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# Discovery of 7-Aryl-Substituted (1,5-Naphthyridin-4-yl) ureas as Aurora Kinase Inhibitors

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As part of our research projects to identify new chemical entities of biological interest, we developed a synthetic approach and the biological evaluation of (7-aryl-1,5-naphthyridin-4-yl)-ureas as a novel class of Aurora kinase inhibitors for the treatment of malignant diseases based on pathological cell proliferation. 1,5-Naphthyridine derivatives showed excellent inhibitory activities toward Aurora kinases A and B, and the most active compound, 1-cyclopropyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (**49**), displayed $IC_{50}$ values of 13 and 107 nM against Aurora kinases A and B, respectively. In addition, the selectivity toward a panel of seven cancer-related protein kinases was highlighted. In vitro ADME properties were also determined in order to rationalize the difficulties in correlating antiproliferative activity with Aurora kinase inhibition. Finally, the good safety profile of these compounds imparts promising potential for their further development as anticancer agents.

## Introduction

Aurora kinases are a family of three highly homologous serine/threonine protein kinases that play a critical role in regulating many of the processes pivotal to mitosis.[1] Three Aurora kinases, designated Aurora A, B, and C, have so far been identified in mammalian cells. They are involved in multiple mitotic events such as regulation of the spindle assembly checkpoint pathway and in the function of centrosomes, cytoskeleton, and cytokinesis.[2]

Aurora A localizes to centrosomes during early S phase, and is involved in centrosome maturation and separation, bipolar spindle assembly, mitotic entry, and mitotic exit. Aurora B, a chromosomal passenger protein, is localized to the centromeres from prophase to the metaphase/anaphase transition, and is required for correct chromosome segregation and cytokinesis. Aurora C plays a role in the regulation of cilia and flagella, localizes to centrosomes from anaphase to cytokinesis, and is predominantly expressed in testis. Overexpression of Aurora A and B has been reported in a number of human malignancies, including colon, breast, pancreatic, and ovarian tumors. The role of Aurora C within tumorigenesis is less well understood.

Both Aurora A and B have been validated as targets for cancer therapy.[3] A number of Aurora kinase inhibitors have been described in recent years,[4] and there are currently about 30 Aurora kinase inhibitors in various stages of preclinical and clinical development.[5] For this reason, continued efforts are being made by numerous research groups to discover new small molecules that target Aurora A or B selectively, or that display dual inhibitory activity. A broad diversity of chemical scaffolds has been reported, including pyrazolopyrimidine **1** (VX-680)[6] and 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole **2** (PHA739358)[7] as pan-Aurora inhibitors, 5*H*-pyrimido[5,4-*d*]-[2]benzazepine derivative **3** (MLN8237)[8] as a selective Aurora A inhibitor, and pyrazoloquinazoline **4** (AZD1152)[9] as a selective Aurora B inhibitor (Figure 1).

More recently, imidazo[4,5-*b*]pyridine-based derivatives were reported as potent pan-Aurora kinase inhibitors.[10] Compound **5** (Figure 2), an orally bioavailable dual FLT3/Aurora kinase inhibitor, has been selected as a preclinical development candidate for the treatment of acute myeloid leukemia. Bisanilinopyrimidine **6** was identified as a highly potent and selective cell-permeable inhibitor of Aurora A and B.[11] Pyrrolotriazine **7** was shown to display the same pharmacological and pharmacokinetic properties.[12] In addition, it exhibits durable antitu-

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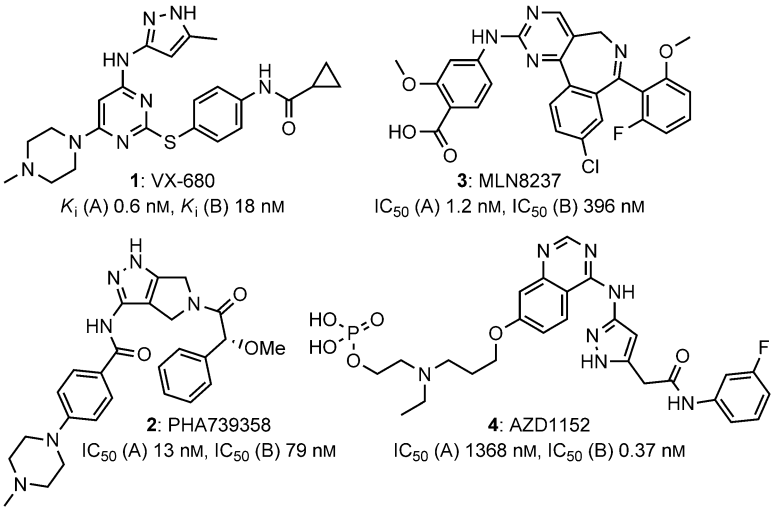



**Figure 1.** Structures of Aurora kinase inhibitors in clinical development.

mor activity in a nude rat HCT116 tumor xenograft model and good in vivo tolerability. Imidazo[1,2-*a*]pyrazine **8** was described as a dual Aurora A/B kinase inhibitor, and off-target kinase selectivity was achieved by introducing a 3-fluoro-4-pyridylacetamide moiety on the pyrazole ring.[13]

The 5,6-diphenylfuro[2,3-*d*]pyrimidin-4-amine derivative **9** exhibited antiproliferative activity in tests against the HCT116 colon cancer cell line ($IC_{50}$ = 400 nM) and showed pan-Aurora kinase inhibition (Figure 2).[14] Structure-based lead optimization of **9** resulted in the identification of **10** as a potent Aurora kinase inhibitor with improved physicochemical properties as well as good in vivo efficacy in a HCT116 tumor xenograft mouse model.[14] The rational redesign of furopyrimidine **9** led to the identification of quinazoline-based Aurora kinase inhibitor **11** with improved antitumor activity (HCT116 $IC_{50}$ = 23 nM).[15]

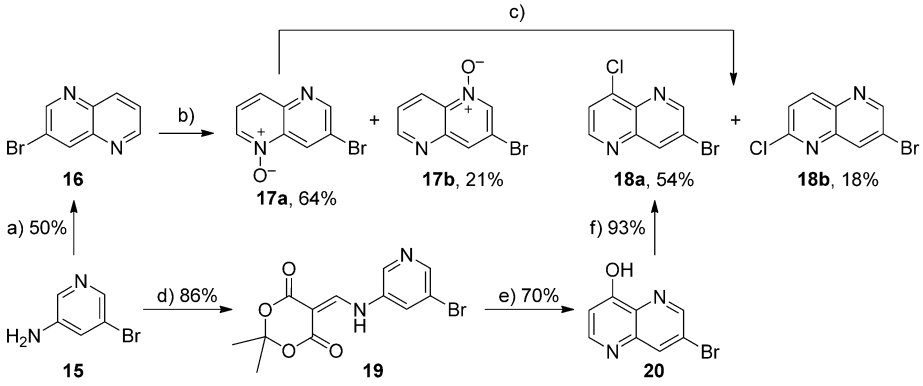
A literature survey revealed that fused polycyclic derivatives were very recently described as pan-Aurora kinase inhibitors. 5*H*-Benzo[*c*][1,8]naphthyridin-6-ones **12** exhibited selective sub-nanomolar Aurora kinase inhibition coupled with antiproliferative effects in a pancreatic cell line, MIAPaCa-2.[16] Benzo[*e*]-pyridoindolones **13** provided water-soluble inhibitors of Aurora kinases, exhibiting antiproliferative activity in the nanomolar range (for maleate salts, HeLa cells $IC_{50}$ = 114 nM (**13a**) and HeLa cells $IC_{50}$ = 63 nM (**13b**)).[17] Finally, phthalazinone pyrazoles **14** showed high Aurora A inhibitory activity, with >1000-fold selectivity over Aurora B and good oral bioavailability.[18]

As part of our ongoing efforts to identify new chemical classes of kinase inhibitors, we previously described a synthetic approach and the biological evaluation of promising pyridopyrazines for the treatment of malignant diseases based on pathological cell proliferation.[19] We were especially interested in obtaining 1,5-naphthyridine derivatives, considered bioisosteres of pyrido[2,3-*b*]pyrazines (Figure 3).[20] Many 1,5-naphthyridine derivatives have been found to exert biological activities in a broad range of therapeutic areas.[21,22] Nevertheless, only a few reports discuss 1,5-naphthyrine-based kinase inhibitors as antitumor agents.[23] Herein we report the development of new (1,5-naphthyridin-4-yl)ureas substituted at the 7-position of the ring by an aryl group (Figure 3). Biological evaluations were performed in order to identify new potent Aurora kinase inhibitors.

## Results and Discussion

### Chemistry

The synthetic route of target heterocyclic ureas **38**–**60** is outlined in Schemes 1 and 2. The strategy required initial access to the key precursor, 3-bromo-8-chloro-1,5-naphthyridine **18a**. The 1,5-naphthyridine ring was built via Skraup synthesis, from 3-amino-5-bromopyridine **15** in the presence of glycerol under oxidative conditions to afford compound **16** in moderate yield (Scheme 1).[24,21c,e] Starting material **15** was commercially available or was readily prepared via Hofmann rearrangement of 5-bromopyridine-3-carboxamide obtained by subsequent chlorination and amination of the corresponding pyridine-3-carboxylic acid.[25] As previously reported,[24b] cyclization took




**Scheme 1.** *Reagents and conditions*: a) glycerol, $FeSO_4 \cdot 7H_2O$, $H_3BO_3$, $H_2SO_4$, *m*-$NO_2PhSO_3Na$, 135 °C, 18 h; b) *m*CPBA, $CH_2Cl_2$, RT, 18 h; c) $POCl_3$, $CH_2Cl_2$, reflux, 2.5 h; d) Meldrum's acid, $CH(OEt)_3$, EtOH, 90 °C, 2 h; e) Dowtherm A, 240 °C, 10 min; f) $POCl_3$, reflux, 2 h.

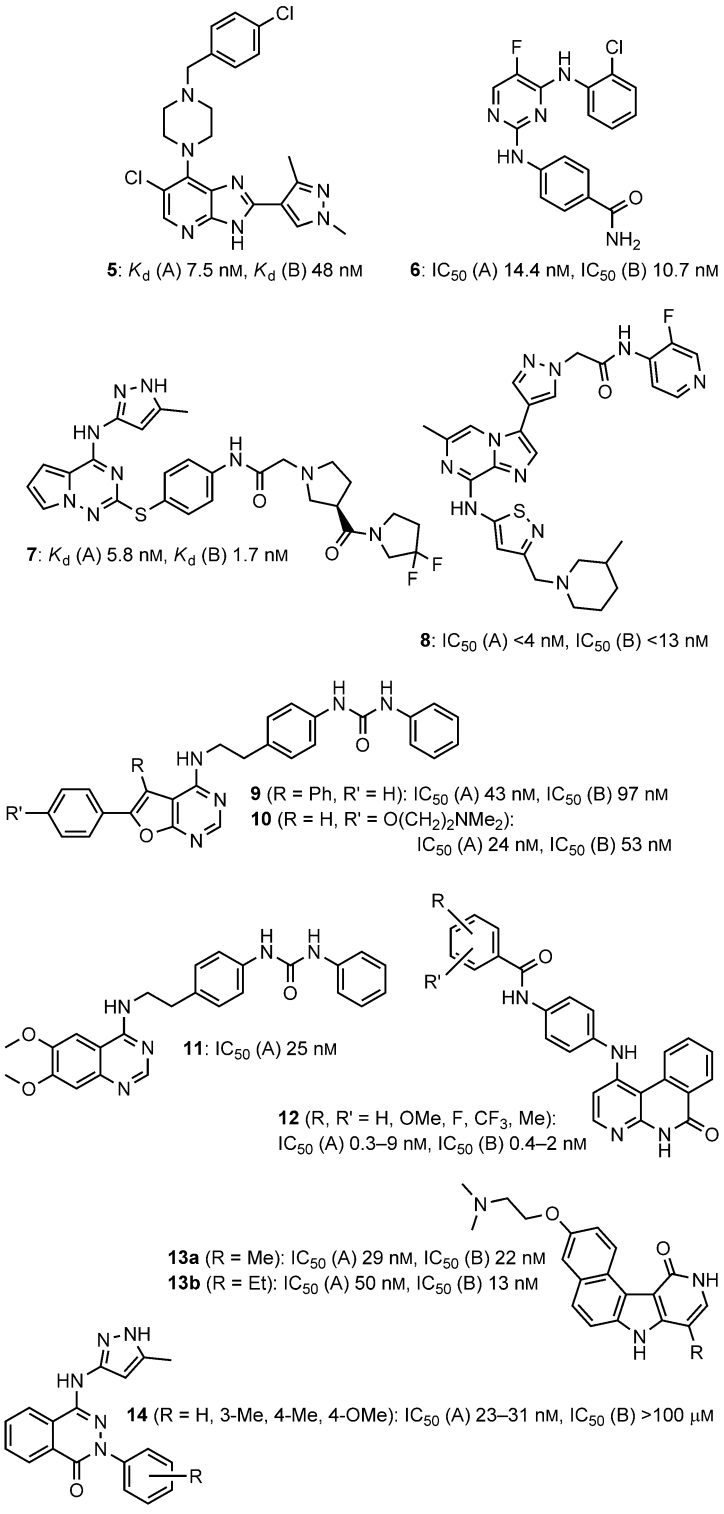



**Figure 2.** Structures of recently described Aurora kinase inhibitors.

place exclusively at the 2-position of aminopyridine **15**, and none of the 1,7-isomer was detected. In addition, the starting aromatic amine was not recovered, and the poor yield (50%) can be explained by the electron-withdrawing effect of the pyridine nitrogen and bromine atoms, rendering the pyridine ring a poor electron donor in the cyclization step. Formation of byproducts such as 1,2,3,4-tetrahydro-1,5-naphthyridine derivatives and 3-methyl- or 3-ethyl-1,5-naphthyridine analogues has also been described.[24b] Meisenheimer reaction of 1,5-naphthyridine-*N*-oxide has been reported to afford the 2- and 4-chloro-1,5-naphthyridine isomers.[26] Thus, 3-bromo-1,5-naphthyridine **16** underwent N-oxidation with 3-chloroperbenzoic acid to give 7-bromo-1,5-naphthyridine-1-oxide **17a** in 60% yield, but in mixture with its regioisomer **17b** in 20% yield.[21e] The compounds were easily separated by silica gel chromatography. Compound **17a** then reacted with phosphorus(III) oxychloride in dichloromethane at reflux to furnish target 3-bromo-8-chloro-1,5-naphthyridine **18a** in 54% yield. As expected,[26] 7-bromo-2-chloro-1,5-naphthyridine isomer **18b** was formed and isolated in 18% yield. This could be an interesting approach to obtain both isomers for further SAR study, but the goal of this medicinal chemistry work was to provide new 4,7-disubstituted 1,5-naphthyridines of biological interest. For this reason, we decided to find an alternative synthetic pathway to circumvent the formation of isomers and to enhance the overall yield of 17% for three steps.

The synthesis of 3-bromo-8-chloro-1,5-naphthyridine was previously described[27] from 3-amino-5-bromopyridine **15** via ethyl 7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate. Hydrolysis of the ester in aqueous sodium hydroxide to the corresponding acid, followed by decarboxylation in quinoline at reflux afforded 7-bromo-1,5-naphthyridin-4-ol. Chlorination of this hydroxy compound by treatment with phosphoryl chloride at reflux gave the desired 1,5-naphthyridine in 28% overall yield. This methodology required a five-step reaction from **15** and also gave poor yield.

In the same manner, to introduce a chlorine atom at position 4 of the 1,5-naphthyridine scaffold, we decided to prepare the corresponding hydroxy precursor (Scheme 1). Nevertheless, this intermediate was prepared by thermolysis (220–240 °C) of the 3-pyridylaminomethylene derivative of Meldrum's acid as described for quinolone synthesis.[28,21f] The use of such an enamine allowed us to carry out thermal cyclization and subsequent decarboxylation in a one-pot procedure.[29] In this context, treatment of 3-amino-5-bromopyridine **15** with Meldrum's acid and triethyl orthoformate furnished the corresponding enamine **19** in 86% yield (Scheme 1). Ring formation was accomplished in Dowtherm A at 240 °C to readily afford the 1,5-naphthyridin-4-ol derivative **20** in 70% yield, without a trace of its 1,7-regioisomer.[28c] Finally, compound **20** reacted with phosphorus(III) oxychloride at reflux to give key precursor **18a** in very good yield.[21e] The choice of this second synthetic pathway appeared to be justified, as compound **18a** was obtained in 56% yield for three steps from **15**, in contrast to the 17% yield for three steps in the first route.

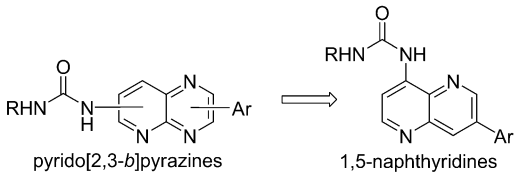



**Figure 3.** General structure of synthesized compounds.

Selective amination of compound **18a**, by substitution of the chlorine atom, was performed in the presence of ammonium hydroxide in a sealed tube at 160 °C to give key heterocyclic amine **21**, a suitable compound for a broad pharmacomodulation at positions 4 and 7 of the 1,5-naphthyridine scaffold (Scheme 2).[30] (7-Bromo-1,5-naphthyridin-4-yl)ureas **22**–**37** were prepared from azaheterocyclic amine **21** using various isocyanates in pyridine at reflux,[31] or in two steps in the presence of triphosgene,[32] triethylamine, and then adding the desired amine. Finally, aromatic moieties were introduced at position 7 of the ring under a palladium-catalyzed Suzuki–Miyaura-type reaction, using boronic acids or esters and leading to target compounds **38**–**60** in low to good yields (Scheme 2).[33]

## Biological activity

(7-Aryl-1,5-naphthyridin-4-yl)ureas **38**–**60** were first examined for their ability to inhibit Aurora kinases A and B (Table 1). In a general trend, all compounds were found to be active against Aurora A and B, except *tert*-butylureas **41**–**43**, which displayed only weak inhibition of Aurora A ($IC_{50} \geq 2.76$ μM). Interestingly, their ethylurea analogues **38**–**40** and cyclopropylurea counterpart **44** proved to be more active. Introduction of a 1-methylpyrazol-4-yl moiety at position 7 of the 1,5-naphthyridine ring was very promising, as compounds **45**, **54**, and **49**, respectively bearing ethyl, *tert*-butyl, and cyclopropyl substituents, displayed very good activities relative to **38**–**44** ($IC_{50}$ (Aurora A) from 0.107 to 0.613 μM versus 0.197 to 5.77 μM, and $IC_{50}$ (Aurora B) from 0.013 to 0.112 μM versus 0.048 to 1.58 μM). Consequently, the pyrazolyl substituent was kept for additional SAR study by designing compounds **45**–**60**.

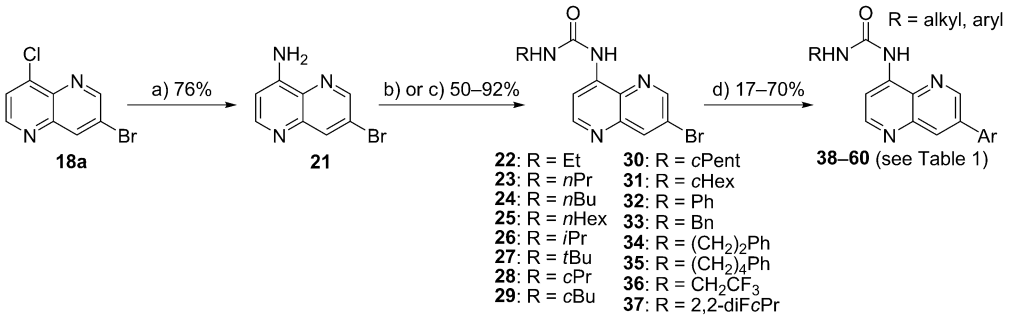
Linear alkylureas **45**–**48** showed decreased activity correlated with increasing in chain length. The same features were observed for the corresponding cycloalkylureas **49**–**52**, but these exhibited better activities, and cyclopropylurea **49** was the most active compound of the series ($IC_{50} = 13$ and 107 nM against Aurora B and A, respectively). Introduction of a phenyl ring on the urea function (compound **55**) was deleterious for activity ($IC_{50} = 1.26$ μM against Aurora B), and kinase inhibition was recovered by inserting an alkyl chain between the phenyl group and the nitrogen atom of the urea function (compounds **56**–**58**, $IC_{50}$ 66–147 nM against Aurora B). Finally, fluorine analogues **59** and **60** of compounds **45** and **49**, respectively, demonstrated a great loss of potency; 2,2-difluorocyclopropylurea **60** was 60-fold less active against Aurora B than the most active compound **49**. All the compounds tested on both Aurora kinases A and B were only slightly selective toward Aurora B and can be considered as pan-Aurora kinase inhibitors.

Compounds **38**–**60** were also tested for their selective inhibition toward a panel of seven cancer-related protein kinases, which include mitogen-activated protein kinase (Erk2),[34] serine/threonine kinases (HIPK1, Pim1),[35,36] receptor tyrosine kinases (KDR, TrkA),[37,38] and non-receptor tyrosine kinases (c-Abl, Yes).[39,40] Data showed that besides inhibiting two Aurora kinases, no additional inhibition was detected for this set of seven protein kinases (see Supporting Information).

Regarding cellular data, cell line assays (HCT116 colon, MDA-MB468 breast, PC3 prostate, A549 NSCLC, and U87MG CNS) were carried out to correlate antiproliferative activity and Aurora kinase inhibition. Unfortunately, only phenylurea **55** from the pyrazolyl series translated into moderate cell activity ($IC_{50}$ A549: 1.16 μM and $IC_{50}$ HCT116: 3.64 μM), as all the compounds remained inactive toward the tested tumor cell lines. Moreover, **55** was observed to be among the less active compounds against Aurora kinase B ($IC_{50} = 1.26$ μM).

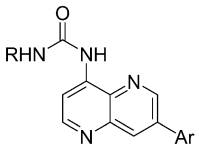
## In vitro ADME properties and safety data

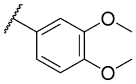
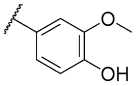
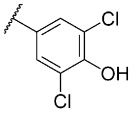
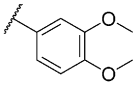
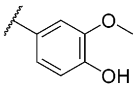
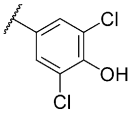
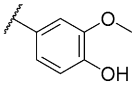
The reason behind the lack of translation of Aurora kinase inhibition into antiproliferative activity is unknown, and must be investigated. Some explanations for the lack of activity include: 1) physicochemical parameters of the compounds are unsuitable for cell membrane permeability, and 2) compounds are excluded from the cells by an efflux mechanism.




**Scheme 2.** *Reagents and conditions*: a) $NH_4OH$, dioxane, sealed tube, 140 °C, 24 h; b) RNCO, pyridine, sealed tube, 140 °C, 24 h; c) 1. triphosgene, $Et_3N$, $CH_2Cl_2$, reflux, 1 h, 2. $RNH_2$, reflux, 2 h; d) arylboronic acid or ester, $Pd(PPh_3)_4$, $Na_2CO_3$, DMF/$H_2O$ (10:1), 80 °C, 5–16 h.

**Table 1.** (7-Aryl-1,5-naphthyridin-4-yl)urea Aurora kinase inhibitors **38**–**60** used in this study and their antiproliferative activity.

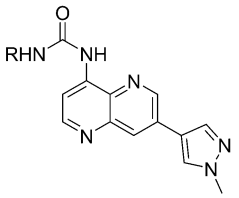



| Compd | R | Ar | Enzyme assays $IC_{50}$ [μM][a] | | Cell proliferation $IC_{50}$ [μM][a] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Aurora A | Aurora B | HCT116 | MDA-MB468 | PC3 | A549 | U87MG |
| **38** | Et |  | 0.881 | 0.136 | >50 | 13.18 | 13.80 | >50 | 9.72 |
| **39** | Et |  | 1.60 | 0.370 | >50 | >50 | >50 | >50 | >50 |
| **40** | Et |  | 0.197 | 0.227 | >50 | >50 | >50 | >50 | >50 |
| **41** | *t*Bu |  | 2.76 | 0.714 | >50 | >50 | >50 | >50 | >50 |
| **42** | *t*Bu |  | 5.77 | 1.58 | >50 | >50 | >50 | >50 | >50 |
| **43** | *t*Bu |  | 3.62 | 0.500 | >50 | >50 | >50 | >50 | >50 |
| **44** | *c*Pr |  | 0.623 | 0.048 | 12.26 | 4.59 | 13.48 | 14.63 | >50 |
| **45** | Et | pyrazolyl | 0.506 | 0.038 | 12.28 | 8.73 | 13.81 | 14.57 | >50 |
| **46** | *n*Pr | pyrazolyl | 0.163 | 0.026 | 13.92 | 10.24 | 13.55 | 9.07 | 13.45 |
| **47** | *n*Bu | pyrazolyl | ND | 0.164 | 8.64 | 20.15 | 13.77 | 18.65 | ND |
| **48** | *n*Hex | pyrazolyl | ND | 0.885 | 15.80 | 20.50 | 15.80 | 26.85 | 15.80 |
| **49** | *c*Pr | pyrazolyl | 0.107 | 0.013 | 15.38 | 7.42 | >50 | >50 | >50 |
| **50** | *c*Bu | pyrazolyl | 0.284 | 0.048 | 6.72 | 7.35 | 15.47 | 15.14 | >50 |
| **51** | *c*Pent | pyrazolyl | ND | 0.108 | 5.98 | 5.78 | 9.57 | 13.01 | ND |
| **52** | *c*Hex | pyrazolyl | ND | 0.354 | 5.03 | 5.84 | >50 | 8.74 | >50 |
| **53** | *i*Pr | pyrazolyl | ND | 0.137 | 3.45 | 10.49 | 7.97 | >50 | ND |
| **54** | *t*Bu | pyrazolyl | 0.613 | 0.112 | 16.69 | >50 | >50 | >50 | >50 |
| **55** | Ph | pyrazolyl | ND | 1.26 | 3.64 | >50 | >50 | 1.16 | >50 |
| **56** | Bn | pyrazolyl | ND | 0.066 | >50 | 4.26 | >50 | >50 | ND |
| **57** | $CH_2CH_2Ph$ | pyrazolyl | ND | 0.086 | 6.93 | 3.83 | 16.25 | 15.80 | ND |
| **58** | $(CH_2)_4Ph$ | pyrazolyl | ND | 0.141 | >50 | >50 | >50 | >50 | >50 |
| **59** | $CH_2CF_3$ | pyrazolyl | 0.332 | 0.129 | 15.01 | 13.51 | 16.39 | >50 | >50 |
| **60** | 2,2-diF-*c*Pr | pyrazolyl | ND | 0.784 | >50 | 15.80 | >50 | 15.80 | >50 |

[a] Values, within ±15% SD, are the mean of at least two independent determinations; ND: not determined; pyrazolyl: 

To determine the lipophilicity profile of the naphthyridine ureas, their partition coefficients at pH 7.4, expressed as log *D*, was derived directly from measurements of their chromatographic hydrophobicity index (CHI; Table 2).[41] CHI values could be estimated rapidly by using a gradient method on a UPLC system. Log $D_{7.4}$ values ranged from 1.6 to 2.8 and were found acceptable for cell permeability. Compounds **45**, **49**, **54**, **58**, and **59** were profiled for aqueous solubility in phosphate-buffered saline (PBS), mouse liver microsomal and plasma stability, and cell permeability in Caco-2[42] cells (Table 2). The aqueous solubility (93–185 μM) in PBS was consistent with the observed lipophilicity and was not a deleterious parameter for cellular assays. Stability tests revealed three analogues—**45**, **49**, and **54**—that showed excellent metabolic stability in mouse plasma. Furthermore, compounds **46** (4.9%), **58** (15.0%), **50** (15.1%), **45** (22.2%), and **49** (51.8%) exhibited

**Table 2.** In vitro ADME properties and safety data for compounds **45**, **46**, **48**–**51**, **53**, **54**, and **56**–**59**.



| Compd | R | CHI[a] | Log $D_{7.4}$[b] | Solubility [μM][c] | MLM [%][d] | MP [%][e] | Caco-2 [$10^{-6}$ cm s$^{-1}$][f] | CYP3A4 inhibition [μM] | hERG binding [μM] |
|---|---|---|---|---|---|---|---|---|---|
| **45** | Et | 52.5 | 1.6 | 185 | 22.2 | 96.6 | ND | ND | ND |
| **46** | *n*Pr | 61.2 | 1.9 | ND | 4.9 | ND | ND | >100 | ND |
| **48** | *n*Hex | 88.4 | 2.7 | ND | ND | ND | ND | ND | ND |
| **49** | *c*Pr | 58.7 | 1.8 | 181 | 51.8 | 92.4 | 59/33 | >200 | >60 |
| **50** | *c*Bu | 64.9 | 2.0 | ND | 15.1 | ND | ND | >100 | >60 |
| **51** | *c*Pent | 71.8 | 2.2 | ND | ND | ND | ND | ND | ND |
| **53** | *i*Pr | 60.8 | 1.9 | ND | ND | ND | ND | ND | ND |
| **54** | *t*Bu | 71.8 | 2.2 | 93 | 83.9 | 90.3 | ND | ND | ND |
| **56** | Bn | 72.3 | 2.2 | ND | ND | ND | ND | ND | ND |
| **57** | $CH_2CH_2Ph$ | 76.9 | 2.4 | ND | ND | ND | ND | ND | ND |
| **58** | $(CH_2)_4Ph$ | 90.2 | 2.8 | 94 | 15.0 | ND | 42/20 | ND | ND |
| **59** | $CH_2CF_3$ | 63.5 | 2.0 | ND | 88.2 | ND | ND | >200 | ND |

[a] Chromatographic hydrophobicity index, determined by RP-UPLC. [b] Calculated from CHI. [c] Measured at pH 7.4, PBS medium +1% BSA. [d] Mouse liver microsomes, percent remaining after 1 h. [e] Mouse plasma, percent remaining after 6 h. [f] Caco-2 permeability b→a/a→b, determined in the presence of 1% BSA. ND: not determined.

low to moderate metabolic stability in liver microsomes, but analogues **54** (83.9%) and **59** (88.2%) were found to be very stable. Moreover, the data listed in Table 2 indicate that hit compound **49**, toward Aurora kinase inhibition, had very good cell permeability, with decreased efflux (0.56; ratio = 0.56, [b→a/a→b]). Phenylbutylurea **58** showed lower but acceptable permeability, with a decreased efflux ratio of 0.48. We observed no inhibition of cytochrome P450, CYP3A4,[43] for compounds **46**, **49**, **50**, and **59**, and no undesired activities at the human hERG[44] channel for compounds **49** and **50**.

## Conclusions

The identification of novel (7-aryl-1,5-naphthyridin-4-yl)ureas, inhibitors of Aurora kinases A/B, is reported herein. Compounds showed excellent Aurora A and B inhibitory activities in the nanomolar range and also displayed selectivity in an enzyme-based inhibition assay against a panel of seven kinases. Unfortunately, all the compounds suffered from a lack of antiproliferative activity in tests against five tumor cell lines.

For the most active compound **49** against Aurora kinases A and B ($IC_{50}$ values of 13 and 107 nM, respectively), we observed permeability values higher than 10 ($P_{app}$ value a→b direction: 59) and we saw no hints for efflux for this compound (b→a/a→b ratio <1). Therefore, it seems we have a very highly permeable structure class in hand. In addition, analogue **49** demonstrated very good aqueous solubility, excellent plasma stability, and acceptable microsomal stability in mouse, associated with a good safety profile. The fact that there is no direct correlation between measured kinase inhibitory potencies and antiproliferative activities with these compounds is difficult to explain. As is almost always observed with kinase inhibitors, the efficacy on isolated enzyme is higher than that on cells. This is likely a consequence of the combination of several factors including interaction with other targets within the cell (multitarget effects), nonspecific binding to cellular proteins (ionic or hydrophobic interactions), intracellular metabolism and possible inactivation, limitations in passage across biological membranes (plasma membrane, nuclear envelope), and high intracellular ATP concentrations. The described derivatives possess good cell-penetration parameters, but their efficiency on the signaling pathway was insufficient to induce significant cell death. In conclusion, this series constitutes a very promising starting point for the design of anticancer agents. Based on the interesting 1,5-naphthyridine scaffold, further pharmacomodulations are in progress with the aim of reaching in vitro and in vivo antiproliferative activities associated with kinase inhibition.

## Experimental Section

### *Chemistry*

**General methods**: Melting points were determined with an Electrothermal IA9300 digital melting point apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz). Chemical shifts ($\delta$) are expressed in ppm relative to tetramethylsilane as internal standard. NMR signals are described as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, sext = sextuplet, m = multiplet and br = broad. Coupling constants (*J*) are given in hertz. IR spectra were obtained in KBr pellets using a PerkinElmer Paragon FTIR 1000 PC spectrometer. Only the most significant absorption bands are reported. Electrospray mass spectrometric analysis was performed on a Waters Acquity UPLC System ZQ 2000 single quadrupole. All tested com-

pounds displayed purity of >97%. All reactions were monitored by thin-layer chromatography (TLC) using 0.2-mm-thick silica gel plates 60 $F_{254}$ (5735 Merck). Column chromatography was carried out with silica gel 60 (70–230 mesh, ASTM, Merck). Chemicals and solvents used were commercially available. Elemental analyses were performed on a Thermo Scientific Elemental Analyzer Flash EA 1112 and were found to be within ±0.4% of theoretical values.

**3-Amino-5-bromopyridine (15)**: In $SOCl_2$ (300 mL) under argon was added 5-bromonicotinic acid (30.0 g, 150 mmol). The reaction mixture was held at reflux for 8 h. After cooling to RT, excess $SOCl_2$ was removed under reduced pressure. Dichloroethane was added (300 mL), and the solution was cooled to −30 °C. $NH_3$ gas was bubbled through the reaction mixture for 20 min, and the mixture was then allowed to cool to RT. $H_2O$ (300 mL) was added, and the aqueous layer was extracted with EtOAc (2×400 mL). The organic extracts were combined and washed with an aqueous solution of $NaHCO_3$ (300 mL). The combined extracts were dried over anhyd $Na_2SO_4$, and the solvents were removed under reduced pressure to give 5-bromopyridine-3-carboxamide as a white powder (26.5 g, 88%): $R_f$=0.39 ($CH_2Cl_2$/EtOH, 96:4); mp: 218–219 °C (lit.[25] 219–219.5 °C); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.02 (d, $J$=2.1 Hz, 1H), 8.89 (d, $J$=2.1 Hz, 1H), 8.47 (t, $J$=2.1 Hz, 1H), 8.27 (br s, 1H), 7.79 ppm (br s, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=164.9, 152.5, 147.2, 137.5, 131.3, 120.0 ppm; IR (KBr): $\tilde{\nu}$=3388, 3192, 3033, 1657, 1621, 1420, 1396 cm$^{-1}$; MS (ESI) $m/z$ (%): 201.0 (100) $[M+H]^+$, 203.1 (100) $[M+H+2]^+$.

To a solution of NaOH (29.8 g, 746 mmol) in $H_2O$ (250 mL) was added $Br_2$ (7.6 mL, 149 mmol) at 0 °C and then 5-bromopyridine-3-carboxamide (25 g, 124 mmol). The reaction mixture was allowed to cool to RT for 20 min and then was heated at 80 °C for 35 min. The resulting solution was cooled at 0 °C and HCl was added until the mixture reached pH 2. The reaction mixture was washed with $CH_2Cl_2$ (300 mL). The aqueous layer was adjusted to pH 10 by the addition of NaOH pellets. The aqueous layer was extracted with $CH_2Cl_2$ (500 mL), the combined organic phases were dried over anhyd $Na_2SO_4$, filtered, and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$/EtOH 98:2 to afford compound **15** as a red solid (15.3 g, 71%); $R_f$=0.28 ($CH_2Cl_2$/EtOH, 96:4); mp: 64–65 °C (lit.[25] 69–69.5 °C); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=7.92 (d, $J$=2.4 Hz, 1H), 7.80 (d, $J$=2.4 Hz, 1H), 7.14 (t, $J$=2.4 Hz, 1H), 5.67 ppm (br s, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=146.6, 136.7, 135.1, 121.5, 120.3 ppm; IR (KBr): $\tilde{\nu}$=3318, 3153, 1646, 1574, 1426, 1246 cm$^{-1}$; MS (ESI) $m/z$ (%): 173.0 (100) $[M+H]^+$, 175.1 (100) $[M+H+2]^+$; Anal. calcd for $C_5H_5BrN_2$: C 34.71, H 2.91, N 16.19, found: C 34.75, H 2.89, N 16.17.

**3-Bromo-1,5-naphthyridine (16)**: In concentrated $H_2SO_4$ (85 mL) was successively added $FeSO_4{\cdot}7H_2O$ (3.58 g, 12.9 mmol), sodium 3-nitrobenzenesulfonate (44.11 g, 198.6 mmol) and $B(OH)_3$ (9.69 g, 158.9 mmol). The reaction mixture was stirred at RT for 30 min. Glycerol (42.96 g, 466.7 mmol), 3-amino-5-bromopyridine **15** (17.20 g, 99.3 mmol) and $H_2O$ (85 mL) were added. The reaction mixture was stirred at 135 °C for 18 h and was allowed to cool to RT. A solution of 8 M NaOH was carefully added until the mixture reached pH 14. The aqueous layer was extracted with EtOAc (300 mL), the organic layer was dried over anhyd $Na_2SO_4$, filtered, and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$ to furnish compound **16** as a white solid (10.38 g, 50%). $R_f$=0.77 ($CH_2Cl_2$/EtOH, 96:4); mp: 108–109 °C (lit.[45] 106–107 °C); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.12 (d, $J$=2.0 Hz, 1H), 9.08 (dd, $J$=8.4, 2.4 Hz, 1H), 8.78 (d, $J$=2.0 Hz, 1H), 8.50 (dd, $J$=8.8, 2.4 Hz, 1H), 7.80 ppm (dd, $J$=8.8, 8.4 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=152.7, 152.1, 143.6, 141.8, 138.5, 137.1, 125.5, 120.1 ppm; IR (KBr): $\tilde{\nu}$=3009, 1553, 1451, 1189, 1062 cm$^{-1}$; MS (ESI) $m/z$ (%): 209.0 (100) $[M+H]^+$, 211.1 (100) $[M+H+2]^+$; Anal. calcd for $C_8H_5BrN_2$: C 45.96, H 2.41, N 13.40, found: C 45.91, H 2.40, N 13.46.

**7-Bromo-1,5-naphthyridine-1-oxide (17a) and 3-bromo-1,5-naphthyridine-1-oxide (17b)**: To a solution of 7-bromo-1,5-naphthyridine **16** (4.43 g, 21.2 mmol) in $CH_2Cl_2$ (165 mL) was added portionwise at 0 °C *meta*-chloroperbenzoic acid (*m*CPBA; 5.23 g, 21.2 mmol). The reaction mixture was stirred at RT for 18 h. The organic layer was washed with an aqueous solution of NaOH (1 M, 200 mL), the aqueous layer was extracted with $CH_2Cl_2$ (400 mL), dried over anhyd $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was separated by column chromatography on silica gel, eluting with $CH_2Cl_2$/EtOH 98:2→96:4 to afford compounds **17a** as a pale-yellow solid (3.05 g, 64%) and **17b** as a yellow solid (1.00 g, 21%).

**7-Bromo-1,5-naphthyridine-1-oxide (17a)**: $R_f$=0.18 ($CH_2Cl_2$/EtOH, 96:4); mp: 148–149 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.21 (d, $J$=2.1 Hz, 1H), 9.10 (d, $J$=2.1 Hz, 1H), 8.75 (d, $J$=6.1 Hz, 1H), 8.06 (d, $J$=8.8 Hz, 1H), 7.80 ppm (dd, $J$=8.8, 6.1 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.0, 143.6, 137.8, 136.6, 129.5, 126.4, 125.8, 120.7 ppm; IR (KBr): $\tilde{\nu}$=3009, 1646, 1487, 1398, 1254, 1086 cm$^{-1}$; MS (ESI) $m/z$ (%): 225.0 (100) $[M+H]^+$, 227.1 (100) $[M+H+2]^+$; Anal. calcd for $C_8H_5BrN_2O$: C 42.70, H 2.24, N 12.45, found: C 42.63, H 2.26, N 12.47.

**3-Bromo-1,5-naphthyridine-1-oxide (17b)**: $R_f$=0.13 ($CH_2Cl_2$/EtOH, 96:4); mp: 153–154 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.12 (d, $J$=4.3 Hz, 1H), 9.03 (s, 1H), 8.86 (d, $J$=7.4 Hz, 1H), 8.36 (s, 1H), 7.88 ppm (dd, $J$=7.4, 4.3 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.9, 145.4, 137.9 (2C), 129.4, 128.6, 126.2, 119.2 ppm; IR (KBr): $\tilde{\nu}$=3006, 1654, 1454, 1377, 1242, 1067 cm$^{-1}$; MS (ESI) $m/z$ (%): 225.0 (100) $[M+H]^+$, 227.0 (100) $[M+H+2]^+$; Anal. calcd for $C_8H_5BrN_2O$: C 42.70, H 2.24, N 12.45, found: C 42.75, H 2.22, N 12.42.

**3-Bromo-8-chloro-1,5-naphthyridine (18a) and 7-bromo-2-chloro-1,5-naphthyridine (18b)**: **Method A**: To a solution of 7-bromo-1,5-naphthyridine-1-oxide **17a** (7.97 g, 35.4 mmol) in $CH_2Cl_2$ (600 mL) was added $POCl_3$ (9.9 mL, 106.2 mmol). The reaction mixture was heated at reflux for 2.5 h. $CH_2Cl_2$ was partially evaporated under reduced pressure. Then, the reaction mixture was cooled in an ice bath and an aqueous solution of 1 M NaOH (200 mL) was carefully added. The aqueous layer was extracted with $CH_2Cl_2$ (500 mL), dried over anhyd $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was separated by column chromatography on silica gel, eluting with $CH_2Cl_2$ to give compounds **18a** as a white solid (4.65 g, 54%) and **18b** as a white solid (1.55 g, 18%).

**3-Bromo-8-chloro-1,5-naphthyridine (18a)**: $R_f$=0.75 ($CH_2Cl_2$/EtOH, 96:4); mp: 162–163 °C (lit.[27] 163–165 °C); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.22 (d, $J$=2.1 Hz, 1H), 8.99 (d, $J$=4.5 Hz, 1H), 8.88 (d, $J$=2.1 Hz, 1H), 8.11 ppm (d, $J$=4.5 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=152.8, 152.7, 144.8, 143.1, 139.1, 138.7, 125.4, 121.5 ppm; IR (KBr): $\tilde{\nu}$=3031, 1646, 1467, 1312, 1220, 1104, 907 cm$^{-1}$; MS (ESI) $m/z$ (%): 242.9 (73) $[M+H]^+$, 245.0 (100) $[M+H+2]^+$, 247.0 (24) $[M+H+4]^+$; Anal. calcd for $C_8H_4BrClN_2$: C 39.46, H 1.66, N 11.51, found: C 39.59, H 1.65, N 11.48.

**7-Bromo-2-chloro-1,5-naphthyridine (18b)**: $R_f$=0.82 ($CH_2Cl_2$/EtOH, 96:4); mp: 168–169 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.15 (d,

$J$=2.1 Hz, 1H), 8.79 (d, $J$=2.1 Hz, 1H), 8.55 (d, $J$=8.8 Hz, 1H), 7.93 ppm (d, $J$=8.8 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$= 152.5, 151.3, 143.2, 140.8, 140.7, 137.5, 126.6, 121.2 ppm; IR (KBr): $\tilde{\nu}$=3027, 1641, 1457, 1322, 1212, 1109, 905 cm$^{-1}$; MS (ESI) $m/z$ (%): 242.9 (76) $[M+H]^+$, 245.0 (100) $[M+H+2]^+$, 246.9 (22) $[M+H+4]^+$; Anal. calcd for $C_8H_4BrClN_2$: C 39.46, H 1.66, N 11.51, found: C 39.51, H 1.69, N 11.43.

**3-Bromo-8-chloro-1,5-naphthyridine (18a). Method B**: 7-Bromo-1,5-naphthyridin-4-ol **20** (4.50 g, 20.0 mmol), described below, was dissolved in $POCl_3$ (9.3 mL, 100.0 mmol) under nitrogen atmosphere and held at reflux for 2 h. The mixture was then cooled and concentrated under vacuo. The solid was taken up with $H_2O$ (100 mL), neutralized with a saturated aqueous solution of $NaHCO_3$, and extracted with $CH_2Cl_2$ (300 mL). The solution was dried over anhyd $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel, eluting with $CH_2Cl_2$ to give compound **18a** as a white solid (4.53 g, 93%).

**5-{[(5-Bromopyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (19)**: A mixture of triethyl orthoformate (2.9 mL, 17.3 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (9.60 g, 66.6 mmol) (Meldrum's acid) was heated at 90 °C for 1.5 h and then cooled to 70 °C. 3-Amino-5-bromopyridine **15** (10.00 g, 57.8 mol) was slowly added over 10 min with an EtOH (20 mL) rinse while maintaining the reaction temperature between 60 and 70 °C. The reaction was then heated for an additional 30 min and allowed to cool to RT. The precipitate was filtered, washed with EtOH (20 mL), and dried to yield compound **19** as a light-yellow crystalline solid (16.26 g, 86%). $R_f$=0.29 ($CH_2Cl_2$/EtOH, 95:5); mp: 199–200 °C (lit.[46] 200–202 °C); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=11.21 (d, $J$=13.5 Hz, 1H), 8.59 (d, $J$=13.5 Hz, 1H), 8.57 (d, $J$=1.8 Hz, 1H), 8.52 (d, $J$=2.4 Hz, 1H), 7.81 (t, $J$=2.1 Hz, 1H), 1.76 ppm (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=165.4, 162.8, 152.4, 148.7, 138.5, 135.4, 127.3, 121.3, 105.7, 89.6, 27.2 ppm (2C); IR (KBr): $\tilde{\nu}$=3150, 3053, 2986, 1722, 1668, 1612, 1557, 1471, 1408, 1377, 1263, 1222, 1196, 1103, 1001 cm$^{-1}$; MS (ESI) $m/z$ (%): 327.1 (100) $[M+H]^+$, 329.0 (100) $[M+H+2]^+$; Anal. calcd for $C_{12}H_{11}BrN_2O_4$: C 44.06, H 3.39, N 8.56, found: C 44.22, H 3.40, N 8.60.

**7-Bromo-1,5-naphthyridin-4-ol (20)**: 5-{[(5-Bromopyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione **19** (10.00 g, 30.6 mmol) was slowly added to Dowtherm A heat transfer fluid (350 mL) over a period of 5 min at 235–240 °C. Following addition, the reaction was maintained for an additional 5 min and then allowed to cool to 40 °C. A brown precipitate formed, which was filtered and washed with petroleum ether (25 mL). The brown solid was suspended in an EtOH/$H_2O$ mixture (90:10, 250 mL), heated to a boil for 30 min, isolated by filtration, and washed with EtOH (30 mL) to yield compound **20** as a dark-brown powder (4.85 g, 70%). $R_f$=0.05 ($CH_2Cl_2$/EtOH, 95:5); mp: >360 °C (lit.[27] >360 °C); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=12.25 (br s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.03 (dd, $J$=7.2, 6.0 Hz, 1H), 6.21 ppm (d, $J$=7.4 Hz, 1H); compound **20** was not soluble enough in [D$_6$]DMSO for $^{13}$C NMR analysis; IR (KBr): $\tilde{\nu}$=3066–2550 (br), 1614, 1602, 1547, 1493, 1414, 1402, 1184, 1120 cm$^{-1}$; MS (ESI) $m/z$ (%): 225.1 (100) $[M+H]^+$, 227.0 (100) $[M+H+2]^+$.

**7-Bromo-1,5-naphthyridin-4-amine (21)**: In a sealed tube, a mixture of 3-bromo-8-chloro-1,5-naphthyridine **18a** (5.00 g, 20.5 mmol) and 28% aqueous $NH_3$ solution (120 mL) in dioxane (120 mL) was heated at 140 °C for 24 h. Then, the reaction mixture was allowed to cool to RT and $H_2O$ (200 mL) was added. The aqueous layer was extracted with EtOAc (400 mL), dried over anhyd $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$, then $CH_2Cl_2$/EtOH 98:2 to give compound **21** as a white solid (3.50 g, 76%); $R_f$=0.32 ($CH_2Cl_2$/EtOH, 96:4); mp: 168–169 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$= 8.82 (d, $J$=2.1 Hz, 1H), 8.43 (d, $J$=2.1 Hz, 1H), 8.40 (d, $J$=5.5 Hz, 1H), 7.08 (br s, 2H), 6.79 ppm (d, $J$=5.5 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=152.5, 151.9, 147.3, 144.3, 138.0, 133.3, 120.0, 104.4 ppm; IR (KBr): $\tilde{\nu}$=3400, 3297, 1640 cm$^{-1}$; MS (ESI) $m/z$ (%): 224.0 (100) $[M+H]^+$, 226.1 (100) $[M+H+2]^+$; Anal. calcd for $C_8H_6BrN_3$: C 42.88, H 2.70, N 18.75, found: C 42.92, H 2.69, N 18.70.

**Method C. General method for the synthesis of ureas 22, 24, 26, 27, 31–33 using isocyanates**: In a sealed reactor, a solution of 7-bromo-1,5-naphthyridin-4-amine **21** (500 mg, 2.23 mmol) and the appropriate isocyanate (4.46 mmol) in pyridine (5 mL) was stirred under argon atmosphere at 140 °C for 24 h. The mixture was allowed to reach RT, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$/EtOH 99:1. The solvent was evaporated to dryness to afford the desired compounds **22**, **24**, **26**, **27** and **31**–**33**.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-ethylurea (22)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with ethyl isocyanate (350 μL, 4.46 mmol) to afford compound **22** as a white powder (553 mg, 84%). $R_f$=0.44 ($CH_2Cl_2$/EtOH, 96:4); mp: 222–223 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.69 (s, 1H), 9.01 (d, $J$=2.1 Hz, 1H), 8.77 (d, $J$=4.8 Hz, 1H), 8.68 (d, $J$=2.1 Hz, 1H), 8.44 (d, $J$=4.8 Hz, 1H), 7.67 (t, $J$=5.8 Hz, 1H), 3.25–3.14 (m, 2H), 1.13 ppm (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$= 154.3, 153.5, 149.1, 144.3, 143.5, 138.7, 133.0, 120.6, 108.5, 34.2, 15.2 ppm; IR (KBr): $\tilde{\nu}$=3281, 3031, 1651, 1515, 1230, 992 cm$^{-1}$; MS (ESI) $m/z$ (%): 295.1 (100) $[M+H]^+$, 297.2 (100) $[M+H+2]^+$; Anal. calcd for $C_{11}H_{11}BrN_4O$: C 44.77, H 3.76, N 18.98, found: C 44.89, H 3.78, N 18.92.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-butylurea (24)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with butylisocyanate (503 μL, 4.46 mmol) to afford compound **24** as a beige powder (360 mg, 50%). $R_f$=0.24 ($CH_2Cl_2$/EtOH, 95:5); mp: 158–160 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.73 (s, 1H), 9.00 (d, $J$=2.0 Hz, 1H), 8.77 (d, $J$=5.2 Hz, 1H), 8.68 (d, $J$=2.0 Hz, 1H), 8.40 (d, $J$=5.2 Hz, 1H), 7.67 (t, $J$=5.2 Hz, 1H), 3.18 (dt, $J$=7.2, 5.2 Hz, 2H), 1.51–1.36 (m, 4H), 0.93 ppm (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.1, 153.2, 149.4, 144.8, 143.7, 138.1, 133.5, 121.0, 108.6, 42.1, 31.9, 19.6, 14.2 ppm; IR (KBr): $\tilde{\nu}$=3256, 3041, 2942, 1657, 1519, 1220, 987 cm$^{-1}$; MS (ESI) $m/z$ (%): 323.2 (100) $[M+H]^+$, 325.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{13}H_{15}BrN_4O$: C 48.31, H 4.68, N 17.34, found: C 48.48, H 4.70, N 17.31.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-isopropylurea (26)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with isopropylisocyanate (438 μL, 4.46 mmol) to afford compound **26** as a white powder (497 mg, 72%). $R_f$=0.43 ($CH_2Cl_2$/EtOH, 95:5); mp: 175–177 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.63 (s, 1H), 9.00 (d, $J$=2.4 Hz, 1H), 8.77 (d, $J$=5.2 Hz, 1H), 8.67 (d, $J$=2.4 Hz, 1H), 8.43 (d, $J$=5.2 Hz, 1H), 7.64 (d, $J$=7.2 Hz, 1H), 3.89–3.81 (m, 1H), 1.17 ppm (d, $J$=6.4 Hz, 6H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$= 154.3, 153.3, 149.1, 144.6, 143.9, 138.3, 133.4, 121.1, 108.7, 43.1, 22.6 ppm (2C); IR (KBr): $\tilde{\nu}$=3223, 3025, 2964, 1645, 1510, 1221, 989 cm$^{-1}$; MS (ESI) $m/z$ (%): 309.2 (100) $[M+H]^+$, 311.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{12}H_{13}BrN_4O$: C 46.62, H 4.24, N 18.12, found: C 46.79, H 4.22, N 18.18.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-*tert*-butylurea (27)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with *tert*-butyl isocyanate (510 μL, 4.46 mmol) to afford compound **27** as a white solid (541 mg, 75%). $R_f$ = 0.43 ($CH_2Cl_2$/EtOH, 96:4); mp: 192–193 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.65 (s, 1H), 8.98 (d, $J$ = 2.1 Hz, 1H), 8.74 (d, $J$ = 5.2 Hz, 1H), 8.66 (d, $J$ = 2.1 Hz, 1H), 8.42 (d, $J$ = 5.2 Hz, 1H), 7.60 (s, 1H), 1.36 ppm (s, 9H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.5 (2C), 148.8, 144.9, 143.6, 138.7, 133.1, 120.4, 108.5, 50.0, 28.9 ppm (3C); IR (KBr): $\tilde{\nu}$ = 3340, 3038, 2932, 1672, 1516, 1190, 990 cm$^{-1}$; MS (ESI) *m/z* (%): 323.2 (100) $[M+H]^+$, 325.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{13}H_{15}BrN_4O$: C 48.31, H 4.68, N 17.34, found: C 48.43, H 4.69, N 17.38.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-cyclohexylurea (31)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with phenyl isocyanate (570 μL, 4.46 mmol) to afford compound **31** as a white powder (429 mg, 55%). $R_f$ = 0.45 ($CH_2Cl_2$/EtOH, 96:4); mp: 179–180 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.69 (s, 1H), 9.00 (d, $J$ = 2.4 Hz, 1H), 8.77 (d, $J$ = 5.2 Hz, 1H), 8.67 (d, $J$ = 2.0 Hz, 1H), 8.43 (d, $J$ = 5.6 Hz, 1H), 7.68 (d, $J$ = 7.6 Hz, 1H), 3.59–3.57 (m, 1H), 1.91–0.92 ppm (m, 10H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.6, 153.5, 148.9, 144.2, 143.6, 138.8, 133.1, 120.5, 108.5, 47.5, 33.5 (2C), 32.0, 24.6 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3260, 3025, 2928, 1695, 1525, 1246, 995 cm$^{-1}$; MS (ESI) *m/z* (%): 349.2 (100) $[M+H]^+$, 351.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{15}H_{17}BrN_4O$: C 51.59, H 4.91, N 16.04, found: C 51.75, H 4.93, N 16.09.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-phenylurea (32)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with phenyl isocyanate (485 μL, 4.46 mmol) to afford compound **32** as a white powder (505 mg, 66%). $R_f$ = 0.60 ($CH_2Cl_2$/EtOH, 96:4); mp: 195–196 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 10.08 (s, 1H), 10.04 (s, 1H), 9.08 (d, $J$ = 2.4 Hz, 1H), 8.86 (d, $J$ = 5.2 Hz, 1H), 8.74 (d, $J$ = 2.4 Hz, 1H), 8.50 (d, $J$ = 5.2 Hz, 1H), 7.57 (d, $J$ = 7.6 Hz, 2H), 7.38 (dd, $J$ = 8.4, 7.6 Hz, 2H), 7.08 ppm (t, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.7, 151.9, 149.3, 143.7, 143.5, 139.2, 139.0, 133.1, 129.1 (2C), 122.8, 120.6, 118.6 (2C), 109.0 ppm; IR (KBr): $\tilde{\nu}$ = 3273, 3015, 1708, 1515, 1422, 1210, 992 cm$^{-1}$; MS (ESI) *m/z* (%): 343.2 (100) $[M+H]^+$, 345.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{15}H_{11}BrN_4O$: C 52.50, H 3.23, N 16.33, found: C 52.64, H 3.21, N 16.30.

**1-Benzyl-3-(7-bromo-1,5-naphthyridin-4-yl)urea (33)**: Using method C, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with benzyl isocyanate (551 μL, 4.46 mmol) to afford compound **33** as a white powder (733 mg, 92%). $R_f$ = 0.28 ($CH_2Cl_2$/EtOH, 95:5); mp: 138–140 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.87 (s, 1H), 9.01 (d, $J$ = 2.0 Hz, 1H), 8.78 (d, $J$ = 5.4 Hz, 1H), 8.74 (d, $J$ = 2.0 Hz, 1H), 8.46 (d, $J$ = 5.2 Hz, 1H), 8.16 (t, $J$ = 5.6 Hz, 1H), 7.39–7.27 (m, 5H), 4.35 ppm (d, $J$ = 5.6 Hz, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.6, 151.8, 149.5, 143.4, 143.2, 139.3, 139.0, 133.5, 129.2 (2C), 128.1 (2C), 122.4, 120.4, 109.2, 45.1 ppm; IR (KBr): $\tilde{\nu}$ = 3263, 3024, 1682, 1517, 1212, 995 cm$^{-1}$; MS (ESI) *m/z* (%): 357.2 (100) $[M+H]^+$, 359.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{16}H_{13}BrN_4O$: C 53.80, H 3.67, N 15.68, found: C 54.01, H 3.68, N 15.72.

**Method D. General method for the synthesis of ureas 23, 25, 28–30, 34–37 using triphosgene and amines**: Under argon atmosphere, a solution of 7-bromo-1,5-naphthyridin-4-amine **21** (500 mg, 2.23 mmol) in $CH_2Cl_2$ (40 mL) was added at 0 °C $Et_3N$ (8.4 mL, 60 mmol) and triphosgene (727 mg, 2.45 mmol). The mixture was stirred at reflux for 1 h. The mixture was allowed to reach RT, and the appropriate alkylamine (4.69 mmol) was added. The mixture was stirred at reflux for 2 h. The mixture was allowed to reach RT, and $H_2O$ (100 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (150 mL). The organic layers were dried over anhyd $Na_2SO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$/EtOH 96:4. The solvent was evaporated to dryness to furnish the desired compounds **23**, **25**, **28**–**30**, and **34**–**37**.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-propylurea (23)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with propylamine (385 μL, 4.69 mmol) to afford compound **23** as a white powder (359 mg, 52%). $R_f$ = 0.40 ($CH_2Cl_2$/EtOH, 96:4); mp: 173–174 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.72 (s, 1H), 8.99 (d, $J$ = 2.0 Hz, 1H), 8.76 (d, $J$ = 5.6 Hz, 1H), 8.66 (d, $J$ = 2.0 Hz, 1H), 8.44 (d, $J$ = 5.6 Hz, 1H), 7.68 (t, $J$ = 5.2 Hz, 1H), 3.15 (q, $J$ = 6.8 Hz, 2H), 1.57–1.47 (m, 2H), 0.96 ppm (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.4, 153.5, 148.9, 144.1, 143.6, 138.8, 133.0, 120.4, 108.5, 40.1, 22.8, 11.5 ppm; IR (KBr): $\tilde{\nu}$ = 3286, 2956, 1697, 1650, 1551, 1516, 1412, 1314, 1246, 1150, 1080 cm$^{-1}$; MS (ESI) *m/z* (%): 309.2 (100) $[M+H]^+$, 311.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{12}H_{13}BrN_4O$: C 46.62, H 4.24, N 18.12, found: C 46.74, H 4.25, N 18.09.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-hexylurea (25)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with 1-hexylamine (619 μL, 4.69 mmol) to afford compound **25** as a white powder (486 mg, 62%). $R_f$ = 0.46 ($CH_2Cl_2$/EtOH, 96:4); mp: 186–187 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.72 (s, 1H), 9.00 (d, $J$ = 2.2 Hz, 1H), 8.76 (d, $J$ = 5.2 Hz, 1H), 8.67 (d, $J$ = 2.2 Hz, 1H), 8.44 (d, $J$ = 5.2 Hz, 1H), 7.66 (t, $J$ = 5.4 Hz, 1H), 5.75 (dt, $J$ = 5.6, 5.4 Hz, 2H), 3.20–3.16 (m, 2H), 3.00–2.96 (m, 2H), 1.51–1.47 (m, 2H); 1.42–1.34 (m, 2H); 0.92 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.5, 153.1, 149.3, 144.7, 143.7, 138.2, 133.6, 121.1, 108.6, 42.4, 31.7, 30.2, 27.2, 21.6, 14.4 ppm; IR (KBr): $\tilde{\nu}$ = 3244, 3032, 2945, 1684, 1515, 1232, 992 cm$^{-1}$; MS (ESI) *m/z* (%): 351.3 (100) $[M+H]^+$, 353.4 (100) $[M+H+2]^+$; Anal. calcd for $C_{15}H_{19}BrN_4O$: C 51.29, H 5.45, N 15.95, found: C 51.48, H 5.47, N 16.01.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-cyclopropylurea (28)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with cyclopropylamine (325 μL, 4.69 mmol) to afford compound **28** as a white powder (446 mg, 65%). $R_f$ = 0.43 ($CH_2Cl_2$/EtOH, 95:5); mp: 205–206 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.62 (s, 1H), 9.00 (d, $J$ = 2.0 Hz, 1H), 8.78 (d, $J$ = 5.2 Hz, 1H), 8.68 (d, $J$ = 2.0 Hz, 1H), 8.43 (d, $J$ = 5.2 Hz, 1H), 7.82 (s, 1H), 2.69–2.63 (m, 1H), 0.72 and 0.47 ppm (br s, 4H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 155.1, 153.6, 149.0, 143.6 (2C), 138.8, 133.0, 120.5, 108.5, 22.5, 6.3 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3217, 3025, 2933, 1691, 1517, 1222, 990 cm$^{-1}$; MS (ESI) *m/z* (%): 307.2 (100) $[M+H]^+$, 309.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{12}H_{11}BrN_4O$: C 46.93, H 3.61, N 18.24, found: C 46.81, H 3.63, N 18.29.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-cyclobutylurea (29)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with cyclobutylamine (400 μL, 4.69 mmol) to afford compound **29** as a white powder (502 mg, 70%). $R_f$ = 0.40 ($CH_2Cl_2$/EtOH, 95:5); mp: 201–202 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.62 (s, 1H), 9.01 (d, $J$ = 2.4 Hz, 1H), 8.77 (d, $J$ = 5.2 Hz, 1H), 8.68 (d, $J$ = 2.4 Hz, 1H), 8.41 (d, $J$ = 5.2 Hz, 1H), 7.98 (d, $J$ = 7.6 Hz, 1H), 4.25–4.16 (m, 1H), 2.32–2.44 and 1.95–1.84 (m, 4H), 1.75–1.64 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.5, 153.2, 149.0, 143.9, 143.6, 138.8, 133.0, 120.4, 108.5, 44.6, 30.9 (2C), 14.7 ppm; IR (KBr): $\tilde{\nu}$ = 3290, 3033, 2938, 1659, 1516, 1219, 995 cm$^{-1}$; MS (ESI) *m/z* (%): 321.2 (100) $[M+H]^+$, 323.3 (100) $[M+H+2]^+$; Anal. calcd for $C_{13}H_{13}BrN_4O$: C 48.62, H 4.08, N 17.44, found: C 48.49, H 4.10, N 17.47.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-cyclopentylurea (30)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with cyclopentylamine (462 μL, 4.69 mmol) to afford compound **30** as a brown powder (381 mg, 51%). $R_f$ = 0.34 ($CH_2Cl_2$/EtOH, 95:5); mp: 183–185 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.65 (s, 1H), 9.00 (d, $J$ = 2.4 Hz, 1H), 8.75 (d, $J$ = 5.2 Hz, 1H), 8.66 (d, $J$ = 2.4 Hz, 1H), 8.42 (d, $J$ = 5.2 Hz, 1H), 7.82 (d, $J$ = 7.3 Hz, 1H), 4.15–4.06 (m, 1H); 1.95–1.24 ppm (m, 8H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.7, 153.3, 149.3, 143.5, 143.4, 138.5, 133.2, 120.4, 108.7, 51.2, 34.9 (2C), 25.3 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3256, 3041, 2938, 1665, 1515, 1223, 994 cm$^{-1}$; mp: 119–121 °C; MS (ESI) *m/z* (%): 335.2 (100) [$M$+H]$^+$, 337.3 (100) [$M$+H+2]$^+$; Anal. calcd for $C_{14}H_{15}BrN_4O$: C 50.16, H 4.51, N 16.71, found: C 50.34, H 4.52, N 16.76.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-(2-phenylethyl)urea (34)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with 2-phenylethylamine (589 μL, 4.69 mmol) to afford compound **34** as a brown powder (538 mg, 65%). $R_f$ = 0.33 ($CH_2Cl_2$/EtOH, 95:5); mp: 119–121 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.89 (s, 1H), 9.00 (d, $J$ = 2.2 Hz, 1H), 8.75 (d, $J$ = 5.3 Hz, 1H), 8.67 (d, $J$ = 2.2 Hz, 1H), 8.45 (d, $J$ = 5.2 Hz, 1H), 7.85 (t, $J$ = 5.7 Hz, 1H), 7.35–7.21 (m, 5H); 3.45 (dt, $J$ = 7.1, 5.7 Hz, 2H), 2.86 ppm (t, $J$ = 7.1 Hz, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.3, 151.5, 149.4, 143.3, 143.0, 139.5, 139.0, 133.7, 129.2 (2C), 128.3 (2C), 122.5, 120.7, 109.1, 42.1, 35.7 ppm; IR (KBr): $\tilde{\nu}$ = 3251, 3042, 1686, 1515, 1209, 1012 cm$^{-1}$; MS (ESI) *m/z* (%): 371.2 (100) [$M$+H]$^+$, 373.3 (100) [$M$+H+2]$^+$; Anal. calcd for $C_{17}H_{15}BrN_4O$: C 55.00, H 4.07, N 15.09, found: C 55.21, H 4.09, N 15.14.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-(4-phenylbutyl)urea (35)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with 4-phenylbutylamine (741 μL, 4.69 mmol) to afford compound **35** as a beige powder (535 mg, 60%). $R_f$ = 0.45 ($CH_2Cl_2$/EtOH, 96:4); mp: 115–116 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.72 (s, 1H), 9.00 (d, $J$ = 2.4 Hz, 1H), 8.76 (d, $J$ = 5.2 Hz, 1H), 8.68 (d, $J$ = 2.4 Hz, 1H), 8.43 (d, $J$ = 5.2 Hz, 1H), 7.67 (t, $J$ = 5.2 Hz, 1H), 7.33–7.19 (m, 5H), 3.21 (q, $J$ = 6.4, 5.2 Hz, 2H), 2.64 (t, $J$ = 7.2 Hz, 2H), 1.69–1.61 (m, 2H), 1.55–1.49 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.4, 153.6, 148.9, 144.1, 143.6, 142.3, 138.8, 133.0, 128.5 (2C), 128.4 (2C), 125.8; 120.4, 108.5, 39.0, 35.0, 29.2, 28.6 ppm; IR (KBr): $\tilde{\nu}$ = 3493, 1651 cm$^{-1}$; MS (ESI) *m/z* (%): 399.3 (100) [$M$+H]$^+$, 401.4 (100) [$M$+H+2]$^+$; Anal. calcd for $C_{19}H_{19}BrN_4O$: C 57.15, H 4.80, N 14.03, found: C 57.11, H 4.81, N 14.06.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-(2,2,2-trifluoroethyl)urea (36)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with 2,2,2-trifluoroethylamine hydrochloride (635 mg, 4.69 mmol) to afford compound **36** as a brown powder (436 mg, 56%). $R_f$ = 0.42 ($CH_2Cl_2$/EtOH, 96:4); mp: 181–182 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.99 (s, 1H), 9.04 (d, $J$ = 2.0 Hz, 1H), 8.82 (d, $J$ = 5.2 Hz, 1H), 8.71 (d, $J$ = 2.0 Hz, 1H), 8.43 (d, $J$ = 5.2 Hz, 1H), 8.30 (t, $J$ = 6.0 Hz, 1H), 4.13–4.03 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.9, 154.2, 150.1, 144.0, 143.9, 139.1, 133.4, 125.6 (q, 1C, $J_{CF}$ = 278 Hz), 121.4, 109.6, 41.3 ppm (q, 1C, $J_{CF}$ = 33 Hz); IR (KBr): $\tilde{\nu}$ = 3261, 3022, 1686, 1509, 1222, 996 cm$^{-1}$; MS (ESI) *m/z* (%): 349.1 (100) [$M$+H]$^+$, 351.2 (100) [$M$+H+2]$^+$; Anal. calcd for $C_{11}H_8BrF_3N_4O$: C 37.84, H 2.31, N 16.05, found: C 37.89, H 2.32, N 15.99.

**1-(7-Bromo-1,5-naphthyridin-4-yl)-3-(2,2-difluorocyclopropyl)-urea (37)**: Using method D, 7-bromo-1,5-naphthyridin-4-amine **21** reacted with 2,2-difluorocyclopropylamine hydrochloride (607 mg, 4.69 mmol) to afford compound **37** as a white powder (590 mg, 77%). $R_f$ = 0.45 ($CH_2Cl_2$/EtOH, 96:4); mp: 184–185 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.70 (s, 1H), 9.03 (d, $J$ = 2.4 Hz, 1H), 8.80 (d, $J$ = 5.2 Hz, 1H), 8.70 (d, $J$ = 2.0 Hz, 1H), 8.41 (d, $J$ = 5.2 Hz, 1H), 8.23 (d, $J$ = 6.0 Hz, 1H), 4.11 (brs, 1H), 2.99–2.64 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 155.2, 153.4, 149.2, 143.9, 143.1, 138.9, 133.1, 120.2, 108.2, 93.7 (t, 1C, $J_{CF}$ = 276 Hz), 32.5, 17.3 ppm (t, 1C, $J_{CF}$ = 22 Hz); IR (KBr): $\tilde{\nu}$ = 3221, 3028, 1662, 1517, 1224, 990 cm$^{-1}$; MS (ESI) *m/z* (%): 343.1 (100) [$M$+H]$^+$, 345.2 (100) [$M$+H+2]$^+$; Anal. calcd for $C_{12}H_9BrF_2N_4O$: C 42.00, H 2.64, N 16.33, found: C 42.15, H 2.65, N 16.39.

**Method E**: **General method for the synthesis of (7-aryl-1,5-naphthyridin-4-yl)ureas 38–60 by Suzuki–Miyaura cross-coupling**: Under argon atmosphere, 1-(7-bromo-1,5-naphthyridin-4-yl)urea (0.70 mmol), arylboronic acid or ester (1.40 mmol), $Na_2CO_3$ (220 mg, 2.10 mmol), and tetrakis(triphenylphosphine) palladium (80 mg, 0.07 mmol) were introduced in a mixture of DMF/$H_2O$ 10:1 (22 mL). The mixture was stirred at 80 °C for 2–16 h. The mixture was allowed to reach RT, and $H_2O$ (100 mL) was added. The aqueous layer was extracted with EtOAc (150 mL). The organic layers were dried over anhyd $Na_2SO_4$, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$/EtOH 96:4. The solvent was evaporated to dryness to afford, after trituration with ($i$Pr)$_2$O, the desired compounds **38**–**60**.

**1-[7-(3,4-Dimethoxyphenyl)-1,5-naphthyridin-4-yl]-3-ethylurea (38)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-ethylurea **22** (207 mg, 0.70 mmol) reacted for 16 h with 3,4-dimethoxyphenylboronic acid (255 mg, 1.40 mmol) to afford compound **38** as a white powder (165 mg, 67%). $R_f$ = 0.31 ($CH_2Cl_2$/EtOH, 96:4); mp: 215–216 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.69 (s, 1H), 9.23 (d, $J$ = 2.1 Hz, 1H), 8.77 (d, $J$ = 5.1 Hz, 1H), 8.58 (d, $J$ = 2.1 Hz, 1H), 8.38 (d, $J$ = 5.1 Hz, 1H), 7.71 (t, $J$ = 5.1 Hz, 1H), 7.55–7.50 (m, 2H), 7.17 (d, $J$ = 9.1 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.29–3.16 (m, 2H), 1.14 ppm (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.4, 152.7, 149.7, 149.6, 147.2, 143.6, 143.1, 136.8, 133.2, 133.0, 129.0, 120.1, 112.5, 111.2, 107.7, 55.9, 55.8, 34.2, 15.2 ppm; IR (KBr): $\tilde{\nu}$ = 3442, 3288, 3032, 1656, 1567, 1517, 1258, 1143, 1020 cm$^{-1}$; MS (ESI) *m/z* (%): 353.2 (100) [$M$+H]$^+$; Anal. calcd for $C_{19}H_{20}N_4O_3$: C 64.76, H 5.72, N 15.90, found: C 64.70, H 5.73, N 15.94.

**1-Ethyl-3-[7-(4-hydroxy-3-methoxyphenyl)-1,5-naphthyridin-4-yl]urea (39)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-ethylurea **22** (207 mg, 0.70 mmol) reacted for 16 h with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (350 mg, 1.40 mmol) to afford compound **39** as a yellow powder (111 mg, 47%). $R_f$ = 0.17 ($CH_2Cl_2$/EtOH, 96:4); mp: 202–203 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.88 (s, 1H), 9.49 (s, 1H), 9.26 (d, $J$ = 1.5 Hz, 1H), 8.80 (d, $J$ = 5.5 Hz, 1H), 8.54 (d, $J$ = 1.5 Hz, 1H), 8.43 (d, $J$ = 5.5 Hz, 1H), 7.77 (t, $J$ = 5.8 Hz, 1H), 7.51 (s, 1H), 7.42 (d, $J$ = 7.9 Hz, 1H), 7.00 (d, $J$ = 7.9 Hz, 1H), 3.95 (s, 3H), 3.28–3.18 (m, 2H), 1.14 ppm (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.5, 152.2, 148.5, 147.6, 147.0, 143.7, 143.2, 137.0, 132.9, 132.6, 127.4, 120.4, 116.3, 111.5, 107.7, 56.2, 34.4, 15.4 ppm; IR (KBr): $\tilde{\nu}$ = 3369, 3025, 1702, 1521, 1252, 1123, 1022 cm$^{-1}$; MS (ESI) *m/z* (%): 339.1 [($M$+H), 100]; Anal. calcd for $C_{18}H_{18}N_4O_3$: C 63.89, H 5.36, N 16.56, found: C 63.99, H 5.37, N 16.53.

**1-[7-(3,5-Dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]-3-ethylurea (40)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-ethylurea **22** (207 mg, 0.70 mmol) reacted for 16 h with 2,6-dichloro-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenol (385 mg, 1.40 mmol) to afford compound **40** as an orange powder (53 mg, 20%). $R_f$ = 0.22 ($CH_2Cl_2$/EtOH, 96:4); mp: >300 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 10.59 (s, 1H), 9.69 (s, 1H), 9.23 (d, $J$ = 2.4 Hz, 1H), 8.78 (d, $J$ = 5.2 Hz, 1H), 8.61 (d, $J$ = 2.4 Hz, 1H), 8.40 (d,

$J$=5.2 Hz, 1H), 8.05 (s, 2H), 7.73 (t, $J$=5.6 Hz, 1H), 3.25–3.17 (m, 2H), 1.14 ppm (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.4, 151.3, 149.6, 149.2, 148.2, 137.0, 133.2, 132.8, 126.8 (2C), 126.2 (2C), 123.4, 115.5, 107.3, 34.5, 15.5 ppm; IR (KBr): $\tilde{\nu}$=3453, 3339, 3041, 1657, 1567, 1246, 1143 cm$^{-1}$; MS (ESI) $m/z$ (%): 377.1 [($M$+H), 100], 379.1 [($M$+H)+2, 71], 381.1 [($M$+H)+4, 12]; Anal. calcd for $C_{17}H_{14}Cl_2N_4O_2$: C 54.13, H, 3.74, N 14.85, found: C 54.02, H 3.73, N 14.88.

**1-*tert*-Butyl-3-[7-(3,4-dimethoxyphenyl)-1,5-naphthyridin-4-yl]-urea (41)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-*tert*-butylurea **27** (226 mg, 0.70 mmol) reacted for 16 h with 3,4-dimethoxyphenylboronic acid (255 mg, 1.40 mmol) to afford compound **41** as a white powder (138 mg, 52%). $R_f$=0.29 ($CH_2Cl_2$/EtOH, 96:4); mp: 215–216 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.67 (s, 1H), 9.21 (d, $J$=2.1 Hz, 1H), 8.72 (d, $J$=5.5 Hz, 1H), 8.57 (d, $J$=2.1 Hz, 1H), 8.36 (d, $J$=5.5 Hz, 1H), 7.63 (s, 1H), 7.55–7.50 (m, 2H), 7.17 (d, $J$=9.1 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 1.14 ppm (s, 9H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.4, 152.7, 149.7, 149.6, 147.2, 143.6, 143.1, 136.8, 133.2, 133.0, 129.0, 120.1, 112.5, 111.2, 107.7, 55.9, 55.8, 34.2, 15.2 ppm (3C); IR (KBr): $\tilde{\nu}$=3442, 3256, 3032, 1662, 1558, 1512, 1268, 1135, 1018 cm$^{-1}$; MS (ESI) $m/z$ (%): 381.1 [($M$+H), 100]; Anal. calcd for $C_{21}H_{24}N_4O_3$: C 66.30, H 6.36, N 14.73, found: C 66.24, H 6.35, N 14.77.

**1-*tert*-Butyl-3-[7-(4-hydroxy-3-methoxyphenyl)-1,5-naphthyridin-4-yl]urea (42)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-*tert*-butylurea **27** (226 mg, 0.70 mmol) reacted for 16 h with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (350 mg, 1.40 mmol) to afford compound **42** as a yellow powder (159 mg, 62%). $R_f$=0.21 ($CH_2Cl_2$/EtOH, 96:4); mp: 158–159 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.66 (s, 1H), 9.41 (s, 1H), 9.19 (d, $J$=2.0 Hz, 1H), 8.73 (d, $J$=5.2 Hz, 1H), 8.53 (d, $J$=2.0 Hz, 1H), 8.35 (d, $J$=5.2 Hz, 1H), 7.62 (s, 1H), 7.50 (d, $J$=1.6 Hz, 1H), 7.40 (dd, $J$=8.0, 1.6 Hz, 1H), 7.99 (d, $J$=8.0 Hz, 1H), 3.95 (s, 3H), 1.14 ppm (s, 9H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=153.7, 152.6, 148.5, 147.7, 147.1, 143.8, 143.2, 137.0, 132.9, 132.8, 127.5, 120.4, 116.3, 111.7, 107.7, 56.1, 49.9, 29.0 ppm (3C); IR (KBr): $\tilde{\nu}$=3339, 2968, 1683, 1519, 1267, 1128, 1030 cm$^{-1}$; MS (ESI) $m/z$ (%): 367.2 [($M$+H), 100]; Anal. calcd for $C_{20}H_{22}N_4O_3$: C 65.56, H 6.05, N 15.29, found: C 65.69, H 6.03, N 15.24.

**1-*tert*-Butyl-3-[7-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]urea (43)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-*tert*-butylurea **27** (226 mg, 0.70 mmol) reacted for 16 h with 2,6-dichloro-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenol (385 mg, 1.40 mmol) to afford compound **43** as a yellow powder (116 mg, 41%). $R_f$=0.31 ($CH_2Cl_2$/EtOH, 96:4); mp >300 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=10.57 (s, 1H), 9.67 (s, 1H), 9.21 (d, $J$=2.4 Hz, 1H), 8.75 (d, $J$=9.2 Hz, 1H), 8.60 (d, $J$=2.4 Hz, 1H), 8.38 (d, $J$=9.2 Hz, 1H), 8.06 (s, 2H), 7.65 (s, 1H), 1.38 ppm (s, 9H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.5, 151.3, 149.6, 149.1, 148.2, 137.1, 133.2, 132.8, 126.8 (2C), 126.1 (2C), 123.4, 115.5, 107.4, 49.4, 29.0 ppm (3C); IR (KBr): $\tilde{\nu}$=3442, 3354, 2947, 1675, 1522, 1456, 1267, 1128 cm$^{-1}$; MS (ESI) $m/z$ (%): 405.1 [($M$+H), 100], 407.1 [($M$+2)+H, 69], 409.1 [($M$+4)+H, 11]; Anal. calcd for $C_{19}H_{18}Cl_2N_4O_2$: C 56.31, H 4.48, N 13.82, found: C 56.38, H 4.50, N 13.74.

**1-Cyclopropyl-3-[7-(4-hydroxy-3-methoxyphenyl)-1,5-naphthyridin-4-yl]urea (44)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-cyclopropylurea **28** (215 mg, 0.70 mmol) reacted for 16 h with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (350 mg, 1.40 mmol) to afford compound **44** as a yellow powder (42 mg, 17%). $R_f$=0.22 ($CH_2Cl_2$/EtOH, 95:5); mp: 235–236 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.63 (s, 1H), 9.42 (s, 1H), 9.21 (s, 1H), 8.78 (d, $J$=5.2 Hz, 1H), 8.55 (s, 1H), 8.34 (d, $J$=5.2 Hz, 1H), 7.85 (s, 1H), 7.51 (s, 1H), 7.41 (d, $J$=7.2 Hz, 1H), 6.98 (d, $J$=7.2 Hz, 1H), 3.95 (s, 3H), 2.72–2.64 (m, 1H), 0.74 and 0.50 ppm (brs, 4H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=153.4, 152.2, 148.6, 147.6, 147.0, 143.6, 143.1, 137.0, 132.8, 132.6, 127.4, 120.2, 116.3, 111.6, 107.5, 55.9, 22.7, 6.8 ppm (2C); IR (KBr): $\tilde{\nu}$=3349, 3236, 2976, 1708, 1579, 1519, 1317, 1124, 1026 cm$^{-1}$; MS (ESI) $m/z$ (%): 351.1 [(M+H), 100]; Anal. calcd for $C_{19}H_{18}N_4O_3$: C 65.13, H 5.18, N 15.99, found: C 65.19, H 5.19, N 15.94.

**1-Ethyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (45)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-ethylurea **22** (207 mg, 0.70 mmol) reacted for 5 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **45** as a white powder (116 mg, 56%). $R_f$=0.10 ($CH_2Cl_2$/EtOH, 95:5); mp: 215–216 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.64 (s, 1H), 9.18 (d, $J$=2.1 Hz, 1H), 8.71 (d, $J$=5.1 Hz, 1H), 8.56 (s,1H), 8.49 (d, $J$=2.1 Hz, 1H), 8.32 (d, $J$=5.1 Hz, 1H), 8.26 (s, 1H), 7.68 (t, $J$=5.1 Hz, 1H), 3.96 (s, 3H), 3.23–3.19 (m, 2H), 1.14 ppm (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.5, 152.7, 146.4, 143.6, 143.4, 137.2, 132.5, 130.7, 130.0, 129.4, 118.2, 107.4, 39.7, 34.2, 15.3 ppm; IR (KBr): $\tilde{\nu}$=3331, 3205, 2972, 1698, 1562, 1258, 1200, 1132 cm$^{-1}$; MS (ESI) $m/z$ (%): 297.1 [($M$+H), 100]; Anal. calcd for $C_{15}H_{16}N_6O$: C 60.80, H 5.44, N 28.36, found: C 60.72, H 5.45, N 28.40.

**1-[7-(1-Methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-3-propyl-urea (46)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-propylurea **23** (216 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **46** as a white powder (152 mg, 70%). $R_f$=0.08 ($CH_2Cl_2$/EtOH, 96:4); mp: 216–217 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$=9.68 (s, 1H), 9.18 (s, 1H), 8.72 (d, $J$=4.8 Hz, 1H), 8.56 (s, 1H), 8.49 (s, 1H), 8.33 (d, $J$=4.8 Hz, 1H), 8.25 (s, 1H), 7.07 (brs, 1H), 3.96 (s, 3H), 3.15 (q, $J$=6.4 Hz, 2H), 1.56–1.49 (m, 2H), 0.96 ppm (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.6, 152.6, 146.4, 143.6, 143.4, 137.2, 132.5, 130.6, 130.0, 129.4, 118.2, 107.4, 41.1, 39.0, 22.8, 11.6 ppm; IR (KBr): $\tilde{\nu}$=3349, 3254, 3030, 2937, 1699, 1560, 1251 cm$^{-1}$; MS (ESI) $m/z$ (%): 311.1 [($M$+H), 100]; Anal. calcd for $C_{16}H_{18}N_6O$: C 61.92, H 5.85, N 27.08, found: C 61.98, H 5.84, N 27.02.

**1-Butyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-urea (47)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-butylurea **24** (226 mg, 0.70 mmol) reacted for 5 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **47** as a pale-yellow powder (54 mg, 24%). $R_f$=0.15 ($CH_2Cl_2$/EtOH, 95:5); mp: 219–220 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=10.12 (s, 1H), 8.86 (d, $J$=2.3 Hz, 1H), 8.64 (d, $J$=5.1 Hz, 1H), 8.48 (s, 1H), 8.38 (d, $J$=2.3 Hz, 1H), 7.97 (d, $J$=5.1 Hz, 1H), 7.87 (s, 1H), 7.60 (t, $J$=5.1 Hz, 1H), 3.95 (s, 3H), 3.42–3.40 (m, 2H), 1.68–1.65, 1.50–1.47 and 1.00–0.96 ppm (m, 7H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$=154.5, 152.7, 146.3, 143.6, 143.2, 137.2, 132.5, 130.7, 130.1, 129.4, 118.1, 107.4, 39.9, 42.3, 31.8, 19.4, 14.3 ppm; IR (KBr): $\tilde{\nu}$=3351, 3245, 2942, 2913, 1663, 1538, 1522, 1203 cm$^{-1}$; MS (ESI) $m/z$ (%): 325.1 [($M$+H), 100]; Anal. calcd for $C_{17}H_{20}N_6O$: C 62.95, H 6.21, N 25.91, found: C 63.18, H 6.19, N 25.99.

**1-Hexyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-urea (48)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-hexylurea **25** (246 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **48** as a white powder (79 mg, 32%). $R_f$=0.03 ($CH_2Cl_2$/EtOH, 96:4); mp: 188–189 °C; $^1$H NMR

(400 MHz, [D$_6$]DMSO): $\delta$ = 9.67 (s, 1H), 9.18 (d, $J$ = 2.4 Hz, 1H), 8.71 (d, $J$ = 9.2 Hz, 1H), 8.56 (s, 1H), 8.49 (d, $J$ = 2.4 Hz, 1H), 8.32 (d, $J$ = 9.2 Hz, 1H), 8.25 (s, 1H), 7.68 (t, $J$ = 5.6 Hz, 1H), 3.96 (s, 3H), 3.18 (dt, $J$ = 6.8, 5.6 Hz, 2H), 1.53–1.46 (m, 2H), 1.40–1.32 (m, 6H), 0.91 ppm (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.6, 152.6, 146.4, 143.6, 143.4, 137.2, 132.5, 130.7, 130.0, 129.4, 118.2, 107.5, 39.0, 31.1, 29.5, 26.2, 23.0, 22.3, 14.1 ppm; IR (KBr): $\tilde{\nu}$ = 3451, 3320, 2947, 1674, 1558, 1523, 1302, 1268 cm$^{-1}$; MS (ESI) $m/z$ (%): 353.2 [($M$+H), 100]; Anal. calcd for $C_{19}H_{24}N_6O$: C 64.75, H 6.86, N 23.85, found: C 64.99, H 6.88, N 23.93.

**1-Cyclopropyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (49)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-cyclopropylurea **28** (215 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **49** as a white powder (125 mg, 58%). $R_f$ = 0.10 ($CH_2Cl_2$/EtOH, 96:4); mp: 223–224 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.59 (s, 1H), 9.18 (d, $J$ = 1.6 Hz, 1H), 8.74 (d, $J$ = 5.2 Hz, 1H), 8.56 (s, 1H), 8.50 (d, $J$ = 1.6 Hz, 1H), 8.32 (d, $J$ = 5.2 Hz, 1H), 8.25 (s, 1H), 7.83 (br s, 1H), 3.96 (s, 3H), 2.71–2.64 (m, 1H), 0.73 and 0.49 ppm (br s, 4H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 155.3, 152.7, 146.5, 143.6, 143.4, 137.2, 132.4, 130.7, 130.0, 129.4, 118.2, 107.4, 39.7, 22.5, 6.4 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3353, 3267, 3040, 2917, 1708, 1553, 1515, 1265, 1195 cm$^{-1}$; MS (ESI) $m/z$ (%): 309.1 [(M+H), 100]; Anal. calcd for $C_{16}H_{16}N_6O$: C 62.32, H 5.23, N 27.26, found: C 62.47, H 5.22, N 27.30.

**1-Cyclobutyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (50)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-cyclobutylurea **29** (225 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **50** as a pale-yellow powder (120 mg, 53%). $R_f$ = 0.10 ($CH_2Cl_2$/EtOH, 96:4); mp: 215–216 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.57 (s, 1H), 9.19 (d, $J$ = 2.4 Hz, 1H), 8.71 (d, $J$ = 5.2 Hz, 1H), 8.56 (s, 1H), 8.49 (d, $J$ = 2.4 Hz, 1H), 8.30 (d, $J$ = 5.2 Hz, 1H), 8.26 (s, 1H), 8.00 (d, $J$ = 7.6 Hz, 1H), 4.26–4.18 (m, 1H), 3.96 (s, 3H), 2.33–2.24 and 1.95–1.86 (m, 4H), 1.75–1.64 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.4, 152.6, 146.4, 143.5, 143.4, 137.2, 132.5, 130.7, 130.0, 129.4, 118.2, 107.4, 44.7, 39.0, 30.9 (2C), 14.6 ppm; IR (KBr): $\tilde{\nu}$ = 3452, 3320, 2935, 1696, 1555, 1515, 1254, 1200 cm$^{-1}$; MS (ESI) $m/z$ (%): 323.1 [($M$+H), 100]; Anal. calcd for $C_{17}H_{18}N_6O$: C 63.34, H 5.63, N 26.07, found: C 63.45, H 5.65, N 26.01.

**1-Cyclopentyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (51)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-cyclopentylurea **30** (235 mg, 0.70 mmol) reacted for 5 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **51** as a white powder (101 mg, 43%). $R_f$ = 0.21 ($CH_2Cl_2$/EtOH, 95:5); mp: 207–208 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.60 (s, 1H), 9.18 (d, $J$ = 1.9 Hz, 1H), 8.71 (d, $J$ = 5.2 Hz, 1H), 8.56 (s, 1H), 8.48 (d, $J$ = 1.9 Hz, 1H), 8.32 (d, $J$ = 5.2 Hz, 1H), 8.26 (s, 1H), 7.75 (d, $J$ = 6.8 Hz, 1H), 4.10–4.02 (m, 1H), 3.97 (s, 3H), 1.92–1.26 ppm (m, 8H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.4, 152.6, 146.3, 143.5, 143.4, 137.1, 132.5, 130.7, 130.0, 129.4, 118.1, 107.4, 51.3, 40.0, 34.5 (2C), 25.5 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3425, 3342, 2972, 2935, 1675, 1551, 1515, 1244, 1163 cm$^{-1}$; MS (ESI) $m/z$ (%): 337.1 [(M+H), 100]; Anal. calcd for $C_{18}H_{20}N_6O$: C 64.27, H 5.99, N 24.98, found: C 64.50, H 6.01, N 25.06.

**1-Cyclohexyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (52)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-cyclohexylurea **31** (244 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **52** as a beige powder (74 mg, 30%). $R_f$ = 0.03 ($CH_2Cl_2$/EtOH, 96:4); mp: 200–201 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.64 (s, 1H), 9.18 (d, $J$ = 2.0 Hz, 1H), 8.71 (d, $J$ = 5.2 Hz, 1H), 8.57 (s, 1H), 8.49 (d, $J$ = 2.0 Hz, 1H), 8.32 (d, $J$ = 5.2 Hz, 1H), 8.26 (s, 1H), 7,69 (d, $J$ = 7.6 Hz, 1H), 3.60–3.58 (m, 1H), 1.21–1.94 (m, 10H), 3.97 ppm (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.4, 152.4, 147.4, 145.2, 142.8, 137.7, 132.8, 131.0, 130.1, 129.9, 118.6, 108.0, 48.6, 40.0, 33.2 (2C), 25.9, 24.8 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3432, 3312, 2946, 1684, 1542, 1516, 1224, 1212 cm$^{-1}$; MS (ESI) $m/z$ (%): 351.2 [($M$+H), 100]; Anal. calcd for $C_{19}H_{22}N_6O$: C 65.12, H 6.33, N 23.98, found: C 65.29, H 6.35, N 24.05.

**1-Isopropyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (53)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-isopropylurea **26** (216 mg, 0.70 mmol) reacted for 5 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **53** as a pale-yellow powder (65 mg, 30%). $R_f$ = 0.12 ($CH_2Cl_2$/EtOH, 95:5); mp: 229–230 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.58 (s, 1H), 9.18 (d, $J$ = 1.9 Hz, 1H), 8.71 (d, $J$ = 5.2 Hz, 1H), 8.56 (s,1H), 8.49 (d, $J$ = 1.9 Hz, 1H), 8.32 (d, $J$ = 5.2 Hz, 1H), 8.25 (s, 1H), 7.65 (t, $J$ = 7.2 Hz, 1H), 3.96 (s, 3H), 3.23–3.19 (m, 1H), 1.71 ppm (d, $J$ = 6.5 Hz, 6H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.6, 152.4, 146.2, 143.4, 143.1, 136.9, 132.2, 130.3, 129.8, 129.2, 118.0, 107.2, 41.1, 38.8, 22.7 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3324, 3213, 2967, 2927, 1669, 1548, 1521, 1251, 1126 cm$^{-1}$; MS (ESI) $m/z$ (%): 311.2 [($M$+H), 100]; Anal. calcd for $C_{16}H_{18}N_6O$: C 61.92, H 5.85, N 27.08, found: C 62.01, H 5.84, N 27.16.

**1-*tert*-Butyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (54)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-*tert*-butylurea **27** (226 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **54** as a pale-yellow powder (118 mg, 52%). $R_f$ = 0.15 ($CH_2Cl_2$/EtOH, 96:4); mp: 215–216 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.61 (s, 1H), 9.16 (d, $J$ = 2.1 Hz, 1H), 8.70 (d, $J$ = 5.1 Hz, 1H), 8.56 (s,1H), 8.48 (d, $J$ = 2.1 Hz, 1H), 8.31 (d, $J$ = 5.1 Hz, 1H), 8.25 (s, 1H), 7.61 (s, 1H), 3.96 (s, 3H), 1.37 ppm (s, 9H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 153.6, 152.6, 146.3, 143.8, 143.4, 137.2, 132.6, 130.6, 129.9, 129.4, 118.2, 107.4, 49.9, 29.0 (3C), 23.0 ppm; IR (KBr): $\tilde{\nu}$ = 3452, 3359, 2969, 1700, 1517, 1263, 1199, 1130 cm$^{-1}$; MS (ESI) $m/z$ (%): 325.1 [($M$+H), 100]; Anal. calcd for $C_{17}H_{20}N_6O$: C 62.95, H 6.21, N 25.91, found: C 63.07, H 6.23, N 25.86.

**1-[7-(1-Methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-3-phenylurea (55)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-phenylurea **32** (240 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **55** as a yellow powder (80 mg, 33%). $R_f$ = 0.63 ($CH_2Cl_2$/EtOH, 96:4); mp: 294–295 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 10.10 (s, 1H), 10.00 (s, 1H), 9.25 (d, $J$ = 2.4 Hz, 1H), 8.80 (d, $J$ = 5.2 Hz, 1H), 8.59 (s, 1H), 8.55 (d, $J$ = 2.4 Hz, 1H), 8.39 (d, $J$ = 5.2 Hz, 1H), 8.29 (s, 1H), 7.58 (d, $J$ = 7.6 Hz, 2H), 7.38 (dd, $J$ = 8.4, 7.6 Hz, 2H), 7.08 (t, $J$ = 7.2 Hz, 1H), 3.99 ppm (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.3, 152.5, 146.4, 143.4, 143.1, 138.9, 137.2, 132.5, 130.6, 130.0, 129.5, 129.1 (2C), 122.7, 118.6 (2C), 118.1, 107.4, 39.2 ppm; IR (KBr): $\tilde{\nu}$ = 3452, 3351, 1717, 1625, 1158, 1525, 1310, 1246, 1184 cm$^{-1}$; MS (ESI) $m/z$ (%): 345.1 [($M$+H), 100]; Anal. calcd for $C_{19}H_{16}N_6O$: C 66.27, H 4.61, N 24.40, found: C 66.20, H 4.63, N 24.45.

**1-Benzyl-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-urea (56)**: Using method E, 1-benzyl-3-(7-bromo-1,5-naphthyridin-

4-yl)urea **33** (250 mg, 0.70 mmol) reacted for 5 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **56** as a pale-yellow powder (95 mg, 38%). $R_f$ = 0.12 ($CH_2Cl_2$/EtOH, 95:5); mp: 237–238 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.81 (s, 1H), 9.19 (d, $J$ = 1.6 Hz, 1H), 8.73 (d, $J$ = 5.2 Hz, 1H), 8.56 (s, 1H), 8.50 (d, $J$ = 1.6 Hz, 1H), 8.35 (d, $J$ = 5.2 Hz, 1H), 8.26 (s, 1H), 8.18 (t, $J$ = 5.6 Hz, 1H), 7.42–7.29 (m, 5H), 4.42 (d, $J$ = 5.6 Hz, 2H), 3.97 ppm (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.5, 152.4, 146.3, 143.3, 143.1, 139.5, 136.9, 132.3, 130.4, 129.8, 129.2, 128.4 (2C); 127.2 (2C); 126.9, 117.9, 107.4, 42.7, 38.8 ppm; IR (KBr): $\tilde{\nu}$ = 3359, 3251, 3070, 1697, 1560, 1517, 1251, 1204 cm$^{-1}$; MS (ESI) *m/z* (%): 359.1 [(*M*+H), 100]; Anal. calcd for $C_{20}H_{18}N_6O$: C 67.02, H 5.06, N 23.45, found: C 67.21, H 5.08, N 23.51.

**1-[7-(1-Methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-3-(2-phenylethyl)urea (57)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-(2-phenylethyl)urea **34** (260 mg, 0.70 mmol) reacted for 5 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **57** as a white powder (182 mg, 70%). $R_f$ = 0.11 ($CH_2Cl_2$/EtOH, 95:5); mp: 222–223 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.71 (s, 1H), 9.17 (d, $J$ = 2.0 Hz, 1H), 8.72 (d, $J$ = 5.2 Hz, 1H), 8.56 (s, 1H), 8.49 (d, $J$ = 1.6 Hz, 1H), 8.34 (d, $J$ = 5.2 Hz, 1H), 8.25 (s, 1H), 7.75 (t, $J$ = 5.6 Hz, 1H), 7.38–7.24 (m, 5H), 3.96 (s, 3H), 3.48–3.43 (m, 2H), 2.84 ppm (t, $J$ = 7.1 Hz, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.3, 152.4, 146.4, 143.4, 142.8, 139.2, 136.9, 132.2, 130.1, 129.8, 129.2, 128.6 (2C); 128.3 (2C); 126.2, 117.9, 107.4, 40.5, 38.7, 35.2 ppm; IR (KBr): $\tilde{\nu}$ = 3359, 3287, 3064, 2930, 1701, 1556, 1517, 1252, 1202 cm$^{-1}$; MS (ESI) *m/z* (%): 373.1 [(*M*+H), 100]; Anal. calcd for $C_{21}H_{20}N_6O$: C 67.73, H 5.41, N 22.57, found: C 67.98, H 5.42, N 22.63.

**1-[7-(1-Methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-3-(4-phenylbutyl)urea (58)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-(4-phenylbutyl)urea **35** (279 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **58** as a white powder (168 mg, 60%). $R_f$ = 0.03 ($CH_2Cl_2$/EtOH, 96:4); mp: 185–186 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.66 (s, 1H), 9.18 (d, $J$ = 2.0 Hz, 1H), 8.72 (d, $J$ = 5.2 Hz, 1H), 8.56 (s, 1H), 8.49 (d, $J$ = 2.0 Hz, 1H), 8.32 (d, $J$ = 5.2 Hz, 1H), 8.26 (s, 1H), 7.69 (t, $J$ = 6.8 Hz, 1H), 7.34–7.19 (m, 5H), 3.96 (s, 3H), 3.22 (q, $J$ = 6.8, 6.4 Hz, 2H), 2.65 (t, $J$ = 7.6 Hz, 2H), 1.72–1.64 (m, 2H), 1.56–1.49 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.6, 152.6, 146.4, 143.6, 143.4, 142.3, 137.2, 132.5, 130.7, 130.0, 129.4, 128.5 (2C), 128.4 (2C), 125.9, 118.2, 107.5, 55.1, 39.0, 35.0, 29.3, 28.6 ppm; IR (KBr): $\tilde{\nu}$ = 3462, 3296, 2931, 1695, 1651, 1553, 1516, 1252, 1205 cm$^{-1}$; MS (ESI) *m/z* (%): 401.1 [(*M*+H), 100]; Anal. calcd for $C_{23}H_{24}N_6O$: C 68.98, H 6.04, N 20.99, found: C 69.09, H 6.03, N 20.94.

**1-[7-(1-Methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]-3-(2,2,2-trifluoroethyl)urea (59)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-(2,2,2-trifluoroethyl)urea **36** (244 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **59** as a white powder (154 mg, 63%). $R_f$ = 0.05 ($CH_2Cl_2$/EtOH, 96:4); mp > 300 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.95 (s, 1H), 9.22 (d, $J$ = 2.0 Hz, 1H), 8.76 (d, $J$ = 5.2 Hz, 1H), 8.57 (s, 1H), 8.52 (d, $J$ = 2.0 Hz, 1H), 8.33 (t, $J$ = 6.4 Hz, 1H), 8.32 (d, $J$ = 5.2 Hz, 1H), 8.27 (s, 1H), 4.13–4.02 (m, 2H), 3.96 ppm (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.5, 152.7, 146.8, 143.4, 143.1, 137.3, 132.4, 130.6, 130.2, 129.5, 128.2 (q, 1C, $J_{CF}$ = 277 Hz), 118.2, 107.9, 40.4 (q, 1C, $J_{CF}$ = 22 Hz), 39.0 ppm; IR (KBr): $\tilde{\nu}$ = 3462, 3323, 2962, 1716, 1564, 1516, 1401, 1246, 1146 cm$^{-1}$; MS (ESI) *m/z* (%): 351.1 [(*M*+H), 100]; Anal. calcd for $C_{15}H_{13}F_3N_6O$: C 51.43, H 3.74, N 23.99, found: C 51.54, H 3.73, N 24.05.

**1-(2,2-Difluorocyclopropyl)-3-[7-(1-methyl-1*H*-pyrazol-4-yl)-1,5-naphthyridin-4-yl]urea (60)**: Using method E, 1-(7-bromo-1,5-naphthyridin-4-yl)-3-(2,2-difluorocyclopropyl)urea **37** (240 mg, 0.70 mmol) reacted for 16 h with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (291 mg, 1.40 mmol) to afford compound **60** as a white powder (104 mg, 43%). $R_f$ = 0.10 ($CH_2Cl_2$/EtOH, 95:5); mp: 229–230 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.65 (s, 1H), 9.20 (d, $J$ = 2.0 Hz, 1H), 8.73 (d, $J$ = 9.2 Hz, 1H), 8.57 (s, 1H), 8.50 (d, $J$ = 2.0 Hz, 1H), 8.30 (d, $J$ = 9.2 Hz, 1H), 8.26 (s, 1H), 8.24 (d, $J$ = 7.2 Hz, 1H), 4.12 (bs, 1H), 3.96 (s, 3H), 3.07–2.91 ppm (m, 2H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 154.1, 152.6, 146.6, 143.4, 143.2, 137.3, 132.4, 130.7, 130.1, 129.4, 118.2, 107.5, 96.2 (t, 1C, $J_{CF}$ = 276 Hz), 39.0, 35.1, 19.5 ppm (t, 1C, $J_{CF}$ = 22 Hz); IR (KBr): $\tilde{\nu}$ = 3445, 3319, 1638, 1585, 1301, 1267, 1159, 1052 cm$^{-1}$; MS (ESI) *m/z* (%): 345.1 [(*M*+H), 100]; Anal. calcd for $C_{16}H_{14}F_2N_6O$: C 55.81, H 4.10, N 24.41, found: C 56.01, H 4.12, N 24.49.

### *Biological assays*

*In vitro kinase inhibition assay*: Recombinant kinases were purchased from Millipore or ProQinase. An AlphaScreen Protein-A Detection Kit (PerkinElmer) was used to quantify kinase activity. For the assessment of $IC_{50}$ values, compounds were tested at ten final concentrations between 3.16 nM and 100 μM. Each kinase, 10 μM ATP, kinase substrate, and the test compound were incubated for 1 h on a 384-well Optiplate in a final volume of 15 μL. The kinase reaction was stopped by adding 10 μL Alpha Beadmix. The readout was performed the following morning using an Envision reader (PerkinElmer). $IC_{50}$ values were calculated with GraphPad Prism software. Kinase testing was performed by the Target Lab (Dr. Seipelt, Preclinical Development) at Æterna Zentaris GmbH, Frankfurt/Main (Germany).

*In vitro antiproliferative assay*: Cytotoxicity assessments were conducted with five diverse tumor cell lines, namely HCT116 (colon), MDA-MB468 (breast), PC3 (prostate), A549 (NSCLC), and U87MG (CNS). The tumor cell lines used were acquired from ATCC. Tumor cells were plated on 96-well plates and allowed to attach overnight; 48 h after cell seeding, test compounds were added at ten final concentrations from 0.0158 to 50 μM in duplicate. After test substance incubations for 48 h, cell proliferation was determined by XTT-PMS methodology.[47] The XTT assay quantifies cellular metabolic activity, which correlates with cellular viability and/or cell number. $IC_{50}$ values were calculated using GraphPad Prism software. Cell cultures were carried out according to the supplier's instructions. XTT testing was performed by the Target Lab (Dr. Seipelt, Preclinical Development) at Æterna Zentaris GmbH, Frankfurt/Main (Germany).

*RP-UPLC method for lipophilicity determination*: To determine the lipophilicity profile of the (7-aryl-1,5-naphthyridin-4-yl)ureas **45**–**60**, chromatographic hydrophobicity indices (CHI) were determined according to an original procedure, based on a reversed-phase UPLC gradient. First, ten reference compounds with known CHI values (Table 3) were injected onto the UPLC system to generate a calibration line from their retention time (CHI = 45.99 × $t_R$ − 48.25, $R^2$ = 0.966). The concentration was 0.2 mg mL$^{-1}$ in MeOH for each compound, and the injected volume was 2 μL. The ureas were analyzed on the same system. The calibration line equation was used to determine the CHI values of ureas. As CHI correlates closely with log $D_{7.4}$ octanol/water partition coefficients, we estimated log $D_{7.4}$ values for the 16 ureas. For that we used a correlation equation

**Table 3.** CHI and log $D_{7.4}$ values for reference compounds.

| Compd | CHI | Log $D_{7.4}$ |
|---|---|---|
| theophylline | 15.76 | −0.33 |
| paracetamol | 18.77 | 0.47 |
| benzimidazole | 30.71 | 1.31 |
| colchicine | 41.37 | 1.07 |
| phenol | 49.0 | 1.54 |
| acetophenone | 64.9 | 1.67 |
| indole | 69.15 | 2.59 |
| propiophenone | 78.41 | 2.18 |
| butyrophenone | 88.49 | 2.69 |
| valerophenone | 97.67 | 3.20 |

obtained from the ten reference compounds ($\log D_{7.4} = 0.031 \times$ CHI − 0.004, $R^2 = 0.902$). The UPLC column used was an Acquity UPLC T3 (2.1 mm i.d., 50 mm length, 1.8 μm particle size) from Waters. A linear mobile-phase gradient was used with a mobile phase A as 100% of $NH_4OAc$ 50 mM in $H_2O$ (adjusted to pH 7.4 with $NH_4OH$) and mobile phase B as 100% MeCN. The gradient table was: 0–0.5 min, 0% B; 0.5–4.0 min, 0→100% B; 4.0–5.5 min, 100% B; 5.5–5.7 min, 100→0% B; 5.7–7.5 min, 0% B at a flow rate of 0.5 mL min$^{-1}$ and a column temperature at 35 °C. The detection wavelength was 254 nm. LC–MS analyses were performed using a Waters UPLC and Waters ZQ mass spectrometer system with electrospray ionization and alternating positive and negative ion quadrupole mass spectrometry and scanning *m/z* 100–900 each second.

*Kinetic solubility*: Kinetic solubility was determined by an HPLC-based UV detection method. Kinetic solubility was assessed in the ADME laboratory (Dr. Blumenstein, Preclinical Development) at Æterna Zentaris GmbH, Frankfurt/Main (Germany).

*Microsomal stability*: Metabolic stability in pooled mouse liver microsomes (in the presence of an NADPH-regenerating system, 1 mg mL$^{-1}$ microsomal protein) was evaluated at 37 °C over time (60 min in liver microsomes) in triplicates at a test concentration of 10 μM. The remaining relative amount of test compound (reflected by integrated peak area) was analyzed at time points 0, 5, 10, 30, and 60 min by an HPLC-based UV detection method. Control incubations were performed with 10 μM testosterone as marker substrate for 15 min at 37 °C in order to demonstrate that the microsomes are fully functional. Negative controls were performed in duplicates by incubation of test compound without NADPH at the same time points. All reactions were started by the addition of NADPH and terminated by precipitation with stop reagent (43% MeCN). Samples were centrifuged for 10 min at 10200 rpm (swinging-bucket rotor), and the particle-free supernatant was transferred into glass vials for HPLC analysis.

*Plasma stability*: Stability in mouse plasma was determined after incubation of test compounds at 37 °C in triplicates at a test concentration of 10 μM. The remaining relative amount of test compound (reflected by integrated peak area) was analyzed at time points 0, 1, 2, 4, and 6 h by an HPLC-based UV detection method. Control incubations were performed accordingly with an internal standard as marker in order to demonstrate that the plasma is fully functional. Duplicates were carried out and stopped after 15 min of incubation with the stop reagent (see below). Negative controls were performed in duplicates by incubation of test compound in phosphate buffer at the same time points. All reactions were terminated by precipitation in a 1:4 ratio with ice-cold stop reagent (75% MeCN). Precipitation was completed by a 15 min incubation period at RT, after which the samples were centrifuged for 15 min at 13000 rpm (swinging-bucket rotor), and the particle-free supernatant was transferred into glass vials for HPLC analysis. Metabolic stability assessments were performed by the ADME laboratory (Dr. Blumenstein, Preclinical Development) at Æterna Zentaris GmbH, Frankfurt/Main (Germany).

*CYP inhibition*: Direct inhibition of CYP3A4/5 was assessed with midazolam (16 μM) as marker substrates by an HPLC-based UV detection method in pooled human liver microsomes. Incubations were carried out as doublets with final concentrations ranging from 0.01 to 200 μM (30 min, 37 °C). Percent inhibition was plotted against concentration to calculate or extrapolate $IC_{50}$ values form the sigmoid curve. Control incubations were performed accordingly, but the reaction mix was precipitated before the addition of NADPH. Negative controls were performed by omission of test compound at the same time points. All reactions were started by addition of NADPH and terminated by precipitation with stop reagent (43% MeCN). Samples were centrifuged for 10 min at 10200 rpm (swinging-bucket rotor), and the particle-free supernatant was transferred into glass vials for HPLC analysis. CYP450 inhibition studies were performed by the ADME laboratory (Dr. Blumenstein, Preclinical Development) at Æterna Zentaris GmbH, Frankfurt/Main (Germany).

*Chromatography*: The test compound samples resulting from the metabolic stability or CYP inhibition experiments were analyzed with a Shimadzu Prominence HPLC system with respect to the loss of peak area of parent compound using a Merck Chromolith Performance column and a Primus Phenomenex Gemini $C_{18}$ precolumn. The analytical parameters were as follows: mobile phase A (10% MeOH, 90% $ddH_20$, 0.09% formic acid, 0.01% TFA, pH 4.0), mobile phase B (90% MeOH, 10% $ddH_20$, 0.09% formic acid, 0.01% TFA, pH 4.0), flow rate: 2.5 mL min$^{-1}$, gradient: 15% B (0–1.00 min), 15→100% B (1.01–10.00 min), 100% B (10.01–11.30 min), 15% B (11.31–13.00 min), stop time: 13.01 min. To meet the requirements of peak detectability, selection, as well as sensitivity at concentrations used, even with test compounds with low extinction coefficients, adequate wavelengths were used, as selected from the UV spectra of the analyte (usually the spectral maximum). Integration of peaks was performed automatically by Shimadzu LCsolution software (Version 1.11 SP1). Peaks with intensities too low to be integrated were set at zero.

*CaCo-2 permeability assay*: To generate a cell monolayer, 80000 Caco-2 cells (ATCC, HTB-37) were seeded in DMEM supplemented with 10% FCS, 1% penicillin/streptomycin and 1% nonessential amino acids per 24-well transwell plate (Corning #3397) and were grown for 21 days by changing the media every second day. On day 21 the medium was replaced by HBSS buffer (Invitrogen #14065) supplemented with 0.25 and 1% BSA for the donor and acceptor compartments, respectively. The compounds were added to the respective donor compartment at a concentration of 3 μm and were incubated for 2 h at 37 °C in duplicates. The respective compound concentrations were determined by LC–MS/MS analysis employing an Agilent 1100 Series system with G1312A pumps and a G1367A autosampler. Mass spectrometry was performed on an API 2000 triple quadrupole mass spectrometer (AB Sciex Instruments, Darmstadt, Germany) with a TurbolonSpray ion source connected to a PC running the standard software, Analyst 1.3.2. Compound concentrations were calculated relative to a calibration standard. Before LC–MS/MS measurement, all samples were cleared from protein and cell debris by precipitation with MeCN at a 1:4 ratio. The rate of permeation of the drug across the cells, d*Q*/d*t*,

was calculated by using standard procedures[48,49] based on measurement at time points of 0 and 2 h.

*hERG assay*: The Predictor hERG assay (Invitrogen #PV 5365) uses a membrane fraction containing hERG channel protein (Predictor hERG Membrane) and a high-affinity red fluorescent hERG channel ligand, or "tracer" (Predictor hERG Tracer Red), in a homogenous, fluorescence polarization (FP)-based format.[50] The assay was performed according to the guidelines of the manufacturer. The data were calculated in percent inhibition according to cells treated with saturating concentrations of the hERG inhibitor E-4031 (Invitrogen #PV 5365) as positive, and non-treated samples as negative controls. $IC_{50}$ values were determined by using the GraphPad Prism analysis program (GraphPad Software).

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