Bioorganic & Medicinal Chemistry 18 (2010) 403–414

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Aminopyridinecarboxamide-based inhibitors: Structure–activity relationship

Dominique F. Bonafoux [a,*], Sheri L. Bonar [b], Michael Clare [a], Ann M. Donnelly [b], Jeanette L. Glaenzer [a], Julia A. Guzova [b], He Huang [a], Nandidni N. Kishore [b], Francis J. Koszyk [a], Patrick J. Lennon [a], Adam Libby [a], Sumathy Mathialagan [b], David S. Oburn [a], Sharon A Rouw [b], Cynthia D. Sommers [b], Catherine S. Tripp [b], Lori J. Vanella [b], Richard Weier [a], Serge G. Wolfson [a], Horng-Chih Huang [a,*]

[a] Department of Medicinal Chemistry, Pfizer Inc., 700 Chesterfield Parkway West, St Louis, MO 63017, United States
[b] Department of Biology, Pfizer Inc., 700 Chesterfield Parkway West, St Louis, MO 63017, United States

ARTICLE INFO

Article history:
Received 25 September 2009
Revised 19 October 2009
Accepted 23 October 2009
Available online 27 October 2009

Keywords:
IKK2
NFkB
Inhibitor

ABSTRACT

Series of aminopyridinecarboxamide-based inhibitors were synthesized and tested against human recombinant IKK-2 and in IL-1β stimulated synovial fibroblasts. The 2-amino-5-chloropyridine-4-carboxamides were identified as the most potent inhibitors with improved cellular activity.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Nuclear factor *kappa* B (NF-κB) is an inducible transcriptional activator that is inappropriately activated and/or disregulated in a number of inflammatory disorders such as arthritis.[1] NF-κB is retained in the cytoplasm in an inactive form by association with regulatory proteins called inhibitors of κB (IκB). Upon stimulation with proinflammatory cytokines such as interleukin 1 beta (IL-1β) or tumor necrosis factor alpha (TNFα), IKK-2 phosphorylates IκB, leading to its degradation and the release of NF-κB in the cytoplasm. The NF-κB subsequently translocates to the nucleus where it binds target genes and regulates their transcription.[2] IKK-2, being the converging point for the activation of NF-κB in response to a variety of proinflammatory stimuli, is therefore an attractive target for the pharmaceutical industry. Various natural products as well as anti-inflammatory agents such as aspirin[3] have been reported to be weak, non-selective inhibitors of IKK-2. More recently, thiophenecarboxamides,[4] indolecarboxamides,[5] benzamides,[6] 2,4-diarylpyridines,[7] aminopyrimidines,[8] β-carbolines,[9] pyrrolopyridines[10] and imidazo(1,2-*a*)thieno(3,2-*e*)pyrazines[11] were shown to be potent IKK-2 inhibitors.

We recently reported that the 8-(5-chloro-2-(4-methylpiperazin-1-yl)isonicotinamido)-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo-[*g*]indazole-3-carboxamide (**PHA-408**) is a selective, ATP-competitive inhibitor, which binds IKK-2 tightly with a relatively slow off rate and is efficacious in a chronic model of arthritis with no adverse effects at maximally efficacious doses (Fig. 1).[12,13]

The 2-chloropyridine-3-carboxamide derivatives **1** and **2**,[14] two early precursor to **PHA-408**, had been found to be potent inhibitors of IKK-2 (Fig. 2) with respective IC_{50}'s of 34 nM and 47 nM, but only showed modest to low activity in our cell based assay (SF-IL-8 IC_{50} = 5 μM and 12 μM, respectively). Thus, we launched a synthetic program to explore the SAR of this template and improve the cellular activity. Our effort relied on the introduction of a variety of solubilizing amines into the 2-chloropyridine-3-carboxamide template, which led us to investigate three chemical series: the 2-aminopyridine-3-carboxamides (**3**, **4**), 6-aminopyridine-2-carboxamides (**5**, **6**) and 2-aminopyridine-4-carboxamides (**7**, **8**).

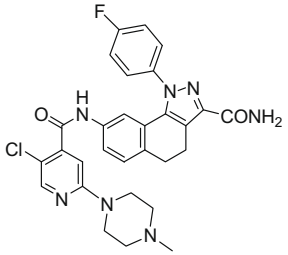


Figure 1. Structure of PHA-408.

* Corresponding authors.
E-mail addresses: dominique.bonafoux@abbott.com (D.F. Bonafoux), horng-chih.huang@pfizer.com (H.-C. Huang).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.10.040

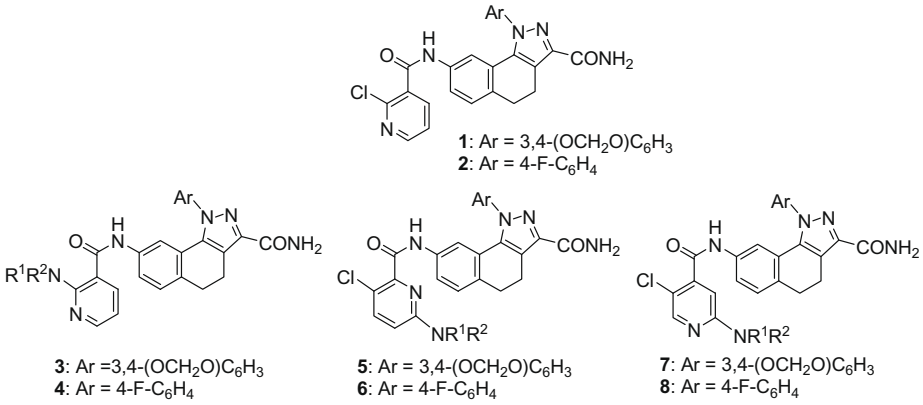


Figure 2. Pyridine analogs of prototype compounds **1** and **2**.

2. Chemistry

2.1. 2-Aminopyridine-3-carboxamides

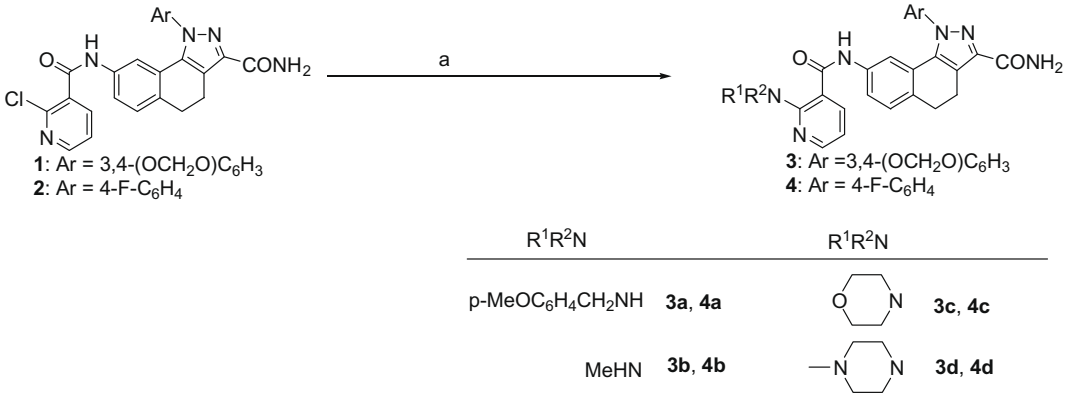
The 2-aminopyridine-3-carboxamides (**3**, **4**) were obtained, with yields ranging from 46% to 75%, by reacting the previously described 2-chloropyridine-3-carboxamides (**1**, **2**)[14] with primary and secondary amines in ethanol at 100 °C in a sealed tube (Scheme 1).

The free amino derivatives **3e** and **4e** were obtained, in 32 and 46% yield, respectively, by deprotection of *p*-methoxybenzylaminopyridines **3a** and **4a** (Scheme 2).

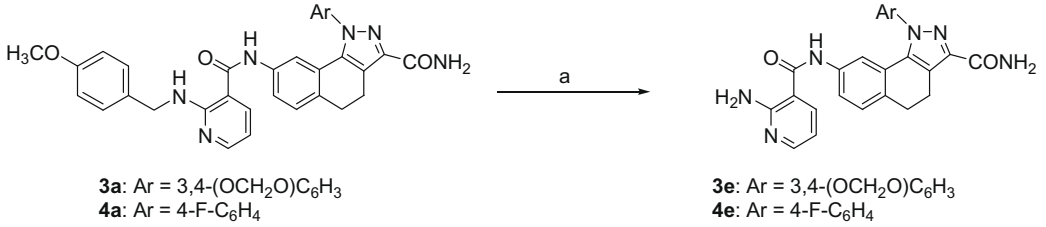
2.2. 6-Aminopyridine-2-carboxamides

3,6-Dichloropyridine-2-carboxamides **12** and **13** were synthesized by coupling the amino dihydrobenzoindazoles **9** and **10**[14] with acid[15] **11** (Scheme 3). Subsequent amination of **12**, under conditions similar to those of Scheme 2, led predominantly to the desired **5a** and **5b**. It is worth noting that the amination of **12** required long reaction times and resulted in significant amounts of byproducts leading to troublesome purifications and modest yields for **5a** (28%) and **5b** (52%).

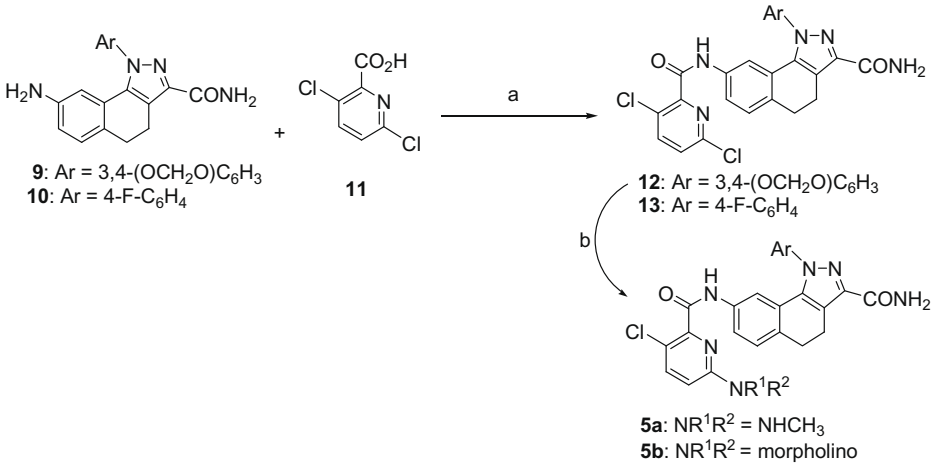
As a result of the low selectivity and the long reaction times associated with the direct amination of the 3,6-dichloropyridine-2-carboxamide **12** (Scheme 3), an alternative synthesis was developed for the preparation of additional 3-chloro-6-aminopyridine-2-carboxamides. This route relied on the synthesis of the 3-chloro-6-morpholino-2-pyridine carboxylic acid hydrochloride (**14**) and the 3-chloro-6-(4-methylpiperazinyl)-2-pyridine carboxylate (**15**) followed by coupling with amine **9** or **10** and afforded the desired products in yields ranging from 61% to 88% (Scheme 4).



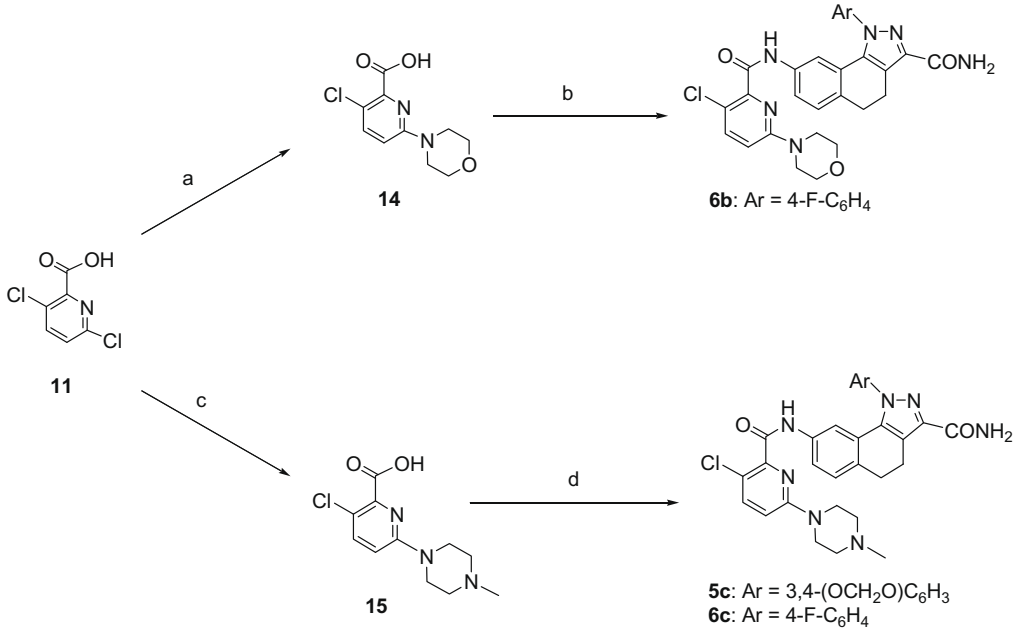
Scheme 1. Reagents and conditions: (a) R_1R_2NH (6 equiv), EtOH, 100 °C.



Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2, rt.



Scheme 3. Reagents and conditions: (a) HATU, Et_3N, DMF, rt; (b) R_1R_2NH (>20 equiv), 82 °C, 5 days.



Scheme 4. Reagents and conditions: (a) morpholine (excess), DMA, 80 °C, 64 h; (b) **10**, HBTU, Et_3N, DMF, rt; (c) *N*-methylpiperazine (excess), DMF, 95 °C, 3 days, (d) **9** or **10**, HBTU, Et_3N, DMF, rt.

2.3. 2-Aminopyridine-4-carboxamides

2,5-Dichloropyridine-4-carboxamides **17** and **18** were synthesized by coupling acid **16**[14] with amines **9** and **10**. In contrast to the 3-chloro-6-aminopyridine-2-carboxamides, the 2-amino-5-chloropyridine-4-carboxamides **7** and **8** could be efficiently synthesized by direct amination of the 2,5-dichloropyridine-4-carboxamides **17** and **18** with satisfactory yields (Scheme 5). This route was thus used for the synthesis of most of the inhibitors in this series. Coupling a 2-amino-5-chloropyridine-4-carboxylic acid to amine **9** or **10** also provided entries to analogs **8a** (**PHA-408**), **7p** and **8p** (Scheme 6).

2-Aminopyridine-4-carboxamides **23a** and **23b**, the des-chloro analogs of **8a** and **8p**, were synthesized according to Scheme 7 by direct amination of intermediate **22**.

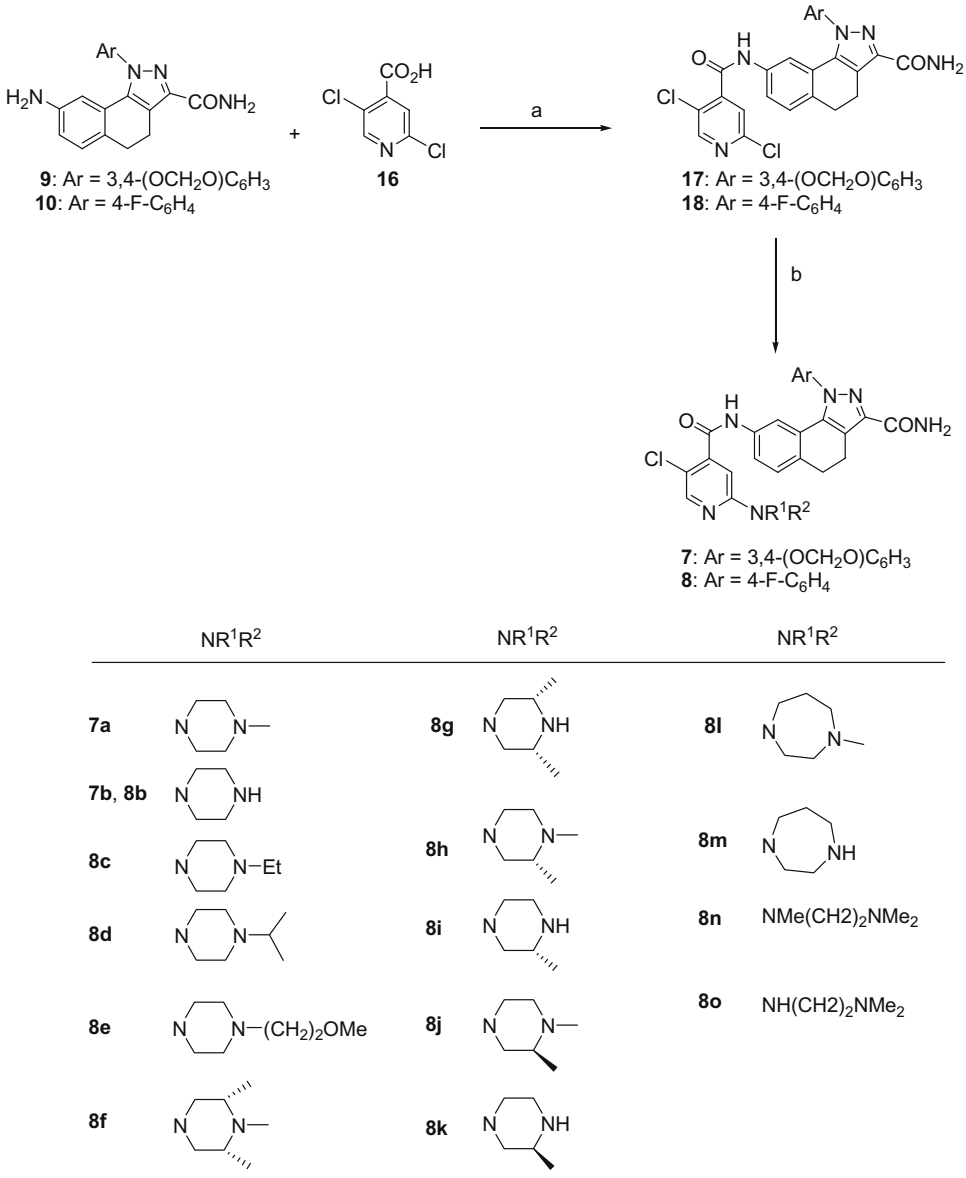
3. Biology

These inhibitors were initially evaluated for inhibition of recombinant human IKK-2.[16,17] Compounds with an IC_{50} on IKK-2 less than about 0.5 μM were subsequently tested in a cellular assay using synovial fibroblasts from rheumatoid arthritis patients. These cells were stimulated with interleukin-1β (IL-1β) and the response to this stimulation was measured as the percentage of inhibition of interleukin-8 (IL-8) production (SF IL-8 IC_{50}).[18]

4. Results and discussion

4.1. 2-Aminopyridine-3-carboxamides

As shown in Table 1, the replacement of the chlorine at the 2-position of the pyridine ring in **1** and **2** with a small amino group (**3e**, **4e**) or sterically more demanding cyclic amino group (**3c**, **3d** and **4c**, **4d**) led, in all cases, to a dramatic loss of potency against IKK-2 compared to prototype compounds **1** and **2**. The most active 2-aminopyridine-3-carboxamide synthesized in this series, **3b** (IKK-2 IC_{50} = 0.210 μM, SF IL-8 IC_{50} = 3.37 μM), was six times less potent on the enzyme than precursor **1**, suggesting that the chloro *ortho* to the carboxamide on the pyridine ring is an important structural feature of this template to achieve good activity on IKK-2.



Scheme 5. Reagents and conditions: (a) HATU, Et_3N, DMF, rt; (b) R_1R_2NH (excess), 100 °C, 24 h.

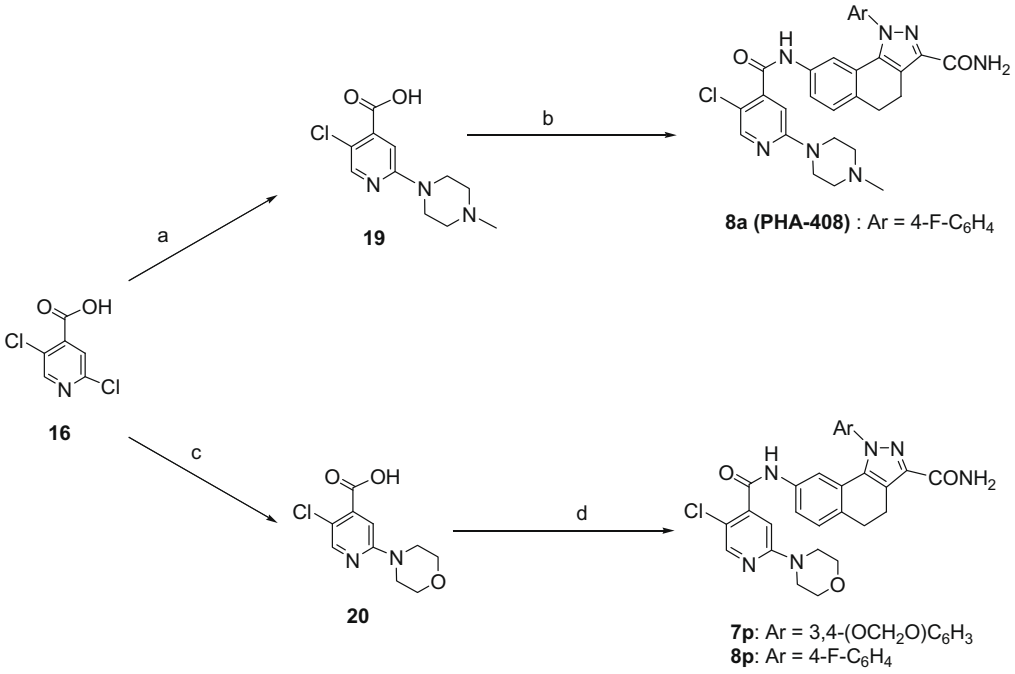
4.2. 6-Aminopyridine-2-carboxamides

Having shown that the *ortho* chloro substituent in the prototype carboxamide **1** was key for potency, we decided to focus on related pyridine systems where the chloro is maintained *ortho* to the carboxyamide moiety. We first studied 3-chloro-6-aminopyridine-2-carboxamides (Table 2), such as **5** and **6**, which were generally more potent IKK-2 inhibitors than the 2-aminopyridine-3-carboxamides (Table 1), especially when the amino substituents were morpholine and *N*-methylpiperazine. The most potent inhibitors in this series, **5c** and **6c**, exhibited modest activity on the enzyme (about 10 times less potent than **1** and **2**) and were found to have modest activity in the SF IL-8 assay. In spite of enhancement of enzyme activity in some analogs, these compounds did not approach the activity of the prototype compounds **1** and **2** and their cellular potency did not show any differentiation. We hypothesized that the pyridyl nitrogen *ortho* to the amide might have formed an internal hydrogen-bond with the amide NH, and unfavorably flipped the trajectory of the substituents on the pyridine ring.

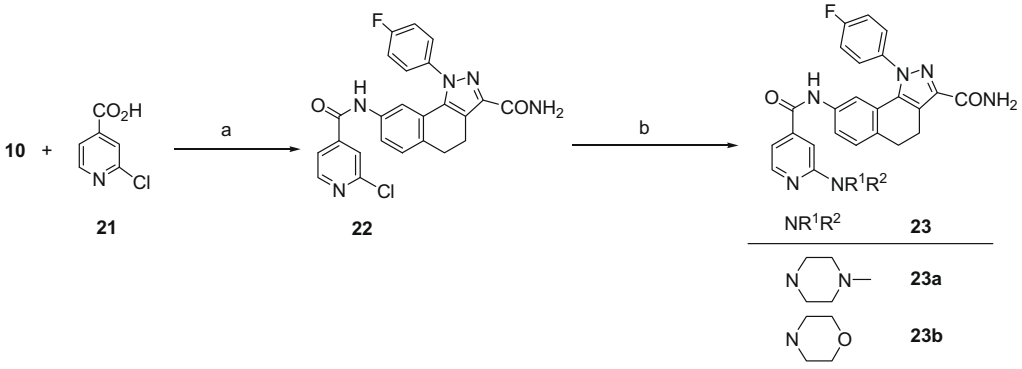
4.3. 2-Amino-5-chloro-pyridine-4-carboxamides

To prevent the hypothesized internal hydrogen-bond formation, we moved the pyridine nitrogen further away from the amide moiety with the 2-amino-5-chloro-pyridine-4-carboxamides which were, in most cases, very potent IKK-2 inhibitors comparable to prototype compounds **1** and **2** with IC_{50}'s ranging from 0.010 μM (**8b**) to 0.146 μM (**8p**) (Table 3). Moreover many showed better potency in the cell assay (Table 3), in particular compounds **7a**, **8a** (**PHA-408**), **8e**, and **7p** featuring N-substituted piperazines or an unsubstituted morpholine, with SF IL-8 IC_{50} values of about 1 μM or less. Further studies to understand the nature of this cell-potency improvement will be reported in due time.

Most of the current series, with an *ortho* chloro, had IKK-2 IC_{50} values below 0.100 μM. As a means to confirm the importance of that *ortho* chloro, the des-chloro analogs of **8a** (**PHA-408**) and **8p** (**23a** and **23b**, respectively) were tested in our in vitro assays. The IKK-2 IC_{50} values for **23a** and **23b** were 0.125 μM and 0.589 μM, respectively, thus 4–5-fold lower than those of the corresponding chloro containing inhibitors **8a** (**PHA-408**) and **8p**, and

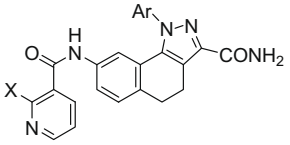


Scheme 6. Reagents and conditions: (a) *N*-methylpiperazine (excess), DMA, 100 °C, 8 days; (b) **10**, HBTU, Et_3N, DMF, rt; (c) morpholine (excess), DMA, 80 °C, 4 days; (d) **9** or **10**, HBTU, Et_3N, DMF, rt.



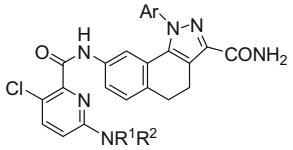
Scheme 7. Reagents and conditions: (a) HATU, Et_3N, DMF, rt; (b) R_1R_2NH (excess), 100 °C.

Table 1
Inhibition of IKK-2 by 2-aminopyridine-3-carboxamides



	X, Ar = 3,4-$(OCH_2O)C_6H_3$	IC_{50} (μM)		X, Ar = 4-F–C_6H_4	IC_{50} (μM)
1	Cl	0.034	**2**	Cl	0.047
3e	NH_2	1.34	**4e**	NH_2	2.32
3b	NHMe	0.210	**4b**	NHMe	3.21
3c	Morpholino	5.91	**4c**	Morpholino	14.2
3d	*N*-Methylpiperazinyl	17.3	**4d**	*N*-Methylpiperazinyl	16.2

Table 2
Inhibition of IKK-2 by 3-chloro-6-aminopyridine-2-carboxamides



5: Ar = 3,4-$(OCH_2O)C_6H_3$
6: Ar = 4-F-C_6H_4

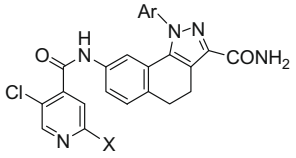
	R^1R^2N	IKK-2 IC_{50} (μM)	SF IL-8 IC_{50} (μM)
5a	MeNH	0.477	5.74
5b	Morpholino	0.612	>100
6b	Morpholino	1.25	3.04
5c	*N*-Methylpiperazinyl	0.297	4.42
6c	*N*-Methylpiperazinyl	0.348	4.83

showed a lack of activity in cells with an SF IL-8 IC_{50} greater than 5 μM. It is worth noting that compound **8a** (**PHA-408**), which selectivity profile against 36 kinases was previously reported,[12] did not inhibit IKK-1 (IKK-1 IC_{50} = 14 μM), nor did it show activity on closely related TBK1 or iKKi.

5. Conclusion

In summary, we showed that the 2-amino-5-chloropyridine-4-carboxamides were potent IKK-2 inhibitors with improved inhibition of IL-8 production in stimulated synovial fibroblasts for several compounds compared to our earlier prototypes **1** and **2**. The

Table 3
Inhibition of IKK-2 by 2-amino-5-chloro-pyridine-4-carboxamides



7: Ar = 3,4-$(O_2CH_2)C_6H_3$
8: Ar = 4-F-C_6H_4

	X	IKK-2 IC_{50} (μM)	SF IL-8 IC_{50} (μM)
1	H, Ar = 3,4-$(OCH_2O)C_6H_4$	0.034	5
2	H, Ar = 4-F-C_6H_4	0.047	12
7a	*N*-Methylpiperazinyl	0.033	0.63
8a	*N*-Methylpiperazinyl	0.025	0.94
7b	Piperazinyl	0.040	1.86
8b	Piperazinyl	0.010	2.47
8c	*N*-Ethylpiperazinyl	0.052	1.53
8d	*N*-*iso*-Propylpiperazinyl	0.107	1.49
8e	*N*-(Methoxyethyl)piperazinyl	0.059	1.02
8f	3,5-Dimethyl-*N*-methylpiperazinyl	0.098	5.5
8g	3,5-Dimethylpiperazinyl	0.046	8.6
8h	(*R*)-3-Methyl-*N*-methylpiperazinyl	0.048	2.18
8i	(*R*)-3-Methylpiperazinyl	0.054	3.98
8j	(*S*)-3-Methyl-*N*-methylpiperazinyl	0.045	1.31
8k	(*S*)-3-Methylpiperazinyl	0.051	1.32
8l	*N*-Methylhomopiperazinyl	0.029	2.36
8m	Homopiperazinyl	0.027	1.94
8n	*N*,*N*,*N*′-Trimethylethylenediamine	0.019	4.18
8o	*N*,*N*-Dimethylethylenediamine	0.070	4.72
7p	Morpholino	0.090	0.849
8p	Morpholino	0.146	2.14

chloro *ortho* to the carboxamide, as well as the piperazinyl groups at the 2-position of the pyridine ring, were identified as key structural features in this series to achieve good selectivity, good cellular activity and good in vivo efficacy as previously reported for **8a** (**PHA-408**).[12]

6. Experimental section

6.1. General methods and material

Column chromatography was performed using 200–400 mesh silica gel. ^{1}H NMR and ^{13}C NMR were obtained on Varian Inova-300 and Varian Inova-400 spectrometers using $CDCl_3$, DMSO-d_6, D_2O or MeOH-d_4 as internal standards. Mass spectra (MS) were recorded with a Micromass ZMD spectrometer. High resolution mass spectra were recorded using a Perseptive Biosystems Mariner TOF mass spectrometer. Elemental analysis were performed by Atlantic MicroLab, GA. The (2*R*,6*S*)-1,2,6-trimethylpiperazine, (2*R*)-1,2-dimethylpiperazine and (2*S*)-1,2-dimethylpiperazine were synthesized according to a procedure described elsewhere.[9]

6.1.1. IKK-2. enzyme assay

Kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). Twenty microliters of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1×10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH. 7.6 and 20 μL enzyme solution (46 nM/rxn or 200 ng/rxn) and 10 μL inhibitor in a final volume of 50 μL. After incubation at 25 °C for 30 min, the reaction was stopped by the addition of 150 μL of AG1XB resin (Supelco Inc./Sigma–Aldrich) in 900 mM sodium format buffer, pH 3 (the resin is in a slurry of 1 volume resin to 2 volumes of sodium formate buffer) was added to each well to stop the reaction. The resin was mixed and allowed to settle for one hour and 50 μL of supernatant was transferred to a top count plate followed by the addition of 150 μL of scintillation fluid (Microscint 40) (Packard) to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard Instrument Co.).

6.1.2. Cell assay

Cytokine production and toxicity determination in IL-1β induced synovial fibroblast cells have been described previously.[15] In brief; synovial fibroblast cells were plated in 96-well plates at 1.5×10^4 cells/well in DMEM (Invitrogen) containing 15% fetal bovine serum (Hyclone) and allowed to attach overnight. The growth media were replaced with DMEM containing 1% fetal bovine serum, and the cells were pre-treated with increasing concentrations of compound or media in (0.2% Me_2SO final) for 1 h prior to an 18 h stimulation with 1 ng/mL IL-1β R&D Systems). Supernatants were collected and analyzed for secreted IL-8 by ELISA. IL-8 concentration was extrapolated from standard curves using a 4 parameter logistic model by Softmax Pro 3.1.2(2) (Molecular Devices). Cytotoxicity was assessed using an Alamar Blue assay (Promega) and was below 20% at the highest concentration of inhibitors tested.

6.2. General procedure for the synthesis of 2-aminopyridine-3-carboxamides

6.2.1. 1-(1,3-Benzodioxol-5-yl)-8-[({2-[(4-methoxybenzyl)amino]-pyridin-3-yl}carbonyl-)amino]-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (3a)

A mixture of 1 (2 g, 4 mmol) and *p*-methoxybenzylamine (2.8 g, 20 mmol) in 10 mL EtOH was stirred at 100 °C for 48 h in a sealed tube. The off-white precipitate that formed in the crude reaction mixture upon cooling down to room temperature was filtered, washed with EtOH and Et_2O and dried under vacuum. Yield 60%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.88–2.94 (m, 4H), 3.71 (s, 3H), 4.56 (d, 2 H, J = 5.6 Hz), 5.98 (s, 2H), 6.60–6.64 (dd, 1H, J = 7.5 Hz, 4.7 Hz), 6.88 (d, 2H, J = 8.4 Hz), 6.96 (s, 2H), 7.11 (s, 1H), 7.23–7.35 (m, 5 H), 7.39 (s, 1H), 7.49 (s, 1H), 7.95 (d, 1H, J = 7.45 Hz), 8.17 (d, 1H, J = 4.7 Hz), 8.23 (t, 1H, J = 5.6 Hz), 10.06 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 29.6, 43.9, 55.7, 102.5, 108.1, 109.0, 110.8, 111.4, 114.4, 115.8, 120.5, 120.7, 120.8, 126.6, 129.2, 129.3, 132.7, 133.1, 134.4, 137.7, 139.8, 142.6, 148.4, 148.6, 152.0, 157.8, 158.8, 164.8, 167.1; Anal. Calcd for $C_{33}H_{28}N_6O_5$: C, 67.34; H, 4.79; N, 14.28. Found: C, 67.08; H, 4.78; N, 14.19.

6.2.2. 1-(4-Fluorophenyl)-8-[({2-[(4-methoxybenzyl)-amino]pyridin-3-yl}carbonyl)amino]-4,5-dihydro-1*H*-benzo[g]indazole-3-carboxamide (4a)

Same procedure as **3a**. Yield 35%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.89–2.95 (m, 4H), 3.72 (s, 3H), 4.53 (d, 2H, J = 5.5 Hz), 6.61 (dd, 1H, J = 7.7 Hz, 4.8 Hz), 6.9 (d, 2H, J = 8.6 Hz), 7.24–7.36 (m, 8H), 7.55–7.60 (m, 3H), 7.94 (dd, 1H, J = 7.7 Hz, 1.7 Hz), 8.17 (dd, 1H, J = 4.8 Hz, 1.7 Hz), 8.21 (t, 1H, J = 5.5 Hz), 10.0 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 29.6, 44.0, 55.7, 110.7, 111.4, 114.4, 115.8, 117.1 (d, J_{C-F} = 23.0 Hz), 120.9, 121.1, 126.4, 128.8 (d, J_{C-F} = 8.7 Hz), 129.2, 129.3, 132.6, 133.1, 136.9 (d, J_{C-F} = 2.8 Hz), 137.6, 137.7, 139.8, 143.1, 152.0, 157.8, 158.8, 162.6 (d, J_{C-F} = 245.7 Hz), 164.4, 167.0; MS m/z (M+1$^+$) 563.

6.2.3. 1-(1,3-Benzodioxol-5-yl)-8-({[2-(methylamino)pyridin-3-yl]carbonyl}amino)-4,5-dihydro-1*H*-benzo[g]indazole-3-carboxamide (3b)

Same procedure as **3a**. Yield 75%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.88–2.95 (m, 4H + 3H), 6.12 (s, 2H), 6.57–6.61 (dd, 1H, J = 7.6 Hz,

4.7 Hz), 6.95–6.98 (dd, 1H, J = 8 Hz, 2 Hz), 7.07 (d, 1H, J = 8 Hz), 7.13 (d, 1H, J = 2 Hz), 7.25–7.34 (m, 3H), 7.45–7.50 (m, 2H), 7.82–7.83 (m, 1H), 7.91–7.95 (dd, 1H, J = 7.6 Hz, 1.7 Hz), 8.18–8.20 (dd, 1H, J = 4.8 Hz, 1.8 Hz), 10.02 (s, 1H).%); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 28.3, 29.6, 102.6, 108.2, 109.2, 110.9, 111.0, 115.8, 120.6, 126.5, 129.2, 132.9, 134.5, 137.4, 137.8, 139.9, 142.7, 148.5, 148.6, 152.1, 158.6, 164.6, 167.0; HRMS calcd for $C_{26}H_{23}N_6O_4$ 483.1775, found 483.1787.

6.2.4. 1-(4-Fluorophenyl)-8-({[2-(methylamino)pyridin-3-yl]-carbonyl}amino)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (4b)

Same procedure as **3a** at 98 °C for 48 h. After cooling down to room temperature, the crude suspension was dissolved in EtOAc and washed twice with H_2O. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. The resulting yellow solid was triturated with Et_2O. Yield 61%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.89–2.95 (m, 4H+3H), 6.57 (dd, 1H, J = 7.7 Hz, 4.8 Hz), 7.28–7.40 (m, 4H), 7.43 (t, 2H, J = 7.7 Hz), 7.55–7.62 (m, 3H), 7.7–7.78 (m, 1H), 7.90 (dd, 1H, J = 7.7 Hz, 1.8 Hz), 8.18 (dd, 1H, J = 4.8 Hz, 1.8 Hz), 10.01 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.4, 28.3, 29.6, 110.9, 111.1, 115.8, 117.2 (d, J_{C-F} = 23.4 Hz), 120.8, 121.1, 126.4, 129.0 (d, J_{C-F} = 8.9 Hz), 129.3, 133.0, 136.9, 137.2 (d, J_{C-F} = 3.6 Hz), 137.8, 139.9, 143.1, 152.1, 158.6, 162.8 (d, J_{C-F} = 245.5 Hz), 164.5, 167.0; HRMS calcd for $C_{25}H_{22}FN_6O_2$ 457.1783, found 457.1752.

6.2.5. 1-(1,3-Benzodioxol-5-yl)-8-{[(2-morpholin-4-ylpyridin-3-yl)carbonyl]amino}-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (3c)

Same procedure as **3a**. Yield 64%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.86–2.92 (m, 4H), 3.17 (t, 4H, J = 4.3 Hz), 3.53 (t, 4H, J = 4.29 Hz), 6.10 (s, 2H), 6.1 (s, 2H), 6.9–7.01 (m, 3H), 7.11 (d, 1H, J = 1.88 Hz), 7.26–7.31 (m, 3H), 7.50–7.52 (m, 2H), 7.68 (dd, 1H, J = 7.5 Hz, 1.88 Hz), 8.25 (dd, 1H, J = 4.7 Hz, 1.88 Hz), 10.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.4, 29.7, 49.7, 66.6, 102.7, 107.9, 109.0, 114.6, 116.2, 119.6, 120.4, 121.0, 121.5, 126.8, 129.5, 132.9, 134.4, 137.9, 139.2, 139.7, 142.7, 148.4, 148.6, 149.5, 158.1, 164.5, 166.4; HRMS calcd for $C_{29}H_{27}N_6O_5$ 539.2037, found 539.2009.

6.2.6. 1-(4-Fluorophenyl)-8-{[(2-morpholin-4-ylpyridin-3-yl)carbonyl]amino}-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (4c)

Same procedure as **3a**. Yield 52%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.89–2.94 (m, 4H), 3.17 (t, 4H, J = 4.4 Hz), 3.54 (t, 4H, J = 4.4 Hz), 6.92 (dd, 1H, J = 7.4 Hz, 4.8 Hz), 7.24–7.41 (m, 5H), 7.54–7.62 (m, 4H), 7.65 (dd, 1H, J = 7.4 Hz, 1.9 Hz), 8.26 (dd, 1H, J = 4.7 Hz, 1.9 Hz), 10.26 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.4, 29.7, 49.7, 66.6, 114.5, 116.1, 117.2 (d, J_{C-F} = 22.8 Hz), 119.7, 121.4, 121.5, 126.7, 128.7 (d, J_{C-F} = 9.1 Hz), 129.7, 133.0, 136.9 (d, J_{C-F} = 2.9 Hz), 138.0, 139.2, 139.8, 143.2, 149.5, 158.0, 162.6 (d, J_{C-F} = 245.6 Hz), 164.5, 166.5; Anal. Calcd for $C_{28}H_{25}N_6O_5$: C, 65.6; H, 4.9; N, 16.4. Found: C, 65.61; H, 4.92; N, 16.58.

6.2.7. 1-(1,3-Benzodioxol-5-yl)-8-({[2-(4-methylpiperazin-1-yl)pyridin-3-yl]carbonyl}-amino)-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (3d)

Same procedure as **3a**. Yield 65%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.13 (s, 3H), 2.28 (t, 4H, br), 2.88–2.94 (m, 4H), 3.20 (t, 4H, br), 6.11 (s, 2H), 6.87–7.03 (m, 3H), 7.11 (d, 1H, J = 1.81 Hz), 7.24–7.49 (m, 5H), 7.66 (dd, 1H, J = 7.45 Hz, 1.81 Hz), 8.25 (dd, 1H, J = 4.83 Hz, 1.81 Hz), 10.26 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.4, 29.7, 46.4, 49.1, 55.1, 102.6, 107.9, 109.1, 114.7, 115.9, 119.7, 120.4, 120.9, 121.4, 126.8, 129.5, 132.8, 134.4, 137.9, 139.1, 139.7, 142.7, 148.5, 148.7, 149.5, 158.3, 164.6, 166.3; HRMS calcd for $C_{30}H_{30}N_7O_4$ 552.2354, found 552.2365.

6.2.8. 1-(4-Fluorophenyl)-8-({[2-(4-methylpiperazin-1-yl)pyridin-3-yl]carbonyl}amino)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (4d)

Same procedure as **3a**. The crude mixture was cooled down to room temperature and partitioned between $CHCl_3$ and H_2O. The organic layer was dried over $MgSO_4$, the solvents removed under vacuum and the resulting solid triturated with Et_2O. Yield 49%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.1 (s, 3H), 2.23 (t, 4H, J = 4.6 Hz), 2.43–2.45 (m, 4H), 3.15 (t, 3H, J = 4.6 Hz), 6.85 (dd, 1H, J = 7.38 Hz, 4.83 Hz), 7.24–7.39 (m, 6H), 7.50–7.60 (m, 4H), 8.19 (dd, 1H, J = 4.83 Hz, 1.88 Hz), 10.2 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.4, 29.7, 46.4, 49.0, 55.1, 114.6, 115.8, 117.2 (d, J_{C-F} = 23.1 Hz), 119.8, 121.3, 121.4, 126.6, 128.7 (d, J_{C-F} = 9.1 Hz), 129.6, 132.9, 136.9 (d, J_{C-F} = 2.8 Hz), 138.0, 139.0, 139.8, 143.2, 149.7, 158.2, 162.6 (d, J_{C-F} = 245.9 Hz), 164.5, 166.4; Anal. Calcd for $C_{30}H_{29}N_7O_4$: C, 66.27; H, 5.37; N, 18.66. Found: C, 66.30; H, 5.36; N, 18.74.

6.2.9. 8-{[(2-Aminopyridin-3-yl)carbonyl]amino}-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (3e)

Compound **3a** (1.96 g, 3.3 mmol) was dissolved in 6 mL CH_2Cl_2 and reacted with 5 mL TFA at room temperature for 36 h. The crude reaction mixture was diluted with CH_2Cl_2 and basified with a saturated aqueous solution of Na_2CO_3. The layers were separated and the organic layer was dried over $MgSO_4$. The solvent was removed under vacuum and the resulting residue was triturated with EtOH. Yield 32%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.88–2.95 (m, 4H), 6.12 (s, 2H), 5.58–6.62 (dd, 1H, J = 7.6 Hz, 4.7 Hz), 6.97–7.08 (m, 4H), 7.17 (d, 1H, J = 1.9 Hz), 7.28 (s, 1H), 7.32 (s, 2H), 7.55 (s, 2H), 7.95–7.98 (dd, 1H, J = 7.7 Hz, 1.7 Hz), 8.11–8.13 (dd, 1H, J = 4.7 Hz, 1.7 Hz), 9.99 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.4, 29.6, 102.6, 108.2, 109.1, 110.5, 111.9, 115.8, 120.6, 120.7, 126.5, 129.2, 132.9, 134.5, 137.6, 137.9, 139.9, 142.6, 148.5, 148.7, 152.3, 159.6, 164.6, 166.9; HRMS calcd for $C_{25}H_{21}N_6O_4$ 469.1619, found 496.1644.

6.2.10. 8-{[(2-Aminopyridin-3-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (4e)

Same procedure as **3e yield** 46%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.85–2.91 (m, 4H), 6.57 (dd, 1H, J = 7.7 Hz, 4.8 Hz), 6.92 (s, br, 2H), 7.24–7.38 (m, 6H), 7.51–7.57 (m, 3H), 7.87 (dd, 1H), J = 7.7 Hz, 1.4 Hz), 8.04 (dd, 1HH, J = 3.4 Hz, 1.4 Hz), 9.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.6, 110.7, 111.9, 115.7, 117.2 (d, J_{C-F} = 23.0 Hz), 120.8, 121.2, 126.4, 128.8 (d, J_{C-F} = 8.9 Hz), 129.3, 133.0, 136.9 (d, J_{C-F} = 2.8 Hz), 137.8, 138.0, 139.8, 143.1, 151.6, 159.1, 162.6 (d, J_{C-F} = 245.7 Hz), 164.5, 166.7; HRMS calcd for $C_{24}H_{20}FN_6O_2$ 443.1626, found 443.1618.

6.3. Synthesis of 3,6-dichloropyridine-2-carboxamides

6.3.1. 1-(1,3-Benzodioxol-5-yl)-8-{[(3,6-dichloropyridin-2-yl)carbonyl]amino}-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (12)

3,6-Dichloro-2-pyridine carboxylic acid (**11**) (1.654 g, 8.14 mmol), HATU (3.27 g, 8.6 mmol) and finally Et_3N (1.68 g, 2.32 mL, 16.6 mmol) were added to a solution of 9 (2 g, 5.74 mol) in 29 mL of DMF. The reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was concentrated to approximately 1/3 of the initial volume. Upon addition of water to this DMF residue, a solid was formed. This solid was triturated with water, filtered, and dried under reduced pressure. Yield 80%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.82–3.01 (m, 4H), 6.11 (s, 2H), 6.97–7.07 (m, 2H), 7.38 (d, 1H, J = 1 Hz), 7.81 (s, 1H), 7.33–7.42 (m, 3H), 7.52 (s, 1H), 7.51 (d, 1H, J = 9 Hz), 8.15 (d, 1H, J = 9 Hz), 10.57 (s, 1H);

^{13}C NMR (DMSO-d_6, 300 MHz): δ 20.4, 29.7, 102.6, 107.9, 109.2, 115.2, 120.1, 120.5, 121.0, 126.9, 127.5, 128.1, 129.7, 133.7, 134.3, 137.1, 139.6, 142.4, 142.7, 148.4, 148.5, 148.7, 152.4, 162.3, 164.6; HRMS calcd for $C_{25}H_{18}Cl_2N_5O_4$ 522.0730, found 522.0709.

6.3.2. 8-{[(3,6-Dichloropyridin-2-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[g]indazole-3-carboxamide (13)

Same procedure as **12**, replacing HATU with HBTU. Yield 89%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.82–3.02 (m, 4H), 7.24–7.43 (m, 6H), 7.51–7.63 (m, 3H), 7.71 (d, 1H, J = 9 Hz), 10.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 20.5, 29.2, 115.0, 117.3 (d, J_{C-F} = 22.9 Hz), 120.1, 121.5, 126.8, 127.5, 128.0, 128.8 (d, J_{C-F} = 8.9 Hz), 129.8, 133.8, 136.8 (d, J_{C-F} = 3.3 Hz), 137.2, 139.7, 142.4, 143.2, 148.4, 152.5, 162.3, 162.7 (d, J_{C-F} = 243.4 Hz), 164.5; HRMS calcd for $C_{24}H_{17}Cl_2FN_5O_2$ 496.0738, found 496.0701.

6.4. Synthesis of 6-amino-3-chloropyridine-2-carboxamides by direct amination

6.4.1. 1-(1,3-Benzodioxol-5-yl)-8-({[3-chloro-6-(methylamino)-pyridin-2-yl]-carbonyl}-amino)-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (5a)

A mixture of 12 (1.042 g, 2.0 mmol) and *N*-methylamine (6 mL of 33 w% solution in EtOH) in 1 mL DMF was stirred for 5 days at 82 °C in a sealed tube. The volatiles were removed under reduced pressure and the resulting residue was purified by reverse phase preparative HPLC. Yield 28%. ^{1}H NMR (DMSO-d_6, 300 MHz,): δ 2.76 (d, 3H, J = 5.5 Hz), 2.84–3.99 (m, 4H), 6.16 (s, 2H), 6.57 (d, 1H, J = 9 Hz), 6.91–7.04 (m, 3H), 7.12 (d, 1H, J = 1 Hz), 7.22–7.34 (m, 3H), 7.46–7.54 (m, 2H), 10.19 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 20.4, 28.5, 29.7, 102.6, 108.0, 109.1, 111.8, 114.8, 114.9, 119.7, 120.5, 120.9, 126.8, 129.4, 129.5, 133.0, 134.4, 137.6, 139.4, 139.7, 142.7, 148.5, 148.6, 157.8, 163.9, 164.6; HRMS calcd for $C_{26}H_{22}ClN_6O_4$ 517.1386, found 517.1397.

6.4.2. 1-(1,3-Benzodioxol-5-yl)-8-{[(3-chloro-6-morpholin-4-ylpyridin-2-yl)carbonyl]-amino}-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (5b)

Same procedure as **5a**. Yield 52%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.91–3.00 (m, 2H), 3.11–3.20 (m, 2H), 3.44–3.53 (m, 4H), 3.82–3.91 (m, 4H), 5.41 (s, 1H), 6.74–6.86 (m, 2H), 6.90–7.04 (m, 2H), 7.16 (d, 1H, J = 1 Hz), 7.28–7.35 (m, 2H), 7.54–7.22 (m, 2H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.2, 29.8, 45.7, 66.6, 102.4, 107.7, 108.5, 111.4, 114.5, 119.3, 120.2, 121.2, 121.8, 126.8, 129.4, 133.6, 134.3, 136.2, 139.9, 141.7, 142.3, 148.7, 148.8, 156.1, 161.2, 164.7; HRMS calcd for $C_{29}H_{26}ClN_6O_5$ 573.1648, found 573.1646.

6.5. Synthesis of 6-amino-3-chloropyridine-2-carboxamides by coupling

6.5.1. 3-Chloro-6-morpholinyl-2-pyridine carboxylic acid hydrochloride (14)

A mixture of 3,6-dichloropyridine-2-carboxylic acid (**11**) (0.55 g, 2.86 mmol) and morpholine (1.37 g, 1.37 mL, 15.7 mmol) in 1.37 mL of *N*,*N*-dimethylacetamide (DMA) was stirred for 24 h at 80 °C. An additional volume of morpholine (1.36 g, 1.36 mL, 15.7 mmol) was added and the reaction mixture stirred at 80 °C for an additional 40 h. After cooling to room temperature, the volatiles were removed under vacuum in the presence of toluene. The residue was dissolved in water and washed with ether to remove the excess morpholine. The aqueous layer was acidified to pH 2 and the product extracted with ether. Crystallization from water afforded a white solid. Yield 53%. MS m/z ($M+1^+$) 243.

6.5.2. Potassium 3-chloro-6-(4-methylpiperazin-1-yl)pyridine-2-carboxylate (15)

A mixture of 3,6-dichloro-2-pyridine carboxylic acid (**11**) (0.60 g, 3.125 mmol) and *N*-methylpiperazine (7.2 g, 7.98 mL, 72 mmol) in 1 mL DMA was stirred at 95 °C for 3 days. The volatiles were removed under vacuum. The resulting residue was washed with a saturated solution of K_2CO_3 and with CH_2Cl_2. Three layers were formed. The middle layer was separated and the solvent removed under reduced pressure. The resulting solid was dried under reduced pressure in the presence of P_4O_{10}. Yield 96%. ^{1}H NMR (D_2O, 300 MHz): δ 2.18 (s, 3H), 2.43 (s, br, 4H), 3.37 (s, br, 4H), 6.77 (d, 1H, J = 9 Hz), 7.58 (d, 1H, J = 9 Hz); MS m/z ($M+1^+$) 256.

6.5.3. 8-{[(3-Chloro-6-morpholin-4-ylpyridin-2-yl)carbonyl]-amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (6b)

3-Chloro-6-morpholinyl-2-pyridine carboxylic acid (**14**) (0.294 g, 1.21 mmol), HBTU 0.385 g (1.2 mmol), and finally Et_3N (0.4 mL, 2.9 mmol) were added to a solution of **10** (0.258 g, 0.8 mmol) in 4 mL of DMF. The reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was concentrated to approximately 1/3 of the initial volume of the reaction mixture. Upon addition of water to this DMF residue, a solid was formed. This solid was triturated with water, filtered, and dried under reduced pressure. Yield 84%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.89–3.01 (m, 2H), 3.06–3.18 (m, 2H), 3.43–3.54 (m, 4H), 3.82–3.94 (m, 4H), 5.39 (s, 1H), 6.65–6.82 (m, 3H), 7.18–7.23 (m, 3H), 7.43–7.56 (m, 3H), 7.62 (m, 1H), 9.18 (s, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 20.1, 29.8, 45.6, 66.6, 111.5, 114.4, 116.7 (J_{C-F} = 23.3 Hz), 119.7, 122.4, 126.5, 128.1 (J_{C-F} = 9.2 Hz), 129.6, 133.7, 136.2, 136.5 (J_{C-F} = 1.9 Hz), 142.4, 142.7, 156.0, 158.0, 161.4, 161.5, 162.5, 162.6 (J_{C-F} = 246.2 Hz), 164.7; HRMS calcd for $C_{28}H_{25}ClFN_6O_3$ 547.1655, found 547.1574.

6.5.4. 1-(1,3-Benzodioxol-5-yl)-8-({[3-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl]-carbonyl}amino)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (5c)

Compound **5c** was obtained by the same procedure as **6b** after acidification of **15**. Yield 61% yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.70 (s, 3H), 2.72–4.30 (m, 12H), 6.02 (s, 2H), 6.92–7.12 (m, 4H), 7.22–7.36 (m, 3H), 7.42–7.53 (m, 2H), 7.77 (d, 1H, J = 9 Hz), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 20.4, 29.5, 43.5, 43.9, 53.3, 103.2, 108.6, 109.7, 111.8, 115.8, 118.0, 120.7, 121.2, 121.7, 127.6, 130.3, 134.0, 135.2, 138.4, 140.5, 141.4, 143.6, 149.4, 149.6, 149.8, 157.4, 164.7, 165.7; HRMS calcd for $C_{30}H_{29}ClN_7O_4$ 586.1964, found 586.1984.

6.5.5. 8-({[3-Chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl]carbonyl}amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (6c)

Same procedure as **5c**. Yield 88%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 2.31–2.39 (m, 4H), 2.84–2.88 (m, 4H), 3.41–3.51 (m, 4H), 6.94 (d, 1H, J = 9 Hz), 7.20 (d, 1H, J = 2 Hz), 7.25–7.40 (m, 4H), 7.48–7.60 (m, 4H), 7.62 (d, 1H, J = 9 Hz), 10.20 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 20.2, 29.9, 42.8, 43.4, 44.4, 52.9,110.6, 115.0, 116.1, 117.2 (J_{C-F} = 23.5 Hz), 120.0, 121.4, 126.6, 128.7 (J_{C-F} = 8.8 Hz), 129.6, 133.2, 136.8 (J_{C-F} = 2.8 Hz), 136.9, 137.6, 139.9, 140.1, 143.2, 148.9, 157.1,162.6 (J_{C-F} = 244.3 Hz), 163.9, 164.5; HRMS calcd for $C_{29}H_{27}ClFN_7O_2$ 560.1972, found 560.1960.

6.6. Synthesis of 2,5-dichloropyridine-4-carboxamides

6.6.1. 1-(1,3-Benzodioxol-5-yl)-8-[(2,5-dichloroisonicoti-noyl)-amino]-4,5-dihydro-1*H*-benzo-[*g*]indazole-3-carboxamide (17)

2,5-Dichloroisonicotinic acid (**16**) (1.65 g, 8.6 mmol), HATU (3.27 g, 8.6 mmol) and finally Et_3N (2.32 mL, 16.6 mmol) were

added to a solution of **9** (2 g, 5.74 mmol) in 29 mL of DMF. The reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was concentrated to about 10 mL of DMF. Upon addition of water to this DMF residue, a white solid was formed, which was triturated with water for 20 min and filtered. The solid was collected, dissolved in THF and dried over $MgSO_4$. Removal of the solvent afforded a brown solid, which was triturated in warm CH_3CN. Yield 73%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.90–2.92 (m, 4H), 6.09 (s, 2H), 6.94–7.04 (m, 2H), 7.12 (d, 1H, J = 2 Hz), 7.26–7.38 (m, 4H), 7.51 (s, 1H), 7.81 (s, 1H), 8.61 (s, 1H), 10.54 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 29.7, 102.6, 107.9, 109.1, 115.0, 120.0, 120.4, 121.0, 123.9, 126.9, 127.7, 129.6, 133.8, 134.3, 137.0, 139.5, 142.7, 146.7, 148.5, 148.6, 149.5, 150.3, 161.7, 164.5; HRMS calcd for $C_{25}H_{18}Cl_2FN_5O_4$ 522.0730, found 522.0725.

6.6.2. 8-[(2,5-Dichloroisonicotinoyl)amino]-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo-[*g*]indazole-3-carboxamide (18)

Same procedure as **17**. Crystallized from CH_3CN. Yield 73%. ^{1}H NMR (DMSO-d_6, 400 MHz): 2.86–2.91 (m, 4H), 7.18 (d, 1H, J = 0.9 Hz), 7.25 (s, 1H), 7.32–7.36 (m, 4H), 7.52–7.56 (m, 3H), 7.75 (s, 1H), 8.57 (s, 1H), 10.49 (s, 1H); 13C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 114.9, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 123.8, 126.7, 127.6, 128.6 (d, J_{C-F} = 9.1 Hz), 129.7, 133.9, 136.7 (d, J_{C-F} = 2.6 Hz), 137.0, 139.5, 143.2, 146.7, 149.5, 150.2, 161.7, 162.6 (d, J_{C-F} = 245.9 Hz), 164.4; HRMS calcd for $C_{24}H_{17}Cl_2FN_5O_2$ 496.0738, found 496.0759.

6.7. Synthesis of 2-amino-5-chloro-pyridine-4-carboxamides by direct amination

6.7.1. 1-(1,3-Benzodioxol-5-yl)-8-{[5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]-amino}-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (7a)

A mixture of 17 (1.2 g, 2.3 mmol) and *N*-methylpiperazine (4.6 mL, 46 mmol) was heated at 100 °C in a sealed tube for 24 h. After removal of the volatiles under vacuum, the residue was partitioned between water and CH_2Cl_2. The organic layer was washed an additional time with water and dried over $MgSO_4$. The crude product mixture was purified by chromatography on silica gel using CH_2Cl_2/MeOH = 12:1 to 10:2. Yield 46%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.18 (s, 3H), 2.34–2.35 (d, 2H, J = 5 Hz), 2.89–2.91 (m, 4H), 3.49 (d, 2H, J = 5 Hz), 6.08 (s, 2H), 6.91–7.03 (m, 3H), 7.1 (d, 1H, J = 2 Hz), 7.24–7.3 (m, 3H), 7.38–7.41 (dd, 1H, J = 8.3 Hz, 2 Hz), 7.49 (s, 1H), 8.13 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.2, 46.4, 54.9, 102.6, 106.6, 107.8, 109.1, 115.1, 115.4, 119.9, 120.3, 120.9, 126.8, 129.5, 133.4, 134.3, 137.5, 139.6, 142.7, 145.2, 147.5, 148.4, 148.6, 158.1, 163.9, 164.5; HRMS calcd for $C_{30}H_{29}ClN_7O_4$ 586.1964, found 586.1988.

6.7.2. 1-(1,3-Benzodioxol-5-yl)-8-[(5-chloro-2-piperazin-1-ylisonicotinoyl)amino]-4,5-dihydro-1*H*-benzo-[*g*]indazole-3-carboxamide (7b)

A mixture of **17** (1 g, 1.8 mmol) and piperazine (3 g, 36 mmol) in 4 mL EtOH was stirred at 95 °C for 24 h. After allowing the reaction mixture to cool down to room temperature, the volatiles were removed under vacuum. The residue was triturated with H_2O and finally with EtOH. Yield: 55%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.71 (s, br, 4H), 2.86–3.30 (m, 4H), 3.39 (s, br, 4H), 6.07 (s, 2H), 6.85 (s, 1H), 6.93–6.95 (dd, 1H, J = 8.2 Hz, 1.9 Hz), 7.00 (d, 1H, J = 8.2 Hz), 7.09 (d, 1H, J = 1.9 Hz), 7.24–7.30 (m, 3H), 7.38–7.41 (dd, 1H, J = 8.2 Hz, 1.74 Hz), 7.49 (s, 1H), 8.12 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 29.7, 45.9, 46.5, 102.6, 106.4, 107.8, 109.1, 115.0, 115.1, 119.9, 120.3, 120.9, 126.8, 129.5, 133.4, 134.3, 137.5, 139.6, 142.7, 145.2, 147.5, 148.4, 148.6, 158.4, 163.9, 164.5; HRMS calcd for $C_{29}H_{27}ClN_7O_4$ 572.1808, found 572.1782.

6.7.3. 8-[(5-Chloro-2-piperazin-1-ylisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8b)

Same procedure as **7b** at 100 °C for 24 h. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH. Yield: 53%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.67 (t, 4H, J = 4.9 Hz), 2.85–2.90 (m, 4H), 3.36 (t, 4H, J = 4.9 Hz), 6.80 (s, 1H), 7.18–7.19 (m, 1H), 7.25 (s, 1H), 7.27–7.35 (m, 3H), 7.37–7.39 (dd, 1H, J = 8 Hz, 2 Hz), 7.51–7.55 (m, 3H), 8.09 (s, 1H), 10.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 29.7,46.0, 46.5, 106.3, 115.0, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.7 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.1, 147.5, 158.4, 162.2 (d, J_{C-F} = 246 Hz), 163.9, 164.4; Anal. Calcd for $C_{28}H_{25}ClFN_7O_2$: C, 61.59; H, 4.62; N, 17.96. Found: C, 61.39; H, 4.69; N, 17.97.

6.7.4. 8-{[5-Chloro-2-(4-ethylpiperazin-1-yl)isonicotinoyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8c)

A mixture of 18 (0.89 g, 1.81 mmol) and 1-ethylpiperazine (2 g, 2.3 mL, 18.1 mmol) in 4.5 mL of DMA was stirred at 100 °C for 21 h. The mixture was poured into water, causing a precipitate to form, which was filtered and washed with water. This solid was dissolved in acetonitrile, dried over $MgSO_4$, and dried under vacuum. The product was slurried in acetonitrile, filtered, and washed with acetonitrile. Yield 75%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.99 (t, 3H, J = 7.2 Hz), 2.32 (q, 2H, J = 7.2 Hz), 2.38 (t, 4H, J = 4.9 Hz), 2.84–2.97 (m, 4H), 3.47 (t, 4H, J = 4.9 Hz), 6.87 (s, 1H), 7.20–7.21 (m, 1H), 7.27 (s, br, 1H), 7.30–7.38 (m, 3H), 7.40 (dd, 1H, J = 8.1 Hz, 2.0 Hz), 7.53–7.58 (m, 3H), 8.13 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 12.6, 20.3, 29.7, 45.4, 52.3, 52.7, 106.4, 115.0, 115.3, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.2, 147.5, 158.1, 162.6 (d, J_{C-F} = 245.7 Hz), 163.9, 164.4; HRMS calcd for $C_{30}H_{30}ClFN_7O_2$ 574.2128, found 574.2153.

6.7.5. 8-{[5-Chloro-2-(4-isopropylpiperazin-1-yl)isonicotinoyl]-amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8d)

Same procedure as **8c**. Yield 72%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.95 (d, 6H, J = 6.4 Hz), 2.44–4.47 (m, 4H overlapping with DMSO), 2.64 (sep, 1H, J = 6.4 Hz), 2.84–2.97 (m, 4H), 3.46 (t, 4H, J = 4.8 Hz), 6.86 (s, 1H), 7.20–7.21 (m, 1H), 7.27 (s, br, 1H), 7.30–7.38 (m, 4H), 7.41 (dd, 1H, J = 8.12 Hz, 2.0 Hz), 7.53–7.58 (m, 3H), 8.12 (s, 1H); 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 18.8, 20.3, 29.7, 45.7, 48.4, 54.4, 106.4, 114.9, 115.2, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.2, 147.5, 158.1, 162.6 (d, J_{C-F} = 246.5 Hz), 163.9, 164.4; HRMS calcd for $C_{31}H_{32}ClFN_7O_2$ 588.2285, found 588.2287.

6.7.6. 8-({5-Chloro-2-[4-(2-methoxyethyl)piperazin-1-yl]isonicotinoyl}amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (8e)

Same procedure as **8c**. The mixture was added to water causing a precipitate to form. This precipitate was filtered and washed with water. The solid was dissolved in THF, dried over $MgSO_4$, and dried under vacuum. The resulting solid was dissolved in EtOH, precipitated by addition of CH_3CN and finally triturated it in this solvent mixture. Yield 54%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.43–2.48 (m, 4H+3H overlapping with DMSO), 2.87–2.93 (m, 4H), 3.42 (t, 2H, J = 5.8 Hz), 3.46 (t, 4H, J = 4.7 Hz), 6.87 (s, 1H), 7.20–7.22 (m, 1H), 7.27 (s, br, 1H), 7.29–7.38 (m, 3H), 7.40 (dd, 1H, J = 8.2 Hz, 1.94 Hz), 7.53–7.58 (m, 3H), 8.12 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.3, 53.4, 57.7, 58.6, 70.6, 106.4, 114.9, 115.3, 117.2 (d, J_{C-F} = 23.2 Hz), 120.0, 121.4, 126.6,

128.6 (d, J_{C-F} = 8.9 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.4, 143.2, 145.2, 147.5, 158.1, 162.6 (d, J_{C-F} = 245.7 Hz), 163.9, 164.4; Anal. Calcd for $C_{31}H_{31}ClFN_7O_3$: C, 61.64; H, 5.17; N, 16.23. Found: C, 61.65; H, 5.22; N, 16.04.

6.7.7. 8-({5-Chloro-2-[(3*R*,5*S*)-3,4,5-trimethylpiperazin-1-yl]-isonicotinoyl}amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8f)

Same procedure as **7b** at 100 °C for 5 days. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH. Yield 77%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.01 (d, 6H, J = 12.3 Hz), 2.05 (m, br, 2H), 2.13 (s, 3H), 2.47–2.53 (2H, m, overlaps with DMSO), 2.88–2.93 (m, 4H), 4.11 (d, 2H, J = 12.3 Hz), 6.92 (s, 1 H), 7.21 (d, 1H, J = 2.0 Hz), 7.27 (s, 1H), 7.3–7.38 (m, 3H), 7.41 (dd, 1H, J = 8.2 Hz, 2.0 Hz), 7.54–7.58 (m, 3H), 8.11 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.3, 20.3, 29.7, 38.0, 51.9, 57.6, 106.3, 114.9, 115.0, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6, (d, J_{C-F} = 8.9 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.3, 147.4, 157.5, 162.6 (d, J_{C-F} = 246.0 Hz), 163.9, 164.4; HRMS calcd for $C_{31}H_{32}ClFN_7O_2$ 588.2285, found 588.2212.

6.7.8. 8-({5-Chloro-2-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8g)

Same procedure as **8c**. The solid was dissolved in CH_3CN, dried over $MgSO_4$, and the solvent stripped. Yield 88%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.97 (d, 6H, J = 6.3 Hz), 2.16–2.26 (m, 3H), 2.61–2.70 (m, 2H), 2.83–2.97 (m, 4H), 4.12 (dd, 2H, J = 1.9 Hz, 12.1 Hz), 6.87 (s, 1H); 7.21–7.22 (m, 1H), 7.28 (s, br, 1H), 7.30–7.39 (m, 3H); 7.41 (dd, 1H, J = 8.19 Hz, 2.01 Hz), 7.54–7.58 (m, 3H), 8.10 (s, 1H); 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.8, 20.3, 29.7, 50.7, 51.9, 106.3, 114.6, 114.9, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 9.3 Hz), 129.6, 133.4, 136.8, 137.5, 139.6, 143.2, 145.2, 147.4, 157.8, 162.6 (d, J_{C-F} = 245.7 Hz), 164.0, 164.4; HRMS calcd for $C_{30}H_{30}ClFN_7O_2$ 574.2128, found 574.2117.

6.7.9. 8-({5-Chloro-2-[(3*R*)-3,4-dimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1H-benzo[*g*]-indazole-3-carboxamide (8h)

Same procedure as **7b** at 100 °C for 4 days. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH. Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.0 (d, 3H, J = 6.17 Hz), 1.96–2.0 (m, 1H), 2.05–2.06 (m, 1H), 2.15 (s, 3H), 2.48–2.54 (m, 1H), 2.74 (d, br, 1H, J = 11.5 Hz), 2.85–2.93 (m, 4H), 4.01–4.09 (m, 2H), 6.89 (s, 1H), 7.21 (d, 1H, J = 2.0 Hz), 7.27 (s, 1H), 7.29–7.38 (m, 2H), 7.41 (dd, 1H, J = 8.2 Hz, 2.0 Hz), 7.53–7.58 (m, 2H), 8.11 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 17.2, 20.3, 29.7, 42.8, 45.4, 51.8, 55.2, 57.6, 106.4, 115.0, 115.2, 117.2 (d, J_{C-F} = 23.2 Hz), 120.0, 121.4, 126.6, 128.7 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.2, 147.5, 157.9, 162.6 (d, J_{C-F} = 246.0 Hz), 163.9, 164.4; HRMS calcd for $C_{30}H_{30}ClFN_7O_2$ 574.2128, found 574.2094.

6.7.10. 8-({5-Chloro-2-[(3*R*)-3-methylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8i)

Same procedure as **8c**. The solid was dissolved in acetonitrile, dried over $MgSO_4$, and the solvent stripped. Yield 72%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.97 (d, 3H, J = 6.2 Hz); 2.28–2.34 (m, 1H), 2.57–2.70 (m, 3H), 2.87–2.93 (m, 5 H), 3.29 (s, br, 1H), 4.05–4.09 (m, 2H), 6.85 (s, 1H), 7.20 (d, 1H, J = 1.8 Hz), 7.27–7.38 (m, 4H), 7.41 (dd, 1H, J = 8.2 Hz, 1.8 Hz), 7.53–7.58 (m, 3H), 8.11 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.9, 20.3, 29.7, 45.6, 45.7, 50.6, 52.6, 106.3, 114.8, 114.9, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 8.9 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 3.0 Hz), 137.5, 139.6, 143.2, 145.2, 147.5, 158.1, 162.2 (d, J_{C-F} = 245 Hz), 164.0, 164.4; HRMS calcd for $C_{29}H_{28}ClFN_7O_2$ 560.1972, found 560.1969.

6.7.11. 8-({5-Chloro-2-[(3*S*)-3,4-dimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (8j)

Same procedure as **7b** at 100 °C for 3 days. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH. Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.0 (d, 3H, J = 6.17 Hz), 1.96–1.98 (m, 1H), 2.02–2.09 (m, 1H), 2.16 (s, 3H), 2.48–2.54 (m, 1H), 2.74 (d, br, 1H, J = 11.7 Hz), 2.85–2.93 (m, 4H), 4.02–4.09 (m, 2H), 6.89 (s, 1H), 7.21 (d, 1H, J = 2.0 Hz), 7.27 (s, 1H), 7.29–7.38 (m, 2H), 7.41 (dd, 1H, J = 8.2 Hz, 2.0 Hz), 7.54–7.58 (m, 2H), 8.11 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 17.2, 20.3, 29.7, 42.8, 45.4, 51.8, 55.2, 57.6, 106.4, 115.0, 115.1, 117.2 (d, J_{C-F} = 23.2 Hz), 120.0, 121.4, 126.6, 128.7 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 3.0 Hz), 137.5, 139.6, 143.2, 145.2, 147.5, 157.9, 162.6 (d, J_{C-F} = 245.8 Hz), 163.9, 164.4; HRMS calcd for $C_{30}H_{30}ClFN_7O_2$ 574.2128, found 574.2098.

6.7.12. 8-({5-Chloro-2-[(3*S*)-3-methylpiperazin-1-yl]-isonicotinoyl}amino)-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]-indazole-3-carboxamide (8k)

Same procedure as **8c**. The solid was dissolved in acetonitrile, dried over $MgSO_4$, and the solvent stripped. Yield 66%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.98 (d, 3H, J = 6.3 Hz), 2.29–2.35 (m, 1H), 2.57–2.71 (m, 3H), 2.87–2.93 (m, 5H), 3.28 (s, br, 1H), 4.04–4.13 (m, 2H), 6.85 (s, 1H), 7.21 (d, 1H, J = 2 Hz), 7.27 (s, br, 1H), 7.29–7.38 (m, 3H), 7.41 (dd, 1H, J = 8.3 Hz, 2.0 Hz), 7.54–7.58 (m, 3H), 8.11 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.8, 20.3, 29.7, 45.5, 45.7, 50.6, 52.5, 106.3, 114.8, 114.9, 117.2 (d, J_{C-F} = 23.2 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.2, 147.4, 158.1, 162.6 (d, J_{C-F} = 245.9 Hz), 163.9, 164.4; HRMS calcd for $C_{29}H_{28}ClFN_7O_2$ 560.1972, found 560.1958.

6.7.13. 8-{[5-Chloro-2-(4-methyl-1,4-diazepan-1-yl)isonicotinoyl]-amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8l)

Same procedure as **7b** at 95 °C for 24 h. After allowing the reaction mixture to cool, the volatiles were removed under vacuum and the residue triturated with H_2O. Yield 71%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.81–1.83 (m, 2H), 2.21 (s, 3H), 2.41 (t, 2H, J = 5.5 Hz), 2.53 (t, 2H, J = 4.56 Hz), 2.87–2.93 (m, 4H), 3.53 (t, 2H, J = 5.5 Hz), 3.63–3.67 (m, 2H), 6.62 (s, 1H), 7.19 (d, 1H, J = 1.9 Hz), 7.27–7.38 (m, 4H), 7.42–7.45 (dd, 1H, J = 8.12 Hz, 1.88 Hz), 7.53–7.58 (m, 3H), 8.07 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.3, 27.4, 29.7, 46.6, 46.7, 47.1, 57.2, 57.8, 104.9, 113.7, 115.0, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 9.1 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 145.0, 147.5, 157.1, 162.6 (d, J_{C-F} = 245 Hz), 164.1, 164.4. Anal. Calcd for $C_{30}H_{29}ClFN_7O_2$: C, 62.77; H, 5.09; N, 17.08. Found: C, 62.52; H, 5.11; N, 17.11.

6.7.14. 8-{[5-Chloro-2-(1,4-diazepan-1-yl)isonicotinoyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8m)

Same procedure as **7b** at 100 °C for 24 h. The white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH. Yield 82%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.68–1.72 (m, 2H), 2.63 (t, 2H, J = 5.84 Hz), 2.79 (t, 2H, J = 5 Hz), 2.91–2.93 (m, 4H), 3.59 (t, 2H, J = 5 Hz), 3.64 (t, 2H, J = 5.84 Hz), 6.62 (s, 1H), 7.2 (d, 1H, J = 2 Hz), 7.28–7.4 (m, 4H), 7.44 (dd, 1H,

J = 8.2 Hz, 2 Hz), 7.55–7.60 (m, 3H), 8.08 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.5, 29.7, 46.7, 48.3, 48.9, 51.0, 105.0, 113.6, 115.0, 117.2 (d, J_{C-F} = 23.2 Hz), 120.0, 121.4, 126.6, 128.7 (d, J_{C-F} = 8.9 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 3.0 Hz), 137.5, 139.6, 143.2, 145.0, 147.6, 157.1, 162.6 (d, J_{C-F} = 245.8 Hz), 164.1, 164.4; HRMS calcd for $C_{29}H_{28}ClFN_7O_3$ 560.1972, found 560.1936.

6.7.15. 8-({5-Chloro-2-[[2-(dimethylamino)ethyl]-(methyl)amino] isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8n)

Same procedure as **7b** at 100 °C for 24 h. After removal of the volatiles under vacuum, the residue was partitioned between water and CH_2Cl_2. The organic layer was washed an additional time with water and dried over $MgSO_4$. The crude product mixture was purified by preparative HPLC. Yield 47%. ^{1}H NMR (DMSO-d_6, 400 MHz): 2.13 (s, 6H), 2.34 (t, 2H, J = 6.7 Hz), 2.87–2.95 (m, 4H), 2.96 (s, 3H), 3.59 (t, 2H, J = 6.7 Hz), 6.58 (s, 1H), 7.2 (d, 1H, J = 2 Hz), 7.27 (s, 1H), 7.29–7.37 (m, 3H), 7.41–7.44 (dd, 1H, J = 8 Hz, 2 Hz), 7.53–7.58 (m, 3H), 8.13 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 37.1, 46.1, 47.8, 56.8, 105.0, 113.8, 114.5, 117.2 (d, J_{C-F} = 23.3 Hz), 120.0, 121.4, 126.6, 128.6, 128.7 (d, J_{C-F} = 8.9 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.5, 139.6, 143.2, 144.9, 147.5, 157.4, 162.6 (d, J_{C-F} = 245 Hz), 164.1, 164.4; HRMS calcd for $C_{29}H_{30}ClFN_7O_2$ 562.2128, found 562.2120.

6.7.16. 8-[(5-Chloro-2-{[2-(dimethylamino)ethyl]amino}-isonicotinoyl)amino]-1-(4-fluoro-phenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8o)

Same procedure as **7b** at 100 °C for 24 h. The white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH and finally purified by reverse phase preparative HPLC. Yield 14%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.13 (s, 6H), 2.34 (t, 2H, J = 6.5 Hz), 2.87–2.92 (m, 4H), 3.29–3.30 (m, 2H), 6.49 (s, 1H), 6.78 (t, 1H, J = 5.3 Hz), 7.2 (d, 1H, J = 2 Hz), 7.27 (s, 1H), 7.29–7.40 (m, 4H), 7.53–7.58 (m, 3H), 7.99 (s, 1H), 10.3 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 39.4, 45.9, 58.7, 107.6, 113.7, 115.0, 117.2 (d, J_{C-F} = 22.8 Hz), 120.0, 121.4, 126.7, 128.7 (d, J_{C-F} = 9.3 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 3.0 Hz), 137.5, 139.6, 143.2, 144.4, 147.5, 158.1, 162.6 (d, J_{C-F} = 245.7 Hz), 164.0, 164.4; HRMS calcd for $C_{28}H_{28}ClFN_7O_2$ 548.1972, found 548.1934.

6.8. 2-Amino-5-chloropyridine-4-carboxamides by coupling with 2-amino-5-chlorocarboxylic acids

6.8.1. 5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinic acid hydrochloride (19)

A mixture of 2,5-dichloropyridine-4-carboxylic acid (**16**) (3 g, 0.0156 mol) and *N*-methylpiperazine (30.7 g, 0.30 mol) in 10 mL of DMA was stirred at 100 °C for 8 days. The volatiles were removed under vacuum. The resulting residue was washed with a saturated solution of K_2CO_3 and with CH_2Cl_2. The solvent was removed under vacuum and the resulting residue dissolved in the minimum amount of water, acidified to pH 1 with an aqueous solution of HCl (1 N) and washed with CH_2Cl_2. The product crystallized from the acidic aqueous layer upon standing at room temperature. Yield: 44%. ^{1}H NMR (D_2O, 300 MHz): δ 2.85 (s, 3H), 3.13 (t, 2H, J = 12.28 Hz), 3.34 (t, 2H, J = 14.3 Hz), 3.56 (d, 2H, J = 12.28 Hz), 4.18 (d, 2H, J = 14.3 Hz), 7.08 (s, 1H), 8.00 (s, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 43.1, 43.4, 52.54, 109.5, 117.6, 142.3, 147.9, 154.4, 169.5.

6.8.2. 5-Chloro-2-morpholin-4-ylisonicotinic acid (20)

A mixture of 2,5-dichloropyridine-4-carboxylic acid (**16**) (1.6 g, 0.0083 mol) and morpholine (10.9 g, 0.125 mol) in 4 mL of DMA was stirred at 80 °C for 4 days. The volatiles were removed under vacuum and the resulting yellow solid partitioned between water and Et_2O. The aqueous layer was acidified to pH 1.5 using an aqueous solution of HCl and extracted once with Et_2O and three times with CH_2Cl_2. The organic extracts were combined and the solvents removed under vacuum. The resulting yellow solid was crystallized from MeOH. Yield: 34%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.45 (t, 4H, J = 4.8 Hz), 3.67 (t, 4H, J = 4.8 Hz), 7.06 (s, 1H), 8.21 (s, 1H), 13.79 (s (br), 1H); ^{13}C HMR (DMSO-d_6, 75 MHz): δ 45.6, 66.4, 107.3, 116.1, 141.3, 148.3, 158.5, 166.8; MS m/z (M+1$^+$) 243.

6.8.3. 8-{[5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]-amino}-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8a)

5-Chloro-2-(*N*-methyl-piperazinyl)isonicotinic acid hydrochloride (**20**) (0.59 g, 2.02 mmol), HATU (0.755 g, 0.00198 mol) and finally Et_3N (1.09 mL, 0.0078 mol) were added to a solution of **10** (0.432 g, 0.00134 mol) in DMF (8 mL). The reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was concentrated to about 3 mL of DMF. Upon addition of water to this DMF residue, a white solid was formed, which was triturated with water for 20 min and filtered. The solid was collected, dissolved in THF and dried over $MgSO_4$. The crude material was purified by chromatography on a silica gel column (MeOH/CH_2Cl_2 = 1:12). Yield 40%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.17 (s, 3H), 2.33 (t, 4H, J = 4.8 Hz), 2.87–2.93 (m, 4H), 3.47 (t, 4H, J = 4.8 Hz), 6.87 (s, 1H), 7.2 (d, 1H, J = 1.9 Hz), 7.27 (s, 1H), 7.29–7.41 (m, 5H), 7.53–758 (m, 3H), 8.13 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.2, 46.4, 54.9, 106.5, 115.0, 115.3, 117.2 (d, J_{C-F} = 23.3 Hz), 120.0, 121.4, 126.6, 128.7 (d, J_{C-F} = 8.8 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 3.0 Hz), 137.5, 139.6, 143.2, 145.2, 147.5, 158.1, 162.6 (d, J_{C-F} = 245 Hz), 163.9, 164.4; HRMS calcd for $C_{29}H_{28}ClFN_7O_2$ 560.1972, found 560.1968.

6.8.4. 1-(1,3-Benzodioxol-5-yl)-8-[(5-chloro-2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (7p)

Same procedure as **8a**. Purified by trituration with Et_2O. Yield: 88%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.88–2.93 (m, 4H), 3.46 (t, 4H, J = 4.6 Hz), 3.66 (t, 4H, J = 4.6 Hz), 6.09 (s, 2H), 6.94 (s, 1H), 6.97 (d, 1H, J = 2 Hz), 7.02 (d, 1H, J = 8.2 Hz), 7.11 (d, 1H, J = 1.9 Hz), 7.25 (s, 1H), 7.29–7.32 (m, 2H), 7.39–7.42 (dd, 1H, J = 8.2 Hz, 2 Hz), 7.5 (s, 1H), 8.19 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.7, 66.5, 102.6, 106.6, 107.9, 109.1, 115.1, 115.9, 119.9, 120.4, 121.0, 126.8, 129.5, 133.4, 134.3, 137.5, 139.6, 142.7, 145.3, 147.5, 148.5, 148.6, 158.3, 163.8, 164.5, HRMS calcd for $C_{29}H_{26}ClN_6O_5$ 573.1648, found 573.1641.

6.8.5. 8-[(5-Chloro-2-morpholin-4-ylisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (8p)

Same procedure as **8a**. The crude solid was triturated with Et2O, EtOH and finally CH_3CN, filtered and dried under vacuum. Yield 82%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.80–2.95 (m, 4H), 3.42 (t, 4H, J = 5 Hz), 3.62 (t, 4H, J = 5 Hz), 6.88 (s, 1H), 7.17–7.21 (m, 1H), 7.23–7.41 (m, 5H), 7.49–7.58 (m, 3H), 8.14 (s, 1H), 10.31 (s, 1H); 13C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.7, 66.5, 106.5, 114.9, 115.8, 117.2 (d, J_{C-F} = 23.0 Hz), 120.0, 121.4, 126.6, 128.6 (d, J_{C-F} = 8.9 Hz), 129.6, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.4, 139.6, 143.2, 145.3, 147.5, 158.3, 162.6 (d, J_{C-F} = 247.6 Hz),164.4; HRMS calcd for $C_{28}H_{25}ClFN_6O_3$ 547.1655, found 547.1683.

6.8.6. 8-[(2-Chloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1*H*-benzo-[*g*]indazole-3-carboxamide (22)

2-Chloroisonicotinic acid (**21**) (2 g, 12.7 mmol), HATU (4.8 g, 12.63 mmol), and finally Et_3N (3 g, 4.2 mL, 30 mmol), were added

to a solution of **10** (2.72 g, 8.46 mmol) in 42 mL of DMF. The mixture was stirred at room temperature for 4 h. The crude reaction mixture was concentrated under vacuum. Upon addition of water to this DMF residue, a white solid was formed, which was triturated with water and filtered. The resulting solid was dissolved in CH_3CN, decolorized with activated carbon, dried over $MgSO_4$, and crystallized from CH_3CN. Yield 45%. ^1H NMR (DMSO-d_6, 400 MHz): 2.83–2.95 (m, 4H), 7.26 (s, 1H), 7.30–7.42 (m, 5H), 7.50–7.58 (m, 3H), 7.66 (dd, 1H, J = 5.1 Hz, 1.3 Hz), 7.78 (s, 1H), 8.53 (d, 1H, J = 5.1 Hz), 10.36 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 115.3, 117.2 (d, J_{C-F} = 23.2 Hz), 120.6, 121.4, 121.8, 122.8, 126.6, 128.6 (d, J_{C-F} = 9.1 Hz), 129.6, 133.8, 136.8 (d, J_{C-F} = 2.8 Hz), 137.4, 139.6, 143.2, 146.0, 151.3, 151.4, 162.6 (d, J_{C-F} = 245.9 Hz), 162.9, 164.4; HRMS calcd for $C_{24}H_{18}ClFN_5O_2$ 462.1128, found 462.1115.

6.8.7. 1-(4-Fluorophenyl)-8-{[2-(4-methylpiperazin-1-yl)-isonicotinoyl]amino}-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (23a)

A mixture of **22** (1 g, 2.17 mmol) and *N*-methylpiperazine (3.3 g, 3.64 mL, 32.9 mmol) in 5 mL DMA was stirred at 100 °C for 88 h. The crude reaction mixture was concentrated. Upon addition of water to this DMA residue, a solid was formed, which was triturated with water. The solid was dissolved in CH_3CN, decolorized with activated carbon, and dried over $MgSO_4$ before being crystallized from CH_3CN. Yield 42%. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.17 (s, 3H), 2.35 (t, 4H, J = 4.8 Hz), 2.82–2.95 (m, 4H), 3.47 (t, 4H, J = 4.8 Hz), 6.85 (d, 1H, J = 5.2 Hz), 7.01 (s, 1H), 7.25 (s, 1H), 7.25–7.30 (m, 2H), 7.33–7.38 (m, 2H), 7.40 (dd, 1H, J = 8.2 Hz, 1.7 Hz), 7.51–7.56 (m, 3H), 8.16 (d, 1H, J = 5.1 Hz), 10.10 (s, 1H); 13C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.2, 46.4, 55.0, 105.4, 11.2, 115.5, 117.1 (d, J_{C-F} = 23.0 Hz), 120.6, 121.3, 126.5, 128.6 (d, J_{C-F} = 9.1 Hz), 129.4, 133.3, 136.8 (d, J_{C-F} = 2.8 Hz), 137.7, 139.7, 143.2, 144.3, 148.9, 159.9, 162.6 (d, J_{C-F} = 245.7 Hz), 164.4, 165.1; HRMS calcd for $C_{29}H_{29}FN_7O_2$ 526.2361, found 526.2322.

6.8.8. 1-(4-Fluorophenyl)-8-[(2-morpholin-4-ylisonicotinoyl)-amino]-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxamide (23b)

Same procedure as for **23a** at 80 °C for 160 h followed by 100 °C for 172 h. The solid was crystallized from CH_3CN. Yield 38%. ^1H NMR (DMSO-d_6): δ 2.56–2.59 (m, 4H), 3.44 (t, 4H, J = 4.8 Hz), 3.66 (t, 4H, J = 4.8 Hz), 6.89 (d, 1H, J = 1.07 Hz), 6.9 (s, 1H), 7.01 (s, br, 1H), 7.25–7.30 (m, 2H), 7.33–7.38 (m, 2H), 7.4 (dd, 1H, J = 8.25 Hz, 1.9 Hz), 7.51–7.56 (m, 3H), 8.19 (d, 1H, J = 5.1 Hz), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3, 29.7, 45.7, 66.6, 105.4, 111.7, 115.5, 117.2 (d, J_{C-F} = 23.0 Hz), 120.6, 121.4, 126.5, 128.6 (d, J_{C-F} = 9.1 Hz), 129.5, 133.4, 136.8 (d, J_{C-F} = 2.8 Hz), 137.7, 139.7, 143.2, 144.4, 148.9, 160.0, 162.6 (d, J_{C-F} = 245.5 Hz), 164.4, 165.1; HRMS calcd for $C_{28}H_{26}FN_6O_3$ 513.2045, found 513.2054.

References and notes

1. (a) Tak, P. P.; Firestein, G. S. *J. Clin. Invest.* **2001**, *107*, 7; (b) Aradhya, S.; Nelson, D. L. *Curr. Opin. Gene Dev.* **2001**, *11*, 300; (c) Baldwin, A. S., Jr. *Annu. Rev. Immunol.* **1996**, *14*, 649.
2. Swenftleben, U.; Karin, M. *Crit. Care Med.* **2002**, *30*, S18.
3. Yin, M.-J.; Yamamoto, Y.; Gaynor, R. B. *Nature* **1998**, *396*, 77.
4. (a) Baxter, A.; Brough, S.; Faull, A.; Johnstone, C.; Mcinally, T.; PCT Int. Appl. WO 0158890 A1, 2001.; (b) Griffiths, D.; Johnstone, C. WO 0310158 A1, 2003.; (c) Baxter, A.; Brough, S.; Cooper, A.; Floettmann, E.; Foster, S.; Harding, C.; Kettle, J.; McInally, T.; Martin, C.; Mobbs, M.; Needham, M.; Newham, P.; Paine, S.; St-Gallay, St.; Salter, S.; Unitt, J.; Xue, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2817; (d) Bonafoux, D.; Bonar, S.; Christine, L.; Clare, M.; Donnelly, A.; Guzova, J.; Kishore, N.; Lennon, P.; Libby, A.; Mathialagan, S.; McGhee, W.; Rouw, S.; Sommers, C.; Tollefson, M.; Tripp, C.; Weier, R.; Wolfson, S.; Min, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2870.
5. (a) Kerns, J. K.; PCT Int. Appl. WO 2007076286 A2, 2007.; (b) Kerns, J. K.; Lindenmuth, M.; Lin, X.; Nie, H.; Thomas, S. M. PCT Int. Appl. WO 034317 A2, 2006.; (c) Deng, J.; Kerns, J. K.; Jin, Q.; Lin, G.; Lin, X.; Lindenmuth, M.; Neipp, C. E.; Nie Hong, T.; Sonia, M.; Widdowson, K. L. PCT Int. Appl. WO 005534 A2, 2007.
6. (a) Morey, J. V.; Christopher, J. A. PCT Int. Appl. WO 025575 A1, 2007.; (b) Christopher, J. A.; Avitabile, B. G.; Bamborough, P.; Champigny, A. C.; Cutler, G. J.; Dyos, S. L.; Grace, K. G.; Kerns, J. K.; Kitson, J. D.; Mellor, G. W.; Morey, J. V.; Morse, M. A.; O'Malley, C. F.; Patel, C. B.; Probst, N.; Rumsey, W.; Smith, Clive A.; Wilson, Michael J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3972; (c) Waelchli, R.; Bollbuck, B.; Bruns, C.; Buhl, T.; Eder, J.; Feifel, R.; Hersperger, R.; Janser, P.; Revesz, L.; Zerwes, H-G.; Schlapbach, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 108.
7. (a) Murata, T.; Sakakibara, S.; Yoshino, T.; Ikegami, Y.; Masuda, T.; Shimada, M.; Shintani, T.; Shimazaki, M.; Lowinger, T. B.; Ziegelbauer, K. B.; Fuchikami, K.; Umeda, M.; Komura, H.; Yoshida, N. WO 03024935 A2, 2002.; (b) Murata, T.; Shimada, M.; Sakakibara, S.; Yoshino, T.; Kadono, H.; Masuda, T.; Shimazaki, M.; Shintani, T.; Fuchikami, K.; Sakai, K.; Inbe, H.; Takeshita, K.; Niki, T.; Umeda, M.; Bacon, K. B.; Ziegelbauer, K. B.; Lowinger, T. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 913.
8. (a) Binghama, A. H.; Davenport, R. J.; Fosbeary, R.; Gowersa, L.; Knighta, R. L.; Lowea, C.; Owena, D. A.; Parrya, D. M.; Pitt, W. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3622; (b) Okamoto, Y.; Kubota, H.; Sato, I.; Hattori, K.; Kanayama, T.; Yokoyama, K.; Terai, Y.; Takeuchi, M. PCT Int. Appl. WO 100341 A1, 2005.; (c) Clare, M.; Hagen, T. J.; Houdek, S. C.; Lennon, P. J.; Weier, R. M.; Xu, X. PCT Int. Appl. WO 040133 A1, 2005.; (d) Bingham, A. H.; Davenport, R. J.; Fosbeary, R.; Gowers, L.; Knight, R. L.; Lowe, C.; Owen, D. A.; Parry, D. M.; Pitt, W. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3622.
9. Castro, A. C.; Dang, L. C.; Soucy, F.; Grenier, L.; Mazdiyasni, H.; Hottelet, M.; Parent, L.; Pien, C.; Palombella, V.; Adams, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2419.
10. Bamborough, P.; Barker, M. D.; Campos, A. A.; Cousins, R. C.; Faulder, P.; Hobbs, H.; Holmes, D. S.; Johnston, M. J.; Liddle, J. P.; Jeremy J.; Pritchard, J. M.; Whitworth, C. PCT Int. Appl. WO 2008034860 A1, 2008.
11. Belema, M.; Bunker, A.; Nguyen, V. N.; Beaulieu, F.; Ouellet, C.; Qiu, Y.; Zhang, Y.; Martel, A.; Burke, J. R.; McIntyre, K. W.; Pattoli, M. A.; Daloisio, C.; Gillooly, K. M.; Clarke, W. J.; Brassil, P. J.; Zusi, F. C.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4284.
12. Mbalaviele, Gabriel; Sommers, Cynthia D.; Bonar, Sheri L.; Mathialagan, Sumathy; Schindler, John F.; Guzova, Julia A.; Shaffer, Alexander F.; Melton, Michele A.; Christine, Lori J.; Tripp, Catherine S.; Chiang, Po-Chang; Thompson, David C.; Hu, Yiding; Kishore, Nandini *J. Pharmacol. Exp. Ther.* **2009**, *329*, 14.
13. Sommers, Cynthia D.; Thompson, Janice M.; Guzova, Julia A.; Bonar, Sheri L.; Rader, Randall K.; Mathialagan, Sumathy; Venkatraman, Neetu; Holway, Vicky Walker; Kahn, Larry E.; Hu, George; Garner, Debra S.; Huang, Horng-Chih; Chiang, Po-Chang; Schindler, John F.; Hu, Yiding; Meyer, Debra M.; Kishore, Nandini N. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 377.
14. Bergmanis, A. A.; Bonafoux, D.; Clare, M.; Crich, J. Z.; Fletcher, T. R.; Geng, L.; Hagen, T. J.; Hamper, B. C.; Hanson, G. J.; Houdek, S. C.; Huang, H.; Iula, D. M.; Koszyk, F. J.; Lennon, P. J.; Liao, S.; Liao, S.; Metz, S.; Mohler, S. B.; Nguyen, M.; Oburn, D. S.; Owen, T. J.; Partis, R. A.; Scates, A. M.; Stealey, M. A.; Tollefson, M. B.; Vazquez, M. L.; Weier, R. M.; Wolfson, S. G.; Xu, X. WO 200324935, 2003.
15. Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, *7*, 1371.
16. Kishore, N.; Huynh, Q. K.; Mathialagan, S.; Hall, T.; Rouw, R.; Creely, D.; Lange, G.; Caroll, J.; Reitz, B.; Donnelly, A.; Boddupalli, H.; Combs, R. G.; Kretzmer, K.; Tripp, C. S. *J. Biol. Chem.* **2002**, *277*, 13840.
17. Huynh, Q. K.; Boddupalli, H.; Rouw, S. A.; Koboldt, C. M.; Hall, T.; Sommers, C.; Hauser, S. D.; Pierce, J. L.; Combs, R. G.; Reitz, B. A.; Diaz-collier, J. A.; Weinberg, R. A.; Hodd, B. L.; Kilpatrick, B. F.; Tripp, C. S. *J. Biol. Chem.* **2000**, *275*, 25883.
18. Kishore, N.; Sommers, C.; Mathialagan, S.; Guzova, J.; Yao, M.; Hauser, S.; Huynh, K.; Bonar, S.; Mielke, C.; Albee, L.; Weier, R.; Graneto, M.; Hanau, C.; Perry, T.; Tripp, C. S. *J. Biol. Chem.* **2003**, *278*, 32861.