma Services). The one exception among the kinases was the protein serine/threonine kinase ERK1 with IC_{50} = 0.98 μM. Compound **52** was devoid of activity at other protein serine/threonine kinases including p38α, PKA, PKC, PKCα, and the tyrosine kinase EGF and insulin receptors. The compound did inhibit the monoamine transporter (rabbit, $IC_{50} \approx 0.5\,\mu$M) and L-type calcium channels (rat, $IC_{50} \approx 3-4\,\mu$M).

Systemic exposure was high in rats following oral administration of **52** at 1, 10, and 100 mg/kg as a 0.5% methylcellulose suspension. In terms of proportionality, there was a 37-fold increase in AUC_{0-24h} between the 1 and 10 mg/kg doses (12-fold difference in C_{max}) and a 9-fold increase in AUC_{0-24h} between the 10 and 100 mg/kg doses (4- to 5-fold difference in C_{max}) (Table 4).

On the basis of the excellent in vitro potency, good selectivity, and oral exposure, compound **52** was selected for further in vivo evaluation in a number of pain models. Compound **52** was tested in the rat carrageenan-induced thermal hyperalgesia model of acute inflammatory pain.[34] Rats received an intraplantar injection of λ-carrageenan (0.1 mL of 1% solution made up in saline) or saline (0.1 mL of 0.9% solution) into one hind paw, and thermal hyperalgesia was determined using a Hargreaves apparatus by measuring the latency to withdraw the paw from a radiant heat stimulus 3 h later. Thermal hyperalgesia was defined as the difference in paw withdrawal latencies determined for rats injected with saline or carrageenan. Compound **52** (0.3, 1, or 3 mg/kg) or vehicle (5 mL/kg 0.5% methylcellulose) was administered orally 2 h after carrageenan (i.e., when the thermal hyperalgesia had already developed). Immediately following testing, blood was collected for the determination of plasma drug levels. The [1,8]naphthyridine **52** significantly reversed thermal hyperalgesia induced by carrageenan injection (Figure 4). The effects of **52** were dose-dependent. A complete reversal of the effects of carrageenan was observed at 3 mg/kg po with associated compound plasma concentration of 1.40 μM. Taking into account plasma protein binding in rat (89.3%, Table 3), this corresponds to a free plasma concentration of 150 nM.

Compound **52** reversed mechanical hyperalgesia in a rat model of persistent inflammation. Rats received an intraplantar complete Freund's adjuvant (CFA, 200 μL) in the left hind paw. The next day the rats were dosed orally once a day for 3 consecutive days with compound **52** (1, 3, or 10 mg/kg), vehicle, or naproxen (20 mg/kg) as the positive control. Mechanical hypersensitivity was recorded as a differential weight-bearing response, measured 0, 1, 2, 4, and 24 h postdosing. In a separate cohort plasma samples were also taken each day, 2 h after dosing compound **52**. Figure 5 shows the difference in weight bearing between ipsilateral (CFA-injected) and contralateral hind paws over the course of the

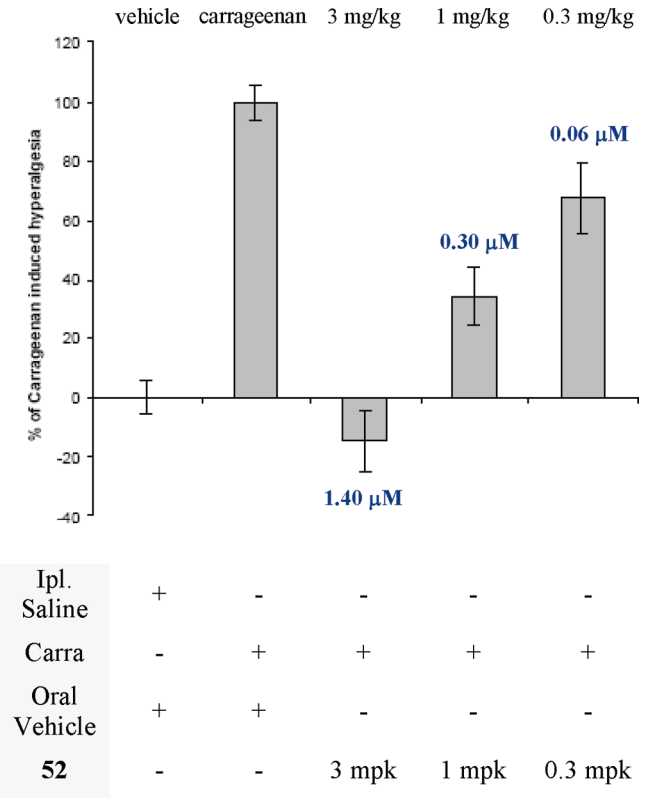


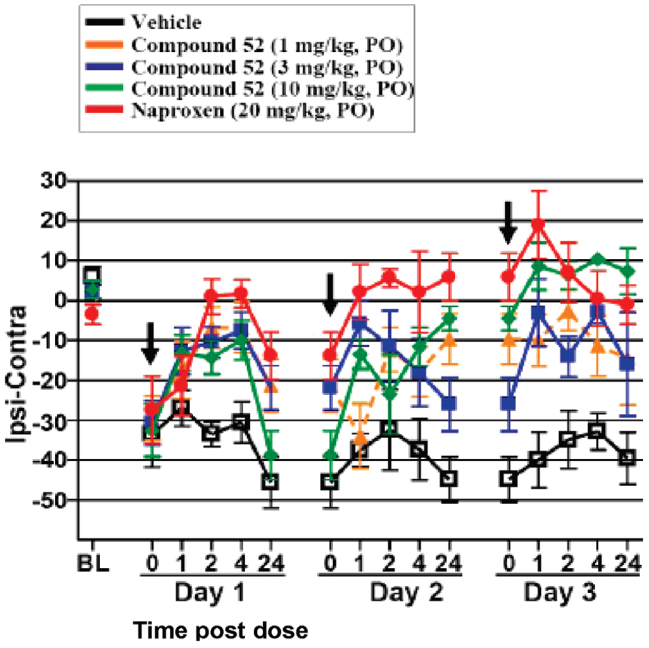
Figure 4. Effect of compound **52** on carrageenan-induced thermal hyperalgesia in rats and plasma concentrations at 3.0, 1.0, and 0.3 mg/kg. Plasma samples were taken immediately after testing ($t \approx$ 1 h), and the associated plasma concentrations are denoted in blue.

study. Compound **52** significantly attenuated the favoring response compared to vehicle at all doses tested, and by day 3, compound **52** (10 mg/kg) had completely reversed the effects of CFA. The magnitude of the effect was equivalent to that observed for rats treated with naproxen (20 mg/kg). Plasma concentrations at 2 h postdose ranged between 2.3 and 5.2 μM for the 10 mg/kg dose. On the basis of an in vitro rat plasma protein binding of 89.3% (Table 3), this corresponds to free plasma concentrations of 0.25 and 0.56 μM, respectively.

Recent reports have indicated that acute administration of brain penetrant TRPV1 antagonists, at doses producing maximal inhibition in acute pain models, causes hyperthermia (~0.5 to 1.5 °C) in rats.[15,35] To investigate this phenomenon with a moderately brain penetrant compound from the azaquinazoline series, compound **52** was dosed at 3 mg/kg po once a day for 4 days to rats fitted with telemetry devices and core body temperature readings were taken (see Supporting Information). On day 1, **52** caused a significant increase (~1.5 °C) in core body temperature above vehicle controls 1 h after dosing and remained elevated for greater than 10 h. The hyperthermic effect was tolerated upon repeat dosing such that by day 4 the core body temperature of rats treated with compound **52** was indistinguishable from that observed for vehicle treated rats.

Conclusion

In summary, we have investigated the importance of inserting nitrogens into the B-, C-, and D-rings of quinazoline **6a** with the goal of addressing issues related to pharmacokinetics (e.g., low oral exposure), druglike properties (e.g., aqueous solubility), and potential metabolic/toxicological risks (e.g., release of TFMA and hERG channel inhibition). To this



Dose of **52** (mg/kg)	Plasma concentration 2h post dose (μM)		
	Day 1	Day 2	Day 3
1.0	0.10	0.39	0.38
3.0	0.23	1.33	0.93
10.0	2.30	5.23	3.26

Figure 5. Effect of compound **52** at 1, 3, and 10 mg/kg, po, in the CFA model of inflammation and spontaneous nociception in rats and plasma levels 2 h after each daily dose (⇓).

end, chemistry was developed to synthesize a number of 6,6-heterocyclic cores. Of particular note was the concise synthesis of the 1,8-napthyridine core (e.g., **52**) which utilized a Friedlander cyclization of two readily available fragments. Acceptable on-target potency was maintained with a number of core examples, while compound **52** demonstrated marked improvements in oral exposure and aqueous solubility while achieving a lowered inhibition of the hERG channel. Importantly, compound **52** was devoid of a TFMA moiety. The 1,8-napthyridine **52** also displayed a good selectivity profile in an off-target screen of over 160 receptors, ion channels, and enzymes. The overall profile of **52** made it an excellent candidate for additional in vivo preclinical studies to assess the pharmacological effects of a TRPV1 antagonist. In rats, the compound significantly attenuated inflammatory pain in both an acute (carrageenan) and a subchronic (CFA) setting, further supporting the utility of a TRPV1 antagonist for the treatment of inflammatory pain states (e.g., osteoarthritis). Oral administration of **52** to rats produced an increase in core body temperature of ~1.5 °C, a finding consistently observed with a number of other TRPV1 antagonists.[35] The observed hyperthermic effect tolerated after repeated doses of **52**.

Experimental Section

General. Melting points were determined using a capillary melting apparatus and were uncorrected. Elemental analyses were obtained for all new compounds and were within 0.4% of theoretical C, H, and N. ^{1}H NMR spectra were recorded in deuteriochloroform (unless otherwise noted) with tetramethylsilane as the internal standard at 400 MHz. Coupling constants (J values) are quoted to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded in deuteriochloroform (unless otherwise noted) at 100 MHz. Mass spectra were recorded on a VG 70SE magnetic sector mass spectrometer. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV_{254} plates. Unless otherwise stated, preparative column chromatography was carried out on 60H silica gel (Merck 9385). Compositions of solvent mixtures are quoted as ratios of volume. Known compounds gave spectral and analytical data consistent with literature values. Analytical HPLC used to determine the purity of target compounds was conducted using two different methods. The results are expressed as retention times in minutes, and the relative content is expressed as a percentage. All final compounds had purity of >95% by both methods (see Supporting Information for conditions and chromatograms).

2-*p*-Tolyl-3-trifluoromethylpyridine (9). To a degassed mixture of 2-chloro-3-(trifluoromethyl)pyridine (**8**) (12.7 g, 70.1 mmol), *p*-tolylboronic acid (9.6 g, 70.6 mmol), and 2 M Na_2CO_3 (175 mmol) in DME (200 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_4$ (3.23 g, 2.8 mmol). The mixture was heated at 80 °C overnight, concentrated, and extracted with ethyl acetate (3 × 400 mL). The combined extracts were dried (Na_2SO_4), concentrated, filtered through a silica gel pad (elution with ethyl acetate), and gave the title compound **9** (13.8 g, 83%). **MS 238 (M + 1), ^{1}H NMR δ ($CDCl_3$) 8.83 (1H, d, J = 4 Hz), 8.06 (1H, d, J = 8 Hz), 7.42−7.37 (3H, m), 7.25 (2H, d, J = 7.5 Hz), 2.42 (3H, s).

2-(4-Methyl-3-nitrophenyl)-3-(trifluoromethyl)pyridine (10). To a solution of 2-*p*-tolyl-3-trifluoromethylpyridine (**9**) (1.99 g, 8.4 mmol) in H_2SO_4 (6 mL) was cautiously added fuming HNO_3 (2 mL). The mixture was stirred for 1 h at RT and poured onto ice−water (30 mL). The mixture was extracted with ethyl acetate (3 × 75 mL) and the combined extracts washed with 1 N NaOH (50 mL), dried (Na_2SO_4), concentrated and afforded the title compound **10** (2.37 g, 100%). MS 283 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.87 (1H, d, J = 4 Hz), 8.20 (1H, s), 8.13 (1H, d, J = 7.5 Hz), 7.67 (1H, d, J = 7 Hz), 7.52−7.43 (2H, m), 2.69 (3H, s).

2-Nitro-4-(3-trifluoromethylpyridin-2-yl)benzoic Acid (11). To a solution of 2-(4-methyl-3-nitrophenyl)-3-(trifluoromethyl)-pyridine (**10**) (2.01 g, 7.1 mmol) in a mixture of pyridine (10 mL) and water (5 mL) was added potassium permanganate (3.99 g, 25.3 mmol) in portions. The mixture was heated at 110 °C for 4 h and cooled to room temperature. Additional potassium permanganate (3.99 g, 25.3 mmol) and water (10 mL) were added. The mixture was reheated at 110 °C for 16 h. The mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated, diluted with water (50 mL), and the aqueous layer was washed with ethyl acetate (50 mL). The aqueous layer was neutralized with 2 N HCl and the precipitate collected and gave the title compound **11** (1.4 g, 63%). MS 313 (M + 1). ^{1}H NMR δ (DMSO) 8.96 (1H, d, J = 4.5 Hz), 8.38 (1H, d, J = 8 Hz), 8.09 (1H, s), 7.99 (1H, d, J = 8.5 Hz), 7.86 (1H, d, J = 7 Hz), 7.86−7.73 (1H, m).

2-Amino-4-(3-trifluoromethylpyridin-2-yl)benzoic Acid (12). A mixture of 2-nitro-4-(3-trifluoromethylpyridin-2-yl)benzoic acid (**11**) (1.2 g, 3.84 mmol) and 10% palladium on carbon (150 mg) in 95% ethanol was hydrogenated (1 atm) for 16 h. The mixture was filtered through Celite and evaporated to yield the title compound **12** (1.01 g, 92%). MS 283 (M + 1). ^{1}H NMR δ (DMSO) 8.87 (1H, d, J = 4 Hz), 8.28 (1H, d, J = 8 Hz), 7.73 (1H, d, J = 9 Hz), 7.67−7.62 (1H, m), 6.78 (1H, s), 6.53 (1H, d, J = 8.5 Hz).

7-(3-Trifluoromethylpyridin-2-yl)quinazolin-4-ol (13). A solution of 2-amino-4-(3-trifluoromethylpyridin-2-yl)benzoic acid

(**12**) (552 mg, 1.95 mmol) in formamide (10 mL) was heated at 145 °C for 4 h. The mixture was cooled to room temperature and water (20 mL) added. The precipitate was collected by filtration, air-dried and afforded the title compound **13** (359 mg, 63%). MS 292 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.93 (1H, d, J = 4 Hz), 8.41 (1H, d, J = 8.5 Hz), 8.19−8.17 (2H, m, J = 8 Hz), 7.95 (1H, s), 7.68 (1H, d J = 7 Hz), 7.58−7.52 (1H, m).

(4-Trifluoromethylphenyl)-[7-(3-trifluoromethylpyridin-2-yl)-quinazolin-4-yl]amine (6a). A mixture of 7-(3-trifluoromethylpyridin-2-yl)quinazolin-4-ol (**13**) (111 mg, 0.38 mmol), 2,6-lutidine (102 mg, 0.95 mmol), $OPCl_3$ (145 mg, 0.95 mmol), and chloroform (HPLC grade, 5 mL) was refluxed for 24 h. The mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The residue was redissolved in dichloromethane and filtered through a short pad of silica gel (elution with ethyl acetate/hexane, 1:1). The resulting solid was dissolved in IPA (5 mL), and 4-(trifluoromethyl)aniline (**14**) (106 mg, 0.66 mmol) was added. The mixture was heated at 80 °C for 4 h, cooled to room temperature, and ethyl acetate (5 mL) was added. The precipitate was collected by filtration and partitioned between ethyl acetate (10 mL) and saturated sodium bicarbonate solution (10 mL). The layers were separated, and the aqueous portion was extracted with ethyl acetate (10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), evaporated and gave the title compound **6a** (112 mg, 68% over two steps). MS 435 (M + 1). ^{1}H NMR δ ($CDCl_3$) 11.75 (1H, br s), 9.03−8.99 (3H, m), 8.42 (1H, d, J = 7 Hz), 8.07−8.04 (3H, m), 7.96 (1H, d, J = 8.5 Hz), 7.87 (2H, d, J = 7.5 Hz), 7.79 (1H, dd, J = 2.5 and 7.5 Hz). Analytical HPLC: method 1, 12.29 (94.9%); method 2, 5.62 (99.4%).

(5-Trifluoromethylpyridin-2-yl)-[7-(3-trifluoromethylpyridin-2-yl)quinazolin-4-yl]amine (17). An identical procedure as described above was followed. The intermediate 4-chloro-7-(3-trifluoromethylpyridin-2-yl)quinazoline was dissolved in DMA (5 mL), and 2-amino-5-trifluoromethyl pyridine (**15**) (105 mg, 0.65 mmol) was added. The mixture was heated at 125 °C for 6 h, cooled to room temperature, and partitioned between ethyl acetate (10 mL) and saturated sodium bicarbonate solution (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by preparative thin layer chromatography (elution with ethyl acetate/hexane, 1:1) and afforded the title compound **17** (34 mg, 21% over two steps). MS 436 (M + 1). ^{1}H NMR δ (DMSO) 10.99 (1H, s), 8.97 (1H, d, J = 5 Hz), 8.86−8.81 (3H, m), 8.68 (1H, d, J = 8 Hz), 8.39 (1H, d, J = 8.5 Hz), 8.26 (1H, d, J = 8 Hz), 7.90 (1H, s), 7.77−7.72 (2H, m). Analytical HPLC: method 1, 12.51 (99.1%); method 2, 5.00 (98.3%).

(6-Trifluoromethylpyridin-3-yl)-[7-(3-trifluoromethylpyridin-2-yl)quinazolin-4-yl]amine Hydrochloride (18). An identical procedure as described above was followed. The intermediate 4-chloro-7-(3-trifluoromethylpyridin-2-yl)quinazoline was dissolved in acetonitrile (5 mL), and 3-amino-6-trifluoromethylpyridine (**16**) (105 mg, 0.65 mmol) was added. The mixture was heated at 80 °C for 8 h and then cooled to room temperature. The resulting precipitate was collected by filtration, washed with ether, air-dried and gave the title compound **18** as the monohydrochloride salt (145 mg, 81% over two steps). MS 436 (M + 1). ^{1}H NMR δ (DMSO) 12.28 (1H, br s), 9.24 (1H, s), 9.17 (1H, d, J = 8.5 Hz), 9.07 (1H, s), 8.99 (1H, d, J = 5 Hz), 8.55 (1H, d, J = 8 Hz), 8.43 (1H, d, J = 8 Hz), 8.12−8.08 (2H, m), 7.99 (1H, d, J = 7.5 Hz), 7.79 (1H, dd, J = 2.5 and 7.5 Hz).

6′-Methoxy-3-trifluoromethyl[2,3′]bipyridinyl (19). A mixture of 2-chloro-3-trifluoromethylpyridine (**8**) (37 g, 0.2 mol), 2-methoxypyridine-5-boronic acid (32 g, 0.21 mol), tetrakis-(triphenylphosphine)palladium(0) (9 g, 7 mmol), and 2 M potassium carbonate (150 mL) in toluene (500 mL) was heated, under a nitrogen atmosphere, at 90 °C for 8 h. The reaction mixture was cooled, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 250 mL), and the combined extracts were washed with 4 M sodium hydroxide (250 mL), water (250 mL), brine (250 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The oil was purified by flash chromatography (elution with ether/hexane, 1:1) and gave the title compound **19** (48.2 g, 95%), a colorless oil. MS 255 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.85 (1H, d, J = 5 Hz), 8.34 (1H, s), 8.09 (1H, d, J = 7.5 Hz), 7.76 (1H, dd, J = 2.5 and 8.5 Hz), 7.46−7.41 (1H, m), 6.82 (1H, d, J = 8 Hz), 3.76 (3H, s).

3-Trifluoromethyl-1′*H*-[2,3′]bipyridinyl-6′-one (20). 6′-Methoxy-3-trifluoromethyl[2,3′]bipyridinyl (**19**) (41 g, 0.16 mol) in HBr (30% in acetic acid, 100 mL) was heated to reflux for 1 h. The mixture was cooled, filtered and the precipitate washed with ether (100 mL). The precipitate was transferred into 10 M sodium hydroxide (500 mL) and stirred for 1 h. The solution was then treated with hydrochloric acid until the solution was approximately pH 7. The white solid was then collected by filtration, air-dried to yield the title compound **20** (36 g, 93%) as a white solid. MS 241 (M + 1). ^{1}H NMR δ (DMSO) 8.87 (1H, d, J = 5 Hz), 8.29 (1H, d, J = 7.5 Hz), 7.68−7.54 (3H, m), 6.46 (1H, d, J = 8 Hz).

6′-Chloro-5′-nitro-3-trifluoromethyl[2,3′]bipyridinyl (21). To a solution of 3-trifluoromethyl-1′*H*-[2,3′]bipyridinyl-6′-one (**20**) (25 g, 0.1 mol) in concentrated sulfuric acid (100 mL) at 0 °C was added dropwise a solution of fuming nitric acid (35 mL) and concentrated sulfuric acid (10 mL). The reaction mixture was then heated to 70 °C for 1 h, cooled, and poured onto ice (500 mL). The mixture was filtered and the filtrate treated with 10 M sodium hydroxide until the solution was at pH 4−5. The precipitate was collected by filtration and air-dried. The white solid (26.2 g, 92%) was dissolved in thionyl chloride (300 mL) and DMF (3 mL) and heated to reflux for 4 h. The volatiles were removed by rotary evaporation, and the residue was partitioned between ethyl acetate (350 mL) and saturated sodium bicarbonate solution (250 mL). The aqueous layer was extracted with further ethyl acetate (250 mL), and the combined organics were washed with brine (250 mL), dried ($MgSO_4$), concentrated and gave the title compound **21** (25 g, 93%), a yellow oil. MS 304 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.94 (1H, d, J = 5 Hz), 8.79 (1H, d, J = 1.5 Hz), 8.45 (1H, d, J = 1.5 Hz), 8.18 (1H, d, J = 8 Hz), 7.60 (1H, dd, J = 2.5 and 8.5 Hz).

6′-Chloro-3-trifluoromethyl[2,3′]bipyridinyl-5′-ylamine (22). To a solution of 6′-chloro-5′-nitro-3-trifluoromethyl[2,3′]bipyridinyl (**21**) (25 g, 0.082 mol) and calcium chloride (11 g, 0.1 mol) in ethanol (300 mL) and water (50 mL) was added iron powder (45 g, 0.82 mol). The solution was heated at reflux for 1.5 h, cooled, and filtered through Celite. The mixture was concentrated under reduced pressure, redissolved in ethyl acetate (300 mL), and washed with brine (200 mL). The solution was concentrated under reduced pressure, purified by flash chromatography (elution with ether/hexane, 1:1), and gave the title compound **22** (19 g, 85%), a pale-yellow solid. MS 274 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.85 (1H, d, J = 4 Hz), 8.10 (1H, d, J = 8 Hz), 7.93 (1H, s), 7.49−7.46 (1H, m), 7.18 (1H, s).

3-Amino-5-[3-(trifluoromethyl)(2-pyridyl)]pyridine-2-carboxamide (23). A solution of 6′-chloro-3-trifluoromethyl[2,3′]bipyridinyl-5′-ylamine **22** (25 g, 0.091 mol), zinc cyanide (6.75 g, 0.058 mol), $Pd_2(dba)_3$ (2.63 g, 2.86 mmol), DPPF (3.16 g, 5.72 mmol) in DMF (250 mL), and water (2.5 mL), under a nitrogen atmosphere, was heated at 120 °C for 1 h. Water (30 mL) was then added and the solution reheated at 120 °C for a further 4 h to complete the hydrolysis. The mixture was cooled to 0 °C, and a solution of saturated ammonium chloride (200 mL), water (200 mL), and ammonium hydroxide (50 mL) was added. After the mixture was stirred at 0 °C for 1 h, the yellow precipitate was filtered and washed with water (200 mL) and a 1:1 mixture of ether/hexane (200 mL). The solid was air-dried and then in a vacuum oven to yield (23 g, 90%) the title compound **23**. MS 283 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.90 (1H, d, J = 4 Hz), 8.12 (1H, d, J = 7 Hz), 7.99 (1H, s), 7.96−7.88 (1H, m), 7.55−7.48 (1H, m), 7.15 (1H, s), 6.06 (2H, brs), 5.48 (1H, brs).

7-(3-Trifluoromethylpyridin-2-yl)pyrido[3,2-*d*]pyrimidin-4-ol (24). A solution of 3-amino-5-[3-(trifluoromethyl)-(2-pyridyl)]pyridine-2-carboxamide (**23**) (283 mg, 1.0 mmol) and triethyl orthoformate (5 mL) was heated at 130 °C for 16 h. The mixture was cooled to room temperature, and the volatiles were removed by rotary evaporation. The residue was triturated with ether/hexane and the white solid collected by filtration, air-dried (267 mg, 91%) and yielded the title compound **24**. MS 293 (M + 1). ^{1}H NMR δ (DMSO) 8.98 (1H, d, J = 5 Hz), 8.80 (1H, s), 8.41 (1H, J = 9 Hz), 8.22 (1H, s), 8.18 (1H, s) 7.77 (1H, dd, J = 2.5 and 8.5 Hz).

4-Chloro-7-(3-trifluoromethylpyridin-2-yl)pyrido[3,2-*d*]pyrimidine (25). A mixture of 7-(3-trifluoromethylpyridin-2-yl)pyrido-[3,2-*d*]pyrimidin-4-ol (**24**) (220 mg, 0.75 mmol), thionyl chloride (5 mL), and DMF (3 drops) was heated at reflux for 3 h. The mixture was evaporated to dryness and the residue partitioned between ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), evaporated and afforded the title compound **25** (202 mg, 87%). MS 311 (M + 1). ^{1}H NMR δ (DMSO) 9.29 (1H, d, J = 2 Hz), 9.27 (1H, s), 9.04 (1H, d, J = 7 Hz), 8.64 (1H, s), 8.47 (1H, d, J = 8.5 Hz), 7.83 (1H, dd, J = 2 and 8.5 Hz).

(4-Trifluoromethylphenyl)-[7-(3-trifluoromethylpyridin-2-yl)-pyrido[3,2-*d*]pyrimidin-4-yl]amine (26). A mixture of 4-chloro-7-(3-trifluoromethylpyridin-2-yl)pyrido[3,2-*d*]pyrimidine (**25**) (622 mg, 2.0 mmol) and 4-(trifluoromethyl)aniline (**14**) (480 mg, 3.0 mmol) in IPA (20 mL) was heated at 80 °C for 2 h. The mixture was cooled to room temperature and the precipitate collected by filtration. The precipitate was partitioned between ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL). The layers were separated, and the aqueous layer was extracted with further ethyl acetate (50 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), evaporated and gave the title compound **26** (765 mg, 88%). MS 436 (M + 1). ^{1}H NMR δ ($CDCl_3$) 11.75 (1H, br s), 9.03−8.99 (3H, m), 8.42 (1H, d, J = 7 Hz), 8.07−8.04 (2H, m), 7.96 (1H, d, J = 8.5 Hz), 7.87 (2H, d, J = 7.5 Hz), 7.79 (1H, dd, J = 2.5 and 7.5 Hz). Analytical HPLC: method 1, 13.02 (99.3%); method 2, 5.84 (99.4%).

2-Acetyl-3-trifluoromethylpyridine (28). A stirred solution of 2-cyano-3-trifluoromethylpyridine (**27**) (179 g, 1.04 mol) and THF (1.2 L) was cooled to 0 °C, and methylmagnesium iodide (3.0 M in ether (694 mL, 2.08 mol) was added dropwise over a period of 1.5 h. The reaction mixture was stirred at 0 °C for a further 0.5 h and then slowly poured over a stirred mixture of ice−water (3 kg). The resulting mixture was acidified with 6 M HCl to pH ∼2 and stirred for a further 0.5 h. The mixture was extracted with ethyl acetate (5 × 1.0 L), and the combined extracts were washed with brine (1.5 L) and dried (Na_2SO_4). The extract was concentrated and gave a dark-brown oil. The oil was distilled under vacuum (45−50 °C at 0.1 Torr) and gave the title compound **28** as a pale-yellow liquid (163.7 g, 83%). ^{1}H NMR δ ($CDCl_3$) 8.78 (1H, d, J = 5 Hz), 8.07 (1H, d, J = 8 Hz), 7.54 (1H, dd, J = 5 and 8 Hz), 2.09 (3H, s).

3-Dimethylamino-1-(3-trifluoromethylpyridin-2-yl)propenone (29). 2-Acetyl-3-trifluoromethylpyridine (**28**) (150 g, 0.79 mol) and $(Me)_2NCH(OMe)_2$ (236 g, 2.0 mol) were combined, and the mixture was heated at 105 °C for 5 h. The mixture was concentrated by rotary evaporation and then under a high vacuum (0.1 Torr) for an additional 1 h and gave the title compound **29** as a brown oil (193 g, 100%). MS 245 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.72 (1H, d, J = 5 Hz), 8.03 (1H, J = 8 Hz), 7.80 (1H, brs), 7.41 (1H, dd, J = 5 and 8 Hz), 5.52 (1H, br d), 3.10 (3H, br s), 2.88 (3H, s).

6-Amino-3′-trifluoromethyl[2, 2′]bipyridinyl-5-carbonitrile (30). Malononitrile (198 g, 3 mol), HCO_2Me (1.0 L), and MeOH (240 mL) were cooled to 0 °C, and thionyl chloride (176 mL, 2.4 mol) was added dropwise over a period of 1 h. The reaction mixture was stirred at 0 °C for a further 1 h, and the resulting yellow solid was collected by filtration. The solid was washed with HCO_2Me (2 × 75 mL) and air-dried for 0.5 h. The solid was dried under vacuum at 25 °C for 1 h and gave 3-amino-3-methoxyacrylonitrile hydrochloride as a white solid (96.4 g, 60%) which was used in the next step without further purification. 3-Dimethylamino-1-(3-trifluoromethylpyridin-2-yl)propenone (**29**) (191.7 g, 0.79 mol), ethanol (2.0 L), NH_4OAc (302.6 g, 9.93 mol), and 3-amino-3-methoxyacrylonitrile hydrochloride (211.2 g, 1.57 mol) were heated at 80 °C for 7 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The solid that separated was collected by filtration and washed with a small amount of cold ethanol. The solid was dissolved in ethyl acetate (750 mL) and the mixture washed with aqueous $NaHCO_3$ (500 mL). The organic extract was dried (Na_2SO_4), concentrated and afforded 6-amino-3′-trifluoromethyl-[2, 2′]bipyridinyl-5-carbonitrile (**30**) as a light-brick-colored solid (85.5 g, 41%). MS 265 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.85 (1H, d, J = 5 Hz), 8.12 (1H, d, J = 8 Hz), 7.84 (1H, d, J = 7.5 Hz), 7.52 (1H, dd, J = 5 and 8 Hz), 7.09 (1H, d, J = 7 Hz), 5.30 (1H, brs).

***N*′-(5-Cyano-3′-trifluoromethyl[2,2′]bipyridinyl-6-yl)-*N*,*N*-dimethylformamidine (31).** A mixture of 6-amino-3′-trifluoromethyl[2, 2′] bipyridinyl-5-carbonitrile (**30**) (2.64 g, 10 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (50 mL) was heated at 110 °C for 1 h. The mixture was cooled to room temperature and the excess reagent removed by evaporation to yield the title compound **31** as a light-brown solid (3.2 g, 100%). MS 320 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.84 (1H, d, J = 5 Hz), 8.70 (1H, s), 8.15 (1H, d, J = 8 Hz), 7.92 (1H, d, J = 7.5 Hz), 7.51 (1H, dd, J = 5 and 8 Hz), 7.35 (1H, d, J = 7 Hz), 3.19 (3H, s), 3.16 (3H, s).

(4-Trifluoromethylphenyl)-[7-(3-trifluoromethylpyridin-2-yl)-pyrido[2,3-*d*]pyrimidin-4-yl]amine (32). A mixture of *N*′-(5-cyano-3′-trifluoromethyl[2,2′]bipyridinyl-6-yl)-*N*,*N*-dimethylformamidine (**31**) (160 mg, 0.5 mmol) and 4-trifluoromethylaniline (**14**) (80 mg, 0.5 mmol) in a solution of AcOH (1 mL) and water (6 mL) was heated at reflux for 6 h. The mixture was cooled to room temperature and basified by dropwise addition of 1 M sodium hydroxide. The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (elution with hexanes/ethyl acetate, 1:2) and gave the title compound **32** as a pale-yellow solid (124 mg, 57%). MS 436 (M + 1). ^{1}H NMR δ (DMSO) 9.75 (1H, d, J = 7.5 Hz), 9.05−9.03 (2H, m), 8.72 (1H, brs), 8.48 (1H, d, J = 7.5 Hz), 8.25 (1H, d, J = 7 Hz), 8.07 (2H, d, J = 7 Hz), 7.90−7.87 (3H, m). Analytical HPLC: method 1, 12.03 (95.4%); method 2, 5.13 (99.1%).

7-(3-Trifluoromethylpyridin-2-yl)pteridin-4-ylamine (33). 2-Acetyl-3-trifluoromethylpyridine (**28**) (2.10 g, 11.1 mmol) was dissolved in HBr (30% by weight in AcOH) (14 mL). The mixture was cooled to 0 °C, and bromine (0.619 mL) was added dropwise. The resulting solution was allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated under reduced pressure and gave 2-bromo-1-(3-trifluoromethylpyridin-2-yl)ethanone hydrobromide (3.85 g, 100%) which was used without further purification in the following step. 4,5,6-Triaminopyrimidine sulfate (1.12 g, 5.0 mmol) was dissolved in a solution of water (45 mL) and barium chloride hydrate (1.77 g, 5.0 mmol). The mixture was heated to 80 °C for 4 h and cooled to room temperature. The solids were removed by filtration and $NaHCO_3$ (1.26 g, 15 mmol), dioxane (20 mL), and 2-bromo-1-(3-trifluoromethylpyridin-2-yl)ethanone hydrobromide (1.00 g, 2.86 mmol) were added to the filtrate. The resulting mixture was stirred for 1 h at room temperature and 1 h at 100 °C. The mixture was cooled, filtered through Celite and the Celite bed washed with ethyl acetate (20 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (4 × 100 mL). The combined organic extracts were dried

(Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dissolved in methanol, and air was bubbled through the solution for 16 h. The methanol was removed under reduced pressure and the residue was purified by column chromatography (elution with hexanes/acetone, 1:1) and afforded the title compound **33** as an off-white solid (192 mg, 23%). MS 293 (M + 1).

(4-Trifluoromethylphenyl)-[7-(3-trifluoromethylpyridin-2-yl)-pteridin-4-yl]amine (34). To a degassed mixture of 7-(3-trifluoromethylpyridin-2-yl)pteridin-4-ylamine (**33**) (73 mg, 0.25 mmol), Cs_2CO_3 (162 mg, 0.5 mmol), 4-(trifluoromethyl)bromobenzene (67 mg, 0.3 mmol) in dioxane (5 mL) under nitrogen were added Pd_2dba_3 (11 mg, 0.0125 mmol) and xantphos (7 mg, 0.0125 mmol). The mixture was heated at 100 °C for 8 h, cooled, water (8 mL) added and extracted with ethyl acetate (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC (elution with hexanes/acetone, 3:1) and gave the title compound **34** as a yellow solid (42 mg, 39%). MS 437 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.29 (1H, s), 9.24 (1H, brs), 9.08 (1H, s), 8.98 (1H, d, J = 5 Hz), 8.28 (1H, d, J = 7 Hz), 8.14 (2H, d, J = 7.5 Hz), 7.74 (2H, d, J = 7.5 Hz), 7.32 (1H, m). Analytical HPLC: method 1, 12.55 (100%); method 2, 5.05 (98.2%).

4-Amino-2-(3-trifluoromethylpyridin-2-yl)pyrimidine-5-carbonitrile (35). 2-Cyano-3-trifluoromethylpyridine (**27**) (2.0 g, 11.5 mmol) in diethyl ether (40 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (3.88 g, 23 mmol) in diethyl ether (40 mL) at 0 °C. The mixture was allowed to return to room temperature and stirred for 2 h. A solution of AcOH (4 mL) and water (16 mL) was added to the mixture which was stirred for a further 1 h. The layers were separated, and the aqueous layer was basified by addition of 4 M sodium hydroxide solution. The resulting solution was extracted with dichloromethane (3 × 50 mL) and the combined extracts were dried ($MgSO_4$) and evaporated to give a white solid (1.43 g, 66%). The solid (1.43 g, 7.56 mmol) was dissolved in a mixture of methanol (40 mL) and triethylamine (4 mL), and (ethoxymethylene)-malononitrile (1.06 g, 8.69 mmol) was added dropwise. The mixture was heated at reflux for 18 h and evaporated. The residue was purified by flash chromatography (elution with 3:1 hexane/acetone) and yielded the title compound **35** as a yellow solid (1.38 g, 69%). MS 266 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.90 (1H, d, J = 1.5 Hz), 8.70 (1H, s), 8.14 (1H, J = 7.5 Hz), 7.56 (1H, dd, J = 2.5 and 8.5 Hz), 5.86 (2H, brs).

(4-Trifluoromethylphenyl)-[7-(3-trifluoromethylpyridin-2-yl)-pyrimido[4,5-*d*]pyrimidin-4-yl]amine (36). A mixture of 4-amino-2-(3-trifluoromethylpyridin-2-yl)pyrimidine-5-carbonitrile (**35**) (200 mg, 0.75 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (5 mL) was heated at 110 °C for 1 h. The mixture was cooled to room temperature and the excess reagent removed by evaporation. The residue was dissolved in a solution of AcOH (2 mL) and water (10 mL). 4-Trifluoromethylaniline (**14**) (120 mg, 0.75 mmol) was added, and the mixture was heated at reflux for 3 h. The mixture was cooled to room temperature and basified by dropwise addition of 1 M sodium hydroxide. The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) and gave the title compound **36** as a pale-yellow solid (160 mg, 49%). MS 437 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.88 (1H, s), 9.10 (1H, brs), 9.04 (1H, s), 8.84 (1H, d, J = 1.5 Hz), 8.16 (1H, d, J = 7.5 Hz), 7.88 (2H, d, J = 8.5 Hz), 7.65 (2H, J = 8.5 Hz), 7.57 (1H, dd, J = 2.5 and 8.5 Hz). Analytical HPLC: method 1, 11.93 (97.2%); method 2, 3.61 (95.3%).

2-Amino-4-(3-trifluoromethylpyridin-2-yl)benzoic Acid Methyl Ester (37). A solution of 2-amino-4-(3-trifluoromethylpyridin-2-yl)benzoic acid (**12**) (5 g, 18 mmol) in methanol (100 mL) was saturated with hydrogen chloride gas. The mixture was heated at reflux for 4 days and then evaporated to dryness. The mixture was partitioned between ethyl acetate (150 mL) and saturated aqueous sodium bicarbonate (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), evaporated and afforded the title compound **37** (4.9 g, 92%) which was used without further purification. MS 297 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.82 (1H, d, J = 5 Hz), 8.08 (1H, d, J = 8.5 Hz), 7.92 (1H, d, J = 8 Hz), 7.45 (1H, dd, J = 5 and 8.5 Hz), 6.77 (2H, m), 3.86 (3H, s).

2,4-Dichloro-7-(3-trifluoromethylpyridin-2-yl)quinoline (38). A solution of 2-amino-4-(3-trifluoromethylpyridin-2-yl)benzoic acid methyl ester (**37**) (296 mg, 1.0 mmol) and AcOH (1 mL) in dioxane (2 mL) was heated at 60 °C for 3 h. The solution was cooled, water (1 mL) was added, and the mixture was evaporated to dryness. Toluene (5 mL) was added to the residue which was evaporated to dryness. The solid was dissolved in THF (4 mL) and added dropwise to a stirred solution of potassium bis(trimethylsilyl)amide (600 mg, 3.0 mmol) in toluene (6 mL) at −78 °C. The mixture was allowed to return to room temperature overnight, and water (10 mL) was added. The mixture was washed with ethyl acetate (20 mL) and the aqueous layer acidified with 4 M hydrochloric acid. The precipitate that formed was collected by filtration, air-dried and gave a white solid. The solid was added in portions to a stirred solution of $OPCl_3$ (5 mL) and the mixture heated at reflux for 18 h. The excess reagent was evaporated and the residue carefully neutralized with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with ethyl acetate (3 × 25 mL), and the combine extracts were dried (Na_2SO_4), concentrated and gave the title compound **38** (264 mg, 77%). MS 343 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.91 (1H, d, J = 5 Hz), 8.30 (1H, d, J = 8.5 Hz), 8.19 (1H, s), 8.16 (1H, d, J = 8 Hz), 7.81 (1H, d, J = 8.5 Hz), 7.58 (1H, s), 7.53 (1H, dd, J = 5 and 8.5 Hz).

4-Chloro-2-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (39) and 2-Chloro-4-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (40). Sodium methoxide (4 M, 0.27 mL, 1.1 mmol) was added dropwise to a solution of 2,4-dichloro-7-(3-trifluoromethylpyridin-2-yl)quinoline (**38**) (342 mg, 1.0 mmol) in THF (10 mL). The mixture was stirred at room temperature for 1 h, water (15 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and evaporated. The mixture was purified by flash chromatography (elution with 2:1 hexane/ether) and afforded first 4-chloro-2-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (**39**) (199 mg, 59%). MS 339 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.89 (1H, d, J = 5 Hz), 8.19 (1H, d, J = 8.5 Hz), 8.13 (1H, d, J = 8.5 Hz), 8.02 (1H, s), 7.60 (1H, d, J = 8.5 Hz), 7.49 (1H, dd, 5 and 8 Hz), 7.08 (1H, s), 4.06 (3H, s). Later fractions contained 2-chloro-4-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (**40**) (101 mg, 30%). MS 339 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.88 (1H, d, J = 5 Hz), 8.23 (1H, d, J = 8.5 Hz), 8.13 (1H, d, J = 8.5 Hz), 8.08 (1H, s), 7.64 (1H, d, J = 8.5 Hz), 7.49 (1H, dd, 5 and 8 Hz), 6.79 (1H, s), 4.09 (3H, s).

4-Methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (41). A mixture of 2-chloro-4-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (**40**) (111 mg, 0.32 mmol), ammonium formate (190 mg, 3 mmol), and 10% palladium on carbon (30 mg) in methanol (10 mL) was stirred at room temperature for 2 h. The mixture was filtered through Celite and evaporated to give the title compound **41** (94 mg, 96%) which was used without further purification. MS 305 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.86 (1H, d, J = 5 Hz), 8.79 (1H, d, J = 5 Hz), 8.28 (1H, d, J = 8.5 Hz), 8.18 (1H, s), 8.10 (1H, d, J = 8 Hz), 7.64 (1H, d, 8.5 Hz), 7.45 (1H, dd, J = 5 and 8 Hz), 6.76 (1H, d, J = 5 Hz), 4.04 (3H, s).

4-Chloro-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (42). A solution of 4-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (**41**) (100 mg, 0.33 mmol) and 33% hydrogen bromide in

AcOH (5 mL) was heated at 100 °C for 18 h. The mixture was evaporated to dryness and the resulting solid added to a stirred solution of $OPCl_3$ (2 mL). The mixture was heated at reflux for 2 h, cooled to room temperature and the excess reagent removed under reduced pressure. The residue was carefully neutralized with saturated $NaHCO_3$ and the mixture extracted with ethyl acetate (3 × 20 mL), dried (Na_2SO_4), concentrated and afforded the title compound **42** (91 mg, 89%). MS 309 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.90 (1H, d, J = 5 Hz), 8.84 (1H, d, J = 5 Hz), 8.33 (1H, d, J = 8.5 Hz), 8.29 (1H, s), 8.14 (1H, d, J = 8 Hz), 7.80 (1H, d, 8.5 Hz), 7.56 (1H, d, J = 5 Hz), 7.50 (1H, dd, J = 5 and 8 Hz).

7-[3-(Trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)-pyridin-2-yl]quinolin-4-amine (43). To a degassed mixture of 4-chloro-7-[3-(trifluoromethyl)pyridin-2-yl]quinoline (**42**) (76 mg, 0.25 mmol), Cs_2CO_3 (162 mg, 0.5 mmol), 2-amino-5-trifluoromethylpyridine (43 mg, 0.3 mmol) in dioxane (5 mL) under nitrogen were added Pd_2dba_3 (11 mg, 0.0125 mmol) and xantphos (7 mg, 0.0125 mmol). The mixture was heated at 100 °C for 3 h, cooled, and water (8 mL) was added. The layer was extracted with ethyl acetate (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) yielded the title compound **43** (74 mg, 68%). MS 435 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.73 (1H, d, J = 5 Hz), 8.56 (1H, s), 8.51 (1H, s), 8.40 (2H, d, J = 8 Hz), 8.11−8.09 (3H, m), 7.85 (1H, d, J = 8.5 Hz), 7.67 (1H, d, J = 9 Hz), 7.53 (1H, d, J = 8.5 Hz), 7.47 (1H, dd, J = 5 and 8 Hz). Analytical HPLC: method 1, 10.80 (100%); method 2, 4.86 (100%).

4-Chloro-2-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]-1,5-naphthyridine (44). Following analogous procedures to those described above, the title compound **44** was prepared. MS 340 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.07 (1H, s), 8.95 (1H, d, J = 5 Hz), 8.41 (1H, s), 8.18 (1H, d, J = 8.5 Hz), 7.57 (1H, dd, 5 and 8 Hz), 7.02 (1H, s), 4.19 (3H, s).

2-Methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]-1,5-naphthyridin-4-amine (45). To a degassed mixture of 4-chloro-2-methoxy-7-[3-(trifluoromethyl)-pyridin-2-yl]-1,5-naphthyridine (**44**) (339 mg, 1.0 mmol), Cs_2CO_3 (650 mg, 2.0 mmol), and 2-amino-5-trifluoromethylpyridine (176 mg, 1.2 mmol) in dioxane (20 mL) under nitrogen were added Pd_2dba_3 (46 mg, 0.05 mmol) and xantphos (29 mg, 0.05 mmol). The mixture was stirred at 100 °C for 3 h, cooled, water (10 mL) was added, and the layer was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated. Purification by column chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) gave the title compound **45** (397 mg, 85%) as a pale-yellow solid. MS 466 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.95 (1H, d, J = 2 Hz), 8.90 (1H, s), 8.58 (1H, s), 8.37 (1H, d, J = 8 Hz), 8.29 (1H, s), 8.19 (1H, d, J = 8 Hz), 8.07 (1H, br s), 7.88 (1H, dd, J = 2 and 8.5 Hz), 7.57−7.54 (1H, m), 7.07 (1H, s), 4.16 (s, 3H).

2-Chloro-7-[3-(trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]-1,5-naphthyridin-4-amine (46). A solution of 2-methoxy-7-[3-(trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]-1,5-naphthyridin-4-amine (**45**) (300 mg, 0.64 mmol) and 33% hydrogen bromide in AcOH (10 mL) was heated at 100 °C for 18 h. The mixture was concentrated to dryness, saturated aqueous sodium bicarbonate (10 mL) added, and the mixture extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried (Na_2SO_4), and concentrated. The residue was added to a stirred solution of phosphorus oxychloride (3 mL) and the mixture heated at reflux for 0.5 h. The mixture was cooled to room temperature and evaporated. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), evaporated and afforded the title compound **46** (191 mg, 63%). MS 470 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.02 (1H, s), 8.98 (1H, d, J = 2 Hz), 8.61−8.57 (2H, m), 8.39−8.34 (2H, m), 8.18 (1H, d, J = 8 Hz), 8.01−7.90 (2H, m), 7.61−7.57 (1H, m).

7-[3-(Trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)-pyridin-2-yl]-1,5-naphthyridin-4-amine (47). A mixture of 2-chloro-7-[3-(trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]-1,5-naphthyridin-4-amine (**46**) (94 mg, 0.20 mmol), ammonium formate (126 mg, 2.0 mmol), and 10% palladium on carbon (25 mg) in methanol (10 mL) was heated at 50 °C for 2 h. The mixture was cooled, filtered through Celite, and evaporated to dryness. The residue was partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by preparative thin layer chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) and yielded the title compound **47** (62 mg, 71%). MS 437 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.95−8.93 (2H, m), 8.63−8.57 (2H, m), 8.34−8.32 (2H, m), 8.26 (1H, s), 8.18 (1H, d, J = 8 Hz), 7.91 (1H, dd, J = 2 and 9 Hz), 7.57−7.52 (2H, m). Analytical HPLC: method 1, 12.63 (97.9%); method 2, 5.48 (98.6%).

***tert*-Butyl-4-chloro-3-formylpyridin-2-yl Carbamate.** To a stirred solution of *tert*-butyl 4-chloropyridin-2-yl carbamate (**48**) (19.5 g, 0.085 mol) in THF (400 mL) at −78 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 80 mL, 0.20 mol). The solution was stirred at −78 °C for 1 h, and DMF (33 mL, 0.4 mol) was then added dropwise. After an additional 1 h at −78 °C the reaction was quenched by the dropwise addition of saturated ammonium chloride solution. The solution was extracted with ethyl acetate (3 × 500 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. Purification by column chromatography (elution with ethyl acetate/hexane, 1:4) gave the title compound, a white solid (15.9 g, 73%). ^{1}H NMR δ ($CDCl_3$) 10.73 (1H, brs), 10.53 (1H, s), 8.52 (1H, d, J = 1.5 Hz), 7.07 (1H, d, J = 1.5 Hz), 1.55 (9H, s).

2-Amino-4-chloronicotinaldehyde (49). Trifluoroacetic acid (42.7 mL, 551 mmol) was added dropwise to a mixture of *tert*-butyl-4-chloro-3-formylpyridin-2-yl carbamate (28.5 g, 110 mmol) in dichloromethane (500 mL), and the resulting mixture was stirred for 18 h. A saturated solution of sodium bicarbonate (400 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 250 mL) and the combined organic extracts were dried ($MgSO_4$), evaporated and gave the title compound **49**, a yellow solid (16.1 g, 94%). ^{1}H NMR δ ($CDCl_3$) 10.45 (1H, s), 8.12 (1H, d, J = 1.5 Hz), 6.69 (1H, d, J = 1.5 Hz), 6.05 (2H, brs).

5-Chloro-2-[3-(trifluoromethyl)pyridin-2-yl]-1,8-naphthyridine (50). Potassium *tert*-butoxide (8.4 g, 75 mmol) was added in portions to a stirred solution of 2-amino-4-chloronicotinaldehyde (**49**) (7.8 g, 50 mmol) and 2-acetyl-3-trifluoromethylpyridine (**28**) (9.45 g, 50 mmol) in THF (200 mL) at −20 °C. The solution was allowed to reach 10 °C and stirred for 2 h. The reaction mixture was evaporated under reduced pressure and the residue diluted with saturated aqueous ammonium chloride (150 mL). The solid was collected by filtration, air-dried and afforded the title compound (**50**) (13.4 g, 87%), a white solid. MS 310 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.09 (1H, d, J = 2 Hz), 8.91 (1H, d, J = 2 Hz), 8.77 (1H, d, J = 8.5 Hz), 8.22 (1H, d, J = 7 Hz), 8.09 (1H, d, J = 8.5 Hz), 7.64 (1H, d, J = 4 Hz), 7.58 (1H, dd, J = 5 and 8 Hz).

(4-Trifluoromethylphenyl)-[7-(3-trifluoromethylpyridin-2-yl)-[1,8]naphthyridin-4-ylamine (51). Hydrochloric acid (2 M in ether, 0.5 mL, 1.0 mmol) was added to a solution of 5-chloro-2-[3-(trifluoromethyl)pyridin-2-yl]-1,8-naphthyridine (**50**) (309 mg, 1.0 mmol) and 4-trifluoromethylaniline (**14**) (161 mg, 1.0 mmol) in IPA (5 mL). The mixture was heated at 80 °C for 16 h. The solid was collected by filtration and partitioned between

ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), evaporated and gave the title compound **51**, a white solid (340 mg, 78%). MS 435 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.98 (1H, d, J = 8.5 Hz), 8.74 (1H, s), 8.62 (1H, m), 8.18 (1H, d, J = 7.5 Hz), 7.78 (1H, d, J = 8.5 Hz), 7.62 (2H, d, J = 7.5 Hz), 7.50 (3H, m), 6.80 (1H, m). Analytical HPLC: method 1, 10.38 (95.0%); method 2, 5.15 (95.0%).

7-[3-(Trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)-pyridin-2-yl]-1,8-naphthyridin-4-amine (52). A mixture of 5-chloro-2-(3-(trifluoromethyl)pyrid-2-yl)-1,8-naphthyridine (**50**) (6.72 g, 21.7 mmol) and 2-amino-5-trifluoromethylpyridine (**15**) (7.13 g, 44 mmol) was heated in a sealed tube at 180 °C for 2 h. The mixture was allowed to cool to room temperature and the resulting solid was dissolved in a small amount of methanol. Sodium hydroxide (1 M, 200 mL) was added and the mixture extracted with ethyl acetate (500 mL). The extract was washed with brine (200 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography (elution with ethyl acetate/hexane, 4:1, and then ethyl acetate) afforded the title compound **52** as a yellow solid (5.85 g, 62%). MS 436 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.99 (1H, s), 8.84 (1H, d, J = 5 Hz), 8.65 (1H, d, J = 8.5 Hz), 8.60 (1H, s), 8.32 (1H, brs), 8.14 (1H, d, J = 8 Hz), 8.06 (1H, s), 7.85−7.79 (2H, m), 7.51 (1H, dd, J = 8 and 5 Hz), 7.22 (1H, d, J = 8.5 Hz). Analytical HPLC: method 1, 10.65 (100%); method 2, 4.36 (100%).

3-[3-(Trifluoromethyl)pyridin-2-yl]pyrido[2,3-*b*]pyrazin-8-amine (53) and 2-(3-Trifluoromethylpyridin-2-yl)pyrido[3,4-*b*]pyrazin-5-amine (54). 1-(3-Trifluoromethylpyridin-2-yl)ethanone (**28**) (2.65 g, 14 mmol) was dissolved in HBr (30% by weight in AcOH) (14 mL). The mixture was cooled to 0 °C, and bromine (0.8 mL) was added dropwise. The resulting solution was allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated under reduced pressure and gave 2-bromo-1-(3-trifluoromethylpyridin-2-yl)ethanone hydrobromide (4.85 g, 100%) which was used without further purification in the following step. To a solution of 2,3,4-triaminopyridine (3.10 g, 25 mmol) in water (200 mL) was added $NaHCO_3$ (6.3 g, 75 mmol), dioxane (100 mL), and 2-bromo-1-(3-trifluoromethylpyridin-2-yl)ethanone hydrobromide (4.85 g). The mixture was heated at 100 °C for 2 h, cooled to room temperature, and extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried (Na_2SO_4). Purification of the residue by column chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) gave a mixture containing the two title compounds **53** and **54** (1.3 g, 32%) which were used in the next step without isolation of the two individual products.

3-[3-(Trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)-pyridin-2-yl]pyrido[2,3-*b*]pyrazin-8-amine (55) and 2-[3-(Trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]pyrido-[3,4-*b*]pyrazin-5-amine (56). To a degassed mixture of 3-[3-(trifluoromethyl)pyridin-2-yl]pyrido[2,3-*b*]pyrazin-8-amine (**53**), 2-(3-trifluoromethylpyridin-2-yl)pyrido[3,4-*b*]pyrazin-5-amine (**54**) (72 mg, 0.25 mmol), Cs_2CO_3 (162 mg, 0.5 mmol), and 2-chloro-5-trifluoromethylpyridine (45 mg, 0.25 mmol) in dioxane (5 mL) under nitrogen were added Pd_2dba_3 (11 mg, 0.0125 mmol) and xantphos (7 mg, 0.0125 mmol). The mixture was stirred at 100 °C for 3 h, cooled, water (10 mL) was added, and the layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Purification by column chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) gave first 3-[3-(trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]pyrido[2,3-*b*]pyrazin-8-amine (**55**) (31 mg, 28%). MS 437 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.42 (1H, s), 9.28 (1H, s), 9.11 (1H, d, J = 5 Hz), 8.95 (1H, d, J = 5 Hz), 8.90 (1H, d, J = 5 Hz), 8.72 (1H, s), 8.25 (1H, d, J = 8 Hz), 7.89 (1H, d, J = 8.5 Hz), 7.61 (1H, dd, J = 5 and 8 Hz), 7.13 (1H, d, J = 8.5 Hz). Analytical HPLC: method 1, 12.37 (100%); method 2, 4.95 (100%).

Later fractions contained, 2-[3-(trifluoromethyl)pyridin-2-yl]-*N*-[5-(trifluoromethyl)pyridin-2-yl]pyrido[3,4-*b*]pyrazin-5-amine (**56**) (25 mg, 23%). MS 437 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.26 (1H, s), 9.00−8.97 (2H, m), 8.61 (1H, s), 8.48 (1H, d, J = 5.5 Hz), 8.25 (1H, d, J = 8.5 Hz), 7.99 (1H, d, J = 8.5 Hz), 7.65 (1H, dd, J = 5 and 8 Hz), 7.50 (1H, d, J = 5.5 Hz). Analytical HPLC: method 1, 13.84 (98.6%); method 2, 6.50 (100%).

1-[2-Amino-4-(3-trifluoromethylpyridin-2-yl)phenyl]ethanone (57). A solution of 2-amino-4-(3-trifluoromethylpyridin-2-yl)-benzoic acid (**12**) (2.8 g, 10 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (2.14 g, 22 mmol), EDCI (2.1 g, 11 mmol), and Hünig's base (5.1 g, 40 mmol) in dichloromethane (100 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL) and extracted with dichloromethane (2 × 100 mL). The combined organics were washed with brine (200 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with 10% hexane in ethyl acetate and then ethyl acetate) and gave *N*-methoxy-*N*-methyl-2-amino-4-(3-trifluoromethylpyridin-2-yl)benzamide as a yellow oil (1.1 g, 34%). MS 326 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.82 (1H, s), 8.05 (1H, d, J = 9 Hz), 7.48−7.40 (2H, m), 6.82−6.78 (2H, m). To a solution of *N*-methoxy-*N*-methyl-2-amino-4-(3-trifluoromethylpyridin-2-yl)benzamide (1.1 g, 3.4 mmol) in THF (30 mL) at 0 °C was added methylmagnesium iodide (3 M in toluene, 3.3 mL, 10 mmol). The mixture was stirred at room temperature for 4 h, poured into 2 M hydrochloric acid (25 mL), and stirred for 1 h. The mixture was neutralized by portionwise addition of sodium bicarbonate and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine (100 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with ethyl acetate) and afforded the title compound **57** as a colorless oil (412 mg, 43%). MS 281 (M + 1). ^{1}H NMR δ ($CDCl_3$) 8.88 (1H, s), 8.18 (1H, d, J = 6 Hz), 7.80 (1H, d, J = 7.5 Hz), 7.57−7.50 (1H, m), 6.82−6.78 (2H, m), 2.80 (3H, s).

7-(3-Trifluoromethylpyridin-2-yl)cinnolin-4-ol (58). To 1-[2-amino-4-(3-trifluoromethylpyridin-2-yl)phenyl]ethanone (**57**) (220 mg, 0.8 mmol) in concentrated hydrochloric acid (2 mL) at 0 °C was added sodium nitrite (70 mg, 1.0 mmol) in water (0.2 mL). After being stirred for 4 h, the solution was evaporated to dryness and water (5 mL) and sodium acetate (328 mg, 4.0 mmol) were added. The mixture was refluxed for 2 h, cooled, and extracted with ethyl acetate (3 × 25 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) and gave the title compound **58** (145 mg, 62%). MS 292 (M + 1). ^{1}H NMR δ ($CDCl_3$) 11.42 (1H, s), 8.86 (1H, d, J = 5 Hz), 8.34 (1H, d, J = 9 Hz), 8.15 (1H, d, J = 7 Hz), 7.88 (1H, s), 7.58 (1H, s), 7.56−7.45 (2H, m).

4-Chloro-7-(3-trifluoromethylpyridin-2-yl)cinnoline (59). A solution of 7-(3-trifluoromethylpyridin-2-yl)cinnolin-4-ol (**58**) (292 mg, 1.0 mmol) in phosphorus oxychloride (10 mL) was heated at reflux for 4 h. The mixture was evaporated to dryness and partitioned between ethyl acetate (75 mL) and saturated sodium bicarbonate solution (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the combined organics were washed with brine, dried (Na_2SO_4) and gave the title compound **59** (256 mg, 87%) which was used without further purification. MS 310 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.38 (1H, s), 8.45 (1H, d, J = 5 Hz), 8.64 (1H, s), 8.22 (1H, d, J = 9 Hz), 8.18 (1H, d, J = 7 Hz), 7.98 (1H, d, J = 8.5 Hz), 7.50−7.46 (1H, m).

(5-Trifluoromethylpyridin-2-yl)-[7-(3-trifluoromethylpyridin-2-yl)cinnolin-4-yl]amine (60). To a degassed mixture of 4-chloro-7-(3-trifluoromethylpyridin-2-yl)cinnoline (**59**) (310 mg, 1.0 mmol),

Cs_2CO_3 (650 mg, 2.0 mmol), and 2-amino-5-trifluoromethylpyridine (**15**) (162 mg, 1.0 mmol) in dioxane (10 mL) under nitrogen were added Pd_2dba_3 (44 mg, 0.05 mmol) and xantphos (28 mg, 0.05 mol). The mixture was stirred at 90 °C for 16 h, concentrated, and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification by column chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) yielded the title compound **60** as a yellow solid (235 mg, 76%). MS 436 (M + 1). ^{1}H NMR δ (DMSO) 10.46 (1H, s), 10.22 (1H, s), 8.99 (1H, d, J = 5 Hz), 8.76 (1H, s), 8.65 (1H, d, J = 9 Hz), 8.42 (1H, s), 8.38 (1H, d, J = 7.5 Hz), 8.14 (1H, d, J = 9 Hz), 7.95 (1H, d, J = 8.5 Hz), 7.78−7.74 (1H, m), 7.54 (1H, d, J = 8.5 Hz). Analytical HPLC: method 1, 11.92 (96.1%); method 2, 5.06 (100%).

5-Hydroxy-2-(3-trifluoromethylpyridin-2-yl)[1,7]naphthyridine-6-carboxylic Acid Ethyl Ester (62). To a solution of 6-methyl-3′-trifluoromethyl[2,2′]bipyridinyl-5-carboxylic acid ethyl ester (**61**) (720 mg, 2.32 mmol) in dichloromethane (25 mL) and water (25 mL) were added 2,2′-azobis(2-methylpropionitrile) (10 mg) and *N*-bromosuccinimide (826 mg, 4.64 mmol). The mixture was heated at 70 °C for 4 h, cooled to room temperature, and diluted with dichloromethane (50 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL), brine (40 mL), dried ($MgSO_4$), and concentrated to give 6-bromomethyl-3′-trifluoromethyl[2,2′]bipyridinyl-5-carboxylic acid ethyl ester (905 mg) which was used in the next step without further purification. A mixture of 6-bromomethyl-3′-trifluoromethyl-[2,2′]bipyridinyl-5-carboxylic acid ethyl ester (905 mg, 2.32 mmol) and methyl 2-(4-methylphenylsulfonamido)acetate (581 mg, 2.35 mmol) in ethanol (15 mL) was heated to 75 °C, and sodium ethoxide (2.68 M in ethanol, 0.98 mL, 2.63 mmol) was added dropwise. The mixture was heated for 1 h, and additional sodium ethoxide (2.68 M in ethanol, 0.98 mL, 2.63 mmol) was added dropwise. The mixture was heated an additional 1 h and cooled to room temperature. The volatiles were removed by evaporation, and the residue was partitioned between ethyl acetate (20 mL) and sodium hydroxide (1 M, 20 mL). The aqueous layer was extracted with additional ethyl acetate (2 × 25 mL), and the organic layers were combined. The aqueous layer was acidified to pH ∼5−6 with 6 M hydrochloric acid and extracted with additional ethyl acetate (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated and gave the title compound **62** (513 mg, 61%). ^{1}H NMR δ ($CDCl_3$) 11.96 (1H, s), 9.15 (1H, s), 8.93 (1H, d, J = 5 Hz), 8.87 (1H, d, J = 8.5 Hz), 8.23 (1H, d, J = 7.5 Hz), 8.11 (1H, d, J = 8.5 Hz), 7.60 (1H, dd, J = 5 and 8 Hz), 4.62 (2H, d), 1.54 (3H, t).

Trifluoromethanesulfonic Acid 2-(3-Trifluoromethylpyridin-2-yl)[1,7]naphthyridin-5-yl Ester (63). A mixture of 5-hydroxy-2-(3-trifluoromethylpyridin-2-yl)[1,7]naphthyridine-6-carboxylic acid ethyl ester (**62**) (147 mg, 0.4 mmol) and 6 M hydrochloric acid (20 mL) was heated at 95 °C for 6 h. Concentrated hydrochloric acid (6 mL) was added and the mixture heated for an additional 12 h. The mixture was poured onto ice−water (25 mL) and treated with 6 M sodium hydroxide until pH ∼4−5 was obtained. The solution was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were dried ($MgSO_4$) and evaporated to give 2-(3-trifluoromethylpyridin-2-yl)[1,7]naphthyridin-5-ol (80 mg, 69%) which was used in the next step without further purification. To a mixture of 2-(3-trifluoromethylpyridin-2-yl)[1,7]naphthyridin-5-ol (80 mg, 0.27 mmol) in dichloromethane (2 mL) was added Hünig's base (78 mg, 0.6 mmol). The mixture was cooled to 0 °C, and triflic anhydride (100 mg, 0.35 mmol) in dichloromethane (1 mL) was added dropwise. The solution was stirred for 2 h, diluted with dichloromethane (10 mL), and washed with saturated aqueous sodium bicarbonate (10 mL). The layers were separated, and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), evaporated and afforded the title compound (**63**) (101 mg, 59% over two steps). MS 424 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.60 (1H, s), 8.93 (1H, d, J = 5 Hz), 8.73 (1H, s), 8.54 (1H, d, J = 8.0 Hz), 8.29 (1H, d, J = 8.5 Hz), 8.25 (1H, J = 7.5 Hz), 7.61 (1H, dd, J = 5 and 8 Hz).

(5-Trifluoromethylpyridin-2-yl)[2-(3-trifluoromethylpyridin-2-yl)[1,7]naphthyridin-5-yl]amine (64). To a degassed mixture of trifluoromethanesulfonic acid 2-(3-trifluoromethylpyridin-2-yl)[1,7]naphthyridin-5-yl ester (**63**) (96 mg, 0.23 mmol), Cs_2CO_3 (244 mg, 0.68 mmol), and 2-amino-5-trifluoromethylpyridine (**15**) (74 mg, 0.45 mmol) in dioxane (3 mL) under nitrogen were added Pd_2dba_3 (21 mg, 0.023 mmol) and xantphos (13 mg, 0.023 mol). The mixture was stirred at 110 °C for 2 h, cooled and ethyl acetate (20 mL) added. The mixture was filtered through Celite, concentrated, and purified by preparative thin layer chromatography (elution with 0.5% ammonium hydroxide and 5% methanol in dichloromethane) and afforded the title compound **64** (61 mg, 61%). MS 436 (M + 1). ^{1}H NMR δ ($CDCl_3$) 9.42 (1H, s), 8.92 (1H, d, J = 5 Hz), 8.65 (1H, s), 8.39 (1H, d, J = 8.5 Hz), 8.24 (1H, d, J = 7.5 Hz), 8.04 (1H, J = 8.0 Hz), 7.58 (1H, dd, J = 5 and 8 Hz), 7.49 (1H, J = 8.5 Hz), 6.92 (1H, J = 8.5 Hz), 6.17 (1H, s). Analytical HPLC: method 1, 11.85 (97.6%); method 2, 5.17 (100%).

Supporting Information Available: Purity methods, chromatograms, and ESI spectra for all final compounds; experimental procedure for the complete Freund's adjuvant in vivo assay; graphs of core body changes in rats following daily dosing (3 mg/kg) of compound **52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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