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Cdc7 Kinase Inhibitors: 5-Heteroaryl-3-Carboxamido-2-Aryl Pyrroles as Potential Antitumor Agents. 1. Lead Finding

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Cdc7 serine/threonine kinase is a key regulator of DNA synthesis in eukaryotic organisms. Cdc7 inhibition through *si*RNA or prototype small molecules causes p53 independent apoptosis in tumor cells while reversibly arresting cell cycle progression in primary fibroblasts. This implies that Cdc7 kinase could be considered a potential target for anticancer therapy. We previously reported that pyrrolopyridinones (e.g., **1**) are potent and selective inhibitors of Cdc7 kinase, with good cellular potency and in vitro ADME properties but with suboptimal pharmacokinetic profiles. Here we report on a new chemical class of 5-heteroaryl-3-carboxamido-2-substituted pyrroles (**1A**) that offers advantages of chemistry diversification and synthetic simplification. This work led to the identification of compound **18**, with biochemical data and ADME profile similar to those of compound **1** but characterized by superior efficacy in an in vivo model. Derivative **18** represents a new lead compound worthy of further investigation toward the ultimate goal of identifying a clinical candidate.

Introduction

The inhibition of DNA synthesis is a well-established strategy in the treatment of hyper-proliferative disorders.[1] However, the toxicity and tumor cell resistance associated with current DNA replication inhibitors[2] make the discovery of novel agents targeting this process by a different mechanism an urgent need. In eukaryotic cells, DNA synthesis is initiated by multiple origins of replication in the genome.[3] Cdc7[a] is a serine/threonine kinase that promotes the firing of the DNA replication origin by phosphorylating one or more subunits of the MCM DNA helicase complex (MCM2−7), thus leading to the unwinding of double-stranded DNA at the origins of replication.[4] In cells, phosphorylation of MCM2 at Ser40 and Ser53 is completely dependent on Cdc7 activity[5] and is essential for the initiation of DNA replication and cell growth.[6] Cdc7 inhibition via RNA interference or prototype small molecules causes tumor cells to enter apoptosis in a p53 independent manner while simply arresting cell cycle progression in normal cells.[7,8] Furthermore, Cdc7 levels are increased in many cancer cell lines and primary tumors, such as breast and lung cancers, compared to matched normal tissues, and this overexpression often correlates with a poor prognosis.[9,10] These findings suggest that alterations in Cdc7 protein abundance or activity may occur during tumor genesis and have important consequences for cell survival, thereby implying that Cdc7 kinase could be considered a target for anticancer therapy.[11]

Our group[12−14] and other investigators[15] have initiated a synthetic chemical effort to identify and characterize Cdc7 inhibitors. In our previous publications,[12,13] we reported on the structure−activity relationship studies and lead optimization effort around the pyrrolopyridinone chemical class, which proved to be a valuable core source of potent and selective Cdc7 kinase inhibitors. This chemotype, exemplified by compound **1** (Figure 1), is generally characterized by favorable physicochemical and in vitro ADME properties, moderate to good potency in cell proliferation assays, and has a known cellular mechanism of action. However, despite this promising profile, our best analogues selected for in-depth in vivo studies generally displayed a suboptimal pharmacokinetic behavior in animal species.

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[a]Abbreviations: Cdc7, cell division cycle 7; Cdk, cyclin-dependent kinase; TAO (or SULU), thousand and one amino acid protein; CK, casein kinase; GSK, glycogen synthase kinase; ATP, adenosine triphosphate MCM, minichromosome maintenance complex; ADME, adsorption-distribution-metabolism-excretion; PK, pharmacokinetics; CL, clearance; *V*ss, distribution volume; AUC, area under curve; *F*, oral bioavailability; PAMPA, parallel artificial membrane permeability assay; TGI, tumor growth inhibition; BrdU, bromodeoxyuridine; 5-FU, fluorouracil; *si*RNA, small interfering RNA; CDI, 1,1′-carbonyldiimidazole; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; HOBt NH_3, 1-hydroxybenzotriazole ammonium salt; DIEA, *N*,*N*-diisopropyl-*N*-ethylamine; MBHA, 4-methylbenzhydrylamine); TBTU, *O*-(benzotriazol 1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene.

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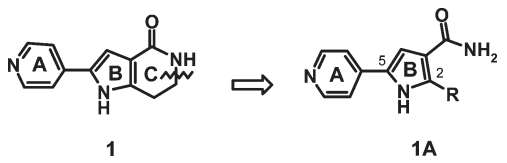
In light of these results, we decided to initiate a medicinal chemistry program with the goal of identifying a related chemical series with improved in vivo PK properties, which also maintains the attractive features typical of the pyrrolopyridinone chemical class.

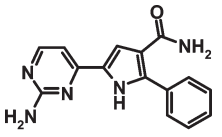
With compound **1** as a starting point, we extensively explored substitution patterns of rings A, B, and C as well as different lactam ring sizes. The opening of the lactam ring was envisioned as an attractive strategy which would offer a new point of diversity for medicinal chemistry intervention.

In fact, the evolution of compound **1A** from **1** implies the possibility of introducing a variety of different R-groups at the 2-position of the pyrrole (Figure 1), providing ease of chemical diversification as well as elimination of stereogenic centers associated with substitutions at the lactam ring.



1 **1A**

Figure 1. Evolution of the pyrrolopyridinone scaffold.



18

Figure 2. Compound **18** (see Table 3).

In this paper, we describe the expansion and development of this new series of 5-heteroaryl-3-carboxamido-2-substituted pyrrole derivatives, which identified new lead compounds. In particular, compound **18** (Figure 2) represents a novel prototype Cdc7 kinase inhibitor, with biochemical and ADME properties profile similar to those of compound **1** but characterized by far superior biological efficacy in in vivo models. In addition, this simple scaffold is amenable to broad optimization, considering the large number of derivatives easily accessible by either phenyl ring substitution or replacement through straightforward synthetic approaches.

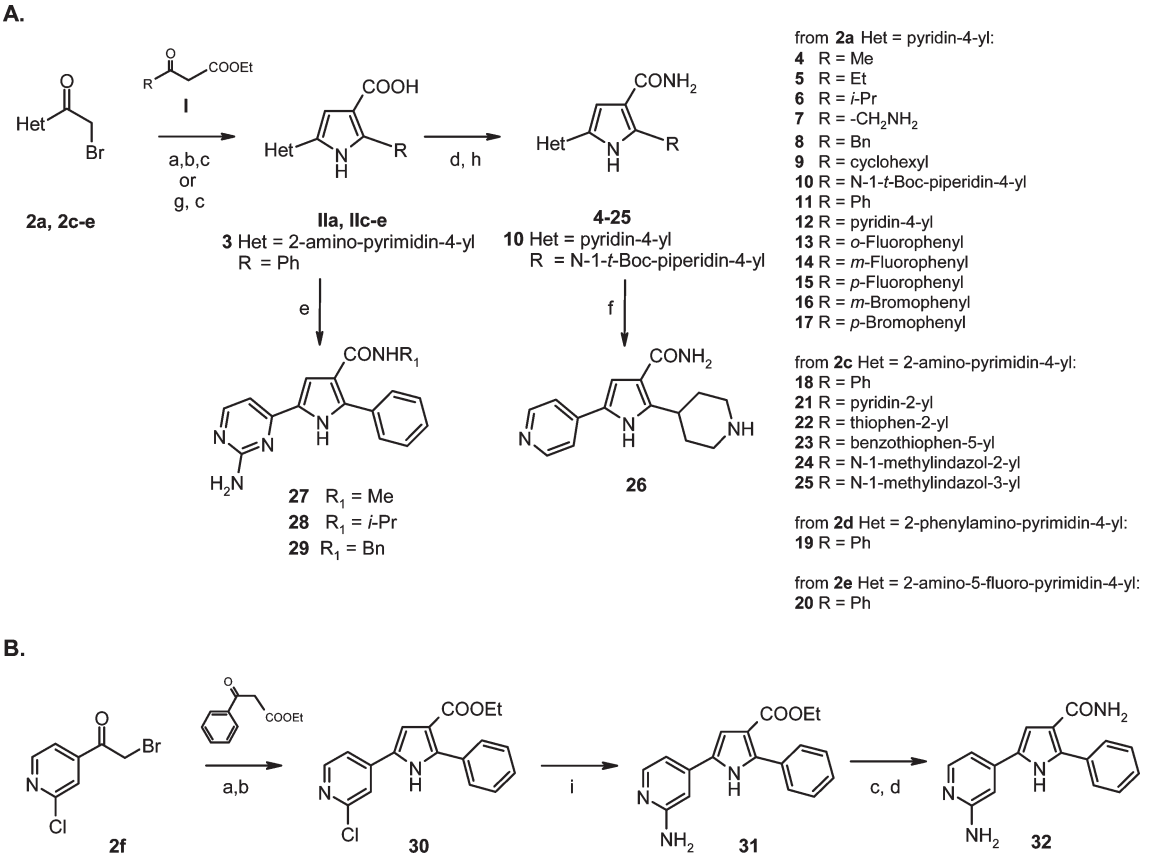
Chemistry

Our strategy for the formation of the pyrrole ring and the subsequent preparation of our target pyrrolecarboxamides is based on two protocols, namely the Hantzsch cyclization[16] and the pyrrole ring closure of α-cyano-γ-ketoesters to yield 2-halopyrroles, versatile starting materials for various synthetic transformations.

In particular, the Hantzsch synthesis of pyrroles was used to prepare compounds **4**−**29** (Scheme 1A) and compound **32** (Scheme 1B).

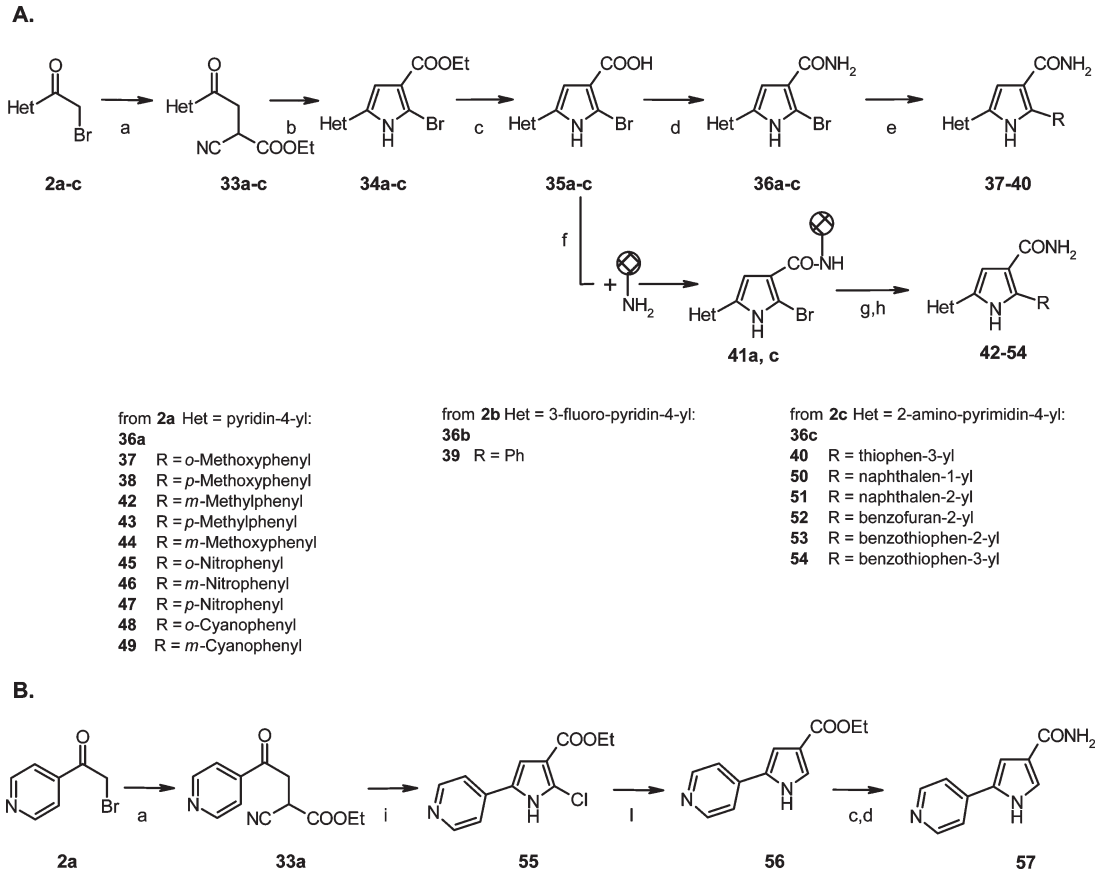
This procedure (Scheme 1A) generally implies the reaction of a series of heteroaromatic bromoketones (**2a**, **2c**−**e**) with

Scheme 1. Synthesis of 2-Substituted Pyrroles via Hantzsch Cyclization[a]



[a] Conditions: (a) NaH, THF or DMF, 0 °C to rt, β-keto ester; (b) NH_4OAc, EtOH, rt; (c) 4 M NaOH, EtOH, reflux or 1.5 M KOH/EtOH, reflux for Het = pyridin-4-yl and R = Me; (d) HOBt·NH_3, DIEA, EDC·HCl, THF, 0 °C to rt, or HOBt·NH_3, DIEA, TBTU, DMF, rt; (e) from **3**, CDI, DMF, 45 °C, then amine in EtOH, rt; (f) from **10**, 2 N HCl, MeOH, 50 °C; (g) methyl 3-aminocrotonate, DMF, rt for Het = pyridin-4-yl and R = Me; (h) 4 M HCl, dioxane, rt for obtaining **7** derived from **I** = 4-*tert*-butoxycarbonylamino-3-oxo-butyric acid ethyl ester; (i) $NH_2COOtBu$, Xantphos, $Pd(OAc)_2$, Cs_2CO_3, dioxane, 140 °C.

Scheme 2. Synthesis of 2-Aryl Pyrroles via α-Cyano-γ-ketoesters Cyclization and Suzuki Coupling[a]



[a] Conditions: (a) ethyl cyanoacetate, NaOEt, DIEA, THF, rt; (b) 33% HBr/AcOH, Et_2O, CH_2Cl_2, 0 °C to rt; (c) 4 M NaOH, EtOH, reflux; (d) HOBt·NH_3, DIEA, EDC·HCl, THF, 0 °C to rt; (e) $RB(OH)_2$, $(Ph_3P)_2PdCl_2$, LiCl, 1 M Na_2CO_3, toluene/EtOH, 100 °C; (f) Rink amide-MBHA resin, DMF, DIEA, EDC·HCl, HOBt, rt; (g) $RB(OH)_2$, $(PPh_3)_2PdCl_2$, LiCl, Cs_2CO_3, DMF/H_2O, 100 °C; (h) CF_3COOH, CH_2Cl_2, rt; (i) 4 N HCl/dioxane, Et_2O, 0 °C to rt; (l) $HCOONH_4$, 10% Pd−C, rt.

the sodium enolates of the appropriate β-ketoesters (general structure **I**) in the presence of ammonium acetate.

Once obtained, the esters were hydrolyzed to the corresponding carboxylic acid derivatives (general structures **IIa**, **IIc**−**e**) and in turn transformed into primary amides by means of hydroxybenzotriazole ammonium salt in the presence of a coupling reagent or with ammonium chloride and TBTU.[17] For the synthesis of compound **4**, methyl 3-amino crotonate replaced the β-ketoester in the Hantzsch cyclization step. Direct amination of the carboxylic esters upon heating with concentrated aqueous or methanolic ammonia proved unsuccessful. In a few cases, secondary amides were obtained by acid activation with 1,1′-carbonyldiimidazole and reaction with the appropriate primary amine in ethanol (**27**−**29**).

Compound **32** (Scheme 1B) was prepared from the 2′-chloro pyridinyl precursor **30**, obtained in turn via Hantzsch reaction with 3-oxo-3-phenylpropionic acid ethyl ester and α-bromoketone **2f**. One-step amination−deprotection reaction was accomplished with palladium acetate, using *t*-butyl carbamate as the aminating agent and Xantphos as the ligand, under controlled microwave heating.[18]

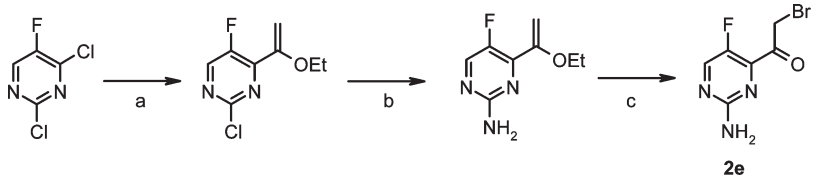
β-Ketoesters, when not commercially available, were prepared by applying the carboxylic acid homologation procedure. The acid was activated as the imidazolide and allowed to react with either commercial monoethylmalonate potassium salt[19] in the presence of magnesium chloride or ethyl hydrogen malonate and magnesium ethoxide.[20]

The alternative approach, based on the cyclization of α-cyano-γ-ketoesters to obtain the final compounds, exploits the reactivity of halogens at the position 2 of the pyrrole ring under different reaction conditions, such as the Suzuki coupling, which allows easy access to a variety of 2-aryl pyrroles. In fact, the action of hydrohalogenic acids in organic solvents on α-cyano-γ-ketoesters provided the 2-halo pyrroles[21] that were transformed into the final compounds **36a**, **37**−**40**, **42**−**54** (Scheme 2A), and into compound **57** (Scheme 2B).

As depicted in Scheme 2, the 2-bromo derivatives **34a**−**c** and the 2-chloro compound **55** were obtained upon treatment of the corresponding α-cyano-γ-ketoesters **33a**−**c** alternatively with hydrobromic and acetic acid in ethyl ether−dichloromethane solvent or with hydrochloric acid in dioxane. Compound **55** was subjected to hydrogenolytic conditions to finally achieve the 2-unsubstituted amide **57** (Scheme 2B), while the bromo derivatives **34a**−**c** were hydrolyzed to the corresponding carboxylic acids **35a**−**c** (Scheme 2A), which represented key intermediates both for solution and for solid phase synthesis of the final derivatives.

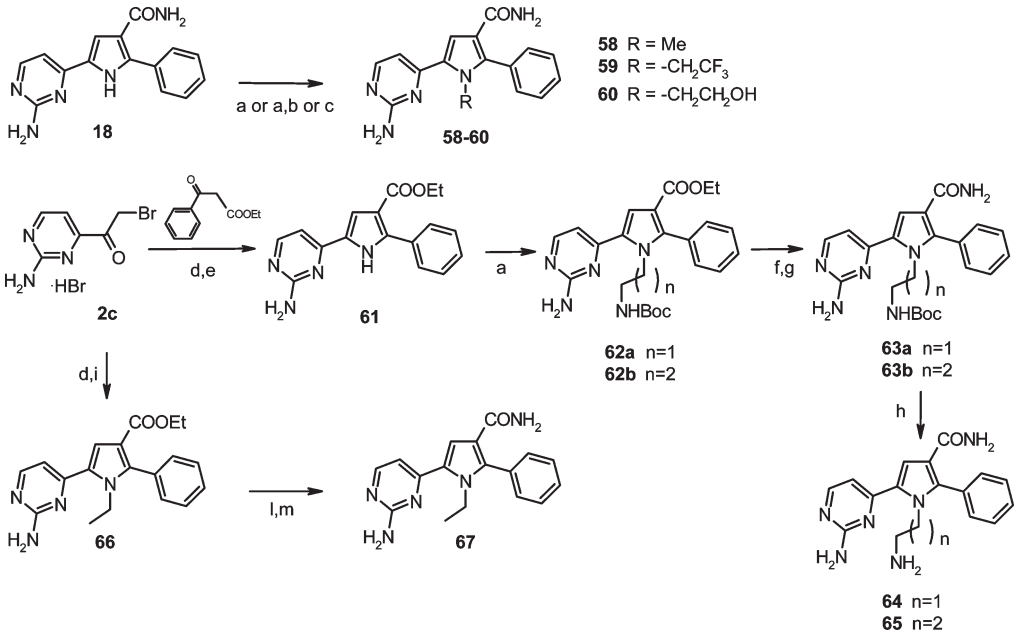
Subsequently, 2-bromo pyrroles **35a**−**c** were transformed into the amides **36a**−**c** and subjected to the Suzuki reaction, thus providing the corresponding 2-aryl pyrroles (Scheme 2A) under solution phase conditions (compounds **37**−**40**). In particular, the Suzuki coupling was carried out by heating the amides **36a**−**c** with commercially available boronic acids and bis(triphenylphosphine) palladium(II) dichloride. For solid phase reactions, Rink amide-MBHA resin[22] was allowed

Scheme 3. Synthesis of **2e**[a]



[a] Conditions: (a) tributyl(1-ethoxyvinyl)stannane, $(PPh_3)_2PdCl_2$, DMF, 70 °C; (b) 30% aq NH_4OH, EtOH, 100 °C; (c) NBS, THF/water, rt.

Scheme 4. Synthesis of *N*-Alkyl Pyrroles[a]



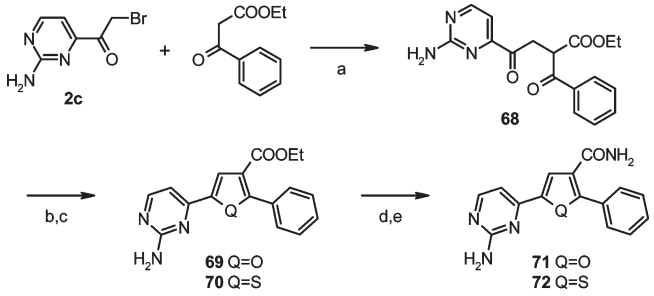
[a] Conditions: (a) alkyl halide, Cs_2CO_3, DMF, 85 °C (for **58** and **60**); (b) TFA, CH_2Cl_2, rt (for **60** deriving from alkyl halide = iodoethanol tetrahydropyranylether); (c) CF_3CH_2OTf, K_2CO_3, CH_3CN, 18-crown-6, reflux (for **59**); (d) NaH, ethyl benzoylacetate, THF, 0 °C to rt; (e) NH_4OAc, EtOH, rt; (f) LiOH, THF/MeOH/water, reflux; (g) NH_4Cl, DMA, DIEA, TBTU, 80 °C; (h) 4 M HCl in dioxane, rt; (i) $EtNH_2$, AcOH, microwaves, 170 °C; (l) 4 M NaOH, EtOH, reflux; (m) HOBt·NH_3, DIEA, EDC·HCl, THF, 0 °C to rt.

to react with the acids **35a**,**c** to provide intermediates **41a**,**c**, from which the products were cleaved with trifluoroacetic acid in dichloromethane at room temperature, directly yielding the primary amides **42**−**54**.

Bromoketones **2a**−**f**, used for both synthetic approaches, are either commercially available (**2a** and **2f**) or were accessed through halogenation of ketones[12,23] (**2b** and **2c**) or enolethers[12] (**2d** and **2e**). The synthesis of **2e** is described in Scheme 3. Commercially available 2,4-dichloro-5-fluoro-pyrimidine was allowed to react with tributyl(1-ethoxyvinyl)stannane in the presence of bis(triphenylphosphine) palladium(II) dichloride in *N*,*N*-dimethylformamide to afford the corresponding 4-vinyl ether. The amino group was introduced at position 2 upon treatment with aqueous concentrated ammonia in ethanol under heating with microwaves, and bromination of the resulting vinyl ether to α-bromo-ketone was accomplished with *N*-bromosuccinimide in aqueous tetrahydrofuran.

In Scheme 4, the preparation of *N*-alkylated pyrroles **58**−**60**, **64**, **65**, and **67** is outlined. Direct alkylation of amide **18** as well as of the intermediate ester derivative **61** with alkyl halides and cesium carbonate in *N*,*N*-dimethylformamide provided the corresponding derivatives **58**, **60**, **64**, and **65**. Compound **18** was treated instead with 2,2,2-trifluoroethyl trifluoromethanesulphonate, potassium carbonate, and crown-ether, providing compound **59**.

Scheme 5. Synthesis of **71** and **72** Analogues[a]

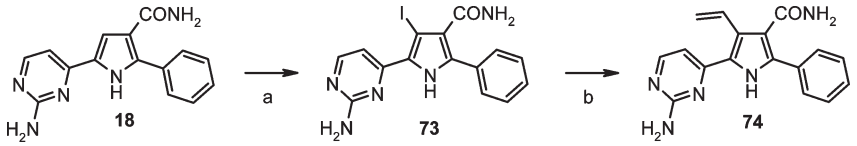


[a] Conditions: (a) NaH, THF, 0 °C to rt; (b) Lawesson's reagent, toluene, reflux; (c) chromatography; (d) 4 M NaOH, EtOH, water, reflux; (e) HOBt·NH_3, DIEA, EDC·HCl, THF, 0 °C to rt.

A different approach was exploited for the preparation of the *N*-ethyl derivative **67**, based on the use of ethylamine in the Hantzsch pyrrole ring formation reaction.

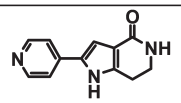
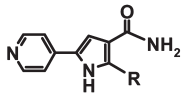
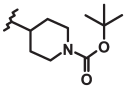
The furan and thiophene analogues **71** and **72** were simultaneously prepared through the Paal−Knorr condensation synthesis[24] (Scheme 5) by exposing 1,4-diketone **68** to the action of the Lawesson's reagent in toluene at reflux temperature. The mixture of the two homologues could be separated easily by flash chromatography.

Scheme 6. Synthesis of **74**[a]



[a] Conditions: (a) NIS, DMF, rt; (b) tributylvinyl stannane, 2,6-dimethyl-4-*tert*-butyl phenol, $Pd(PPh_3)_4$, dioxane, DMF, 110 °C.

Table 1. SAR: Opening the Lactam Ring (IC_{50}, μM)[a]

Cpd #		Cdc7
1		0.010±0.004
		
	R	
4		0.516 ± 0.105
5		0.482 ± 0.090
6		0.463 ± 0.009
7		4.8
8		0.859 ± 0.087
9		0.293 ± 0.076
10		>10
11		0.009 ± 0.003
12		0.200 ± 0.008
26		1.3
36a	Br	0.197 ± 0.022
57	H	0.280 ± 0.069

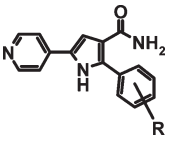
[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$).

Compound **18** was variously halogenated as described elsewhere[25] to obtain derivatives **73** and **75**−**77**. The 4-iodo pyrrole derivative **73** was in turn transformed into the 4-allyl derivative **74** by vinylation via the Stille cross-coupling reaction protocol.[26] The reaction occurred by heating **73** with tributylvinylstannane in the presence of tetrakis(triphenylphosphine)palladium(0) in dioxane/DMF (Scheme 6).

Results and Discussion

As we mentioned earlier, the opening of the lactam ring was the first step toward the design of a novel chemical series of Cdc7 kinase inhibitors based on the 5-heteroaryl-3-carboxamido-2-substituted pyrrole template.

Table 2. SAR: Variations of Aryl Substituent R (IC_{50}, μM)[a]



compd	R	Cdc7	A2780[b]	compd	R	Cdc7	A2780[b]
11	H	0.009 ± 0.003	2.0	**37**	o-OMe	0.126 ± 0.011	6.5
13	o-F	0.008 ± 0.004	1.5	**44**	m-OMe	0.058 ± 0.029	7.3
14	m-F	0.023 ± 0.014	2.4	**38**	p-OMe	0.023 ± 0.007	2.6
15	p-F	0.014 ± 0.006	2.5	**45**	o-NO_2	0.039 ± 0.019	2.3
16	m-Br	0.056 ± 0.021	2.0	**46**	m-NO_2	0.044 ± 0.016	9.2
17	p-Br	0.073 ± 0.028	1.2	**47**	p-NO_2	0.117 ± 0.051	>10
42	m-Me	0.162 ± 0.155	4.9	**48**	o-CN	0.131 ± 0.054	2.8
43	p-Me	0.060 ± 0.010	1.8	**49**	m-CN	0.216 ± 0.042	>10

[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

In the absence of the crystallographic structure of the target protein, we used a homology model of Cdc7 kinase based on Cdk2 kinase, as reported in our previous publications.[12,13] The docking studies and the SAR of the pyrrolopyridinone series correlates well with a binding mode where the nitrogen of the pyridyl ring accepts a hydrogen bond from the hinge region, while the lactamic moiety forms hydrogen bonds between the carbonyl and the conserved lysine residue and between the NH and the conserved aspartate via electrostatic interaction. In the present work, we therefore assumed a similar binding mode and orientation in the ATP pocket also within this novel series of compounds.

The first set of compounds prepared maintained the primary amide and were varied only at position 2 of the pyrrole, with substituents spanning from hydrogen to larger alkyl and aromatic groups (Table 1).

The data in Table 1 clearly prove that the tolerance toward the different substitutions is very limited, as only the phenyl derivative **11** retained good activity on Cdc7 kinase, comparable to that of our reference compound **1**. Moving from phenyl to cyclohexyl and 4-pyridyl analogues **9** and **12**, respectively, the potency dropped nearly 20- to 30-fold, as for the unsubstituted compound **57** and the bromo derivative **36a**. The alkyl derivatives **4**−**6** suffered a 50-fold decrease in potency, whereas the amino derivatives **7**, **10**, and **26** displayed an even greater loss of activity, showing IC_{50} values in the micromolar range. Finally, the benzyl analogue **8** also proved to be much less active, nearly 90-fold with respect to compound **11**.

Given the excellent potency as well as good selectivity over Cdk2 demonstrated by compound **11**, we decided to investigate a possible structural interpretation. As judged from a preliminary modeling analysis, the phenyl derivative **11** looked particularly interesting compared to the other derivatives in Table 1 because it showed a potentially favorable binding mechanism to Cdc7 kinase. A T-shaped interaction between

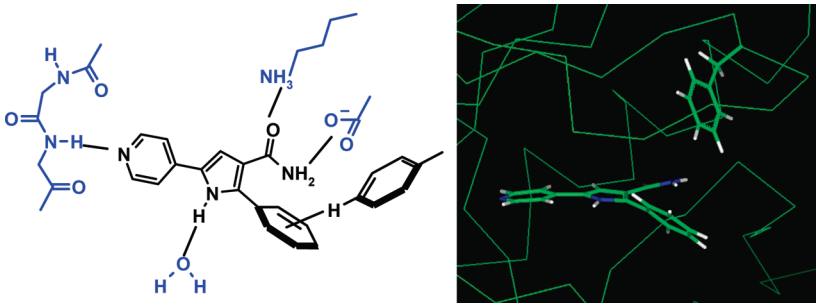
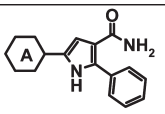
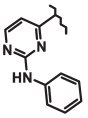
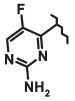
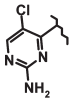
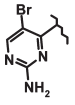


Figure 3. Predicted binding mode of compound **11** in the Cdc7 kinase homology model.

Table 3. SAR: Variations of Ring A (IC_{50}, μM)[a]



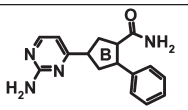
Cpd #	A	Cdc7	A2780[b]	IC_{50}<100 nM on:
11		0.009 ± 0.003	2.0	
18		0.022 ± 0.013	0.8	
19		0.053 ± 0.035	1.8	GSK3β
20		0.018 ± 0.013	0.2	
32		0.136 ± 0.079	>10	
39		0.008 ± 0.003	0.5	GSK3β
75		0.005 ± 0.001	0.2	SULU1, CK2
76		0.002 ± 0.001	0.11	SULU1, CK2, Cdk2/A

[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

the phenyl R group of the ligand and the phenylalanine of the glycine-rich loop appeared feasible (Figure 3).[27] Cdk2 kinase would be unable to perform such interaction, having a tyrosine residue at that position. In fact, the two front-runners **1** and **11** are equipotent against the Cdc7 kinase (Cdc7 IC_{50} = 0.010 μM and Cdc7 IC_{50} = 0.009 μM, respectively), but **11** is 5 times more selective over Cdk2/CycA kinase (Cdk2/CycA IC_{50} = 0.240 μM for **1** and Cdk2/CycA IC_{50} = 1.1 μM for **11**). The same ratio holds true in the aminopyrimidinyl series, (e.g., **18**) when compared to its lactamic homologue.

This binding hypothesis is confirmed by the weaker activity of derivatives **4**−**7**, **9**, **10**, **26**, **36a**, and **57** due to the lack of the aromatic moiety at position 2 of the pyrrole nucleus. Furthermore, this model explains the poor activity of compound **8**, where the conformational freedom of the benzyl substituent disfavors an efficient interaction between the phenyl ring of the ligand and the phenyl ring of the phenylalanine residue. The reduced activity of compound **12** can be explained by the desolvation penalty of burying the pyridine in a clearly hydrophobic pocket. In the docking studies, molecules of

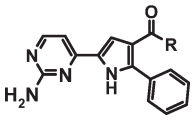
Table 4. SAR: Variations of the Central Core B (IC_{50}, μM)



Cpd #	B	Cdc7	A2780[b]
18		0.022 ± 0.013	0.8
71		0.640 ± 0.213	8
72		0.410 ± 0.167	6.3
73		0.052 ± 0.018	0.14
74		1.146 ± 0.431	3.9
77		0.038 ± 0.014	0.12

[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

Table 5. SAR: Variations of Side Chain R (IC_{50}, μM)[a]



compd	R	Cdc7	A2780[b]
3	OH	0.090 ± 0.007	> 10
18	NH_2	0.022 ± 0.013	0.8
27	NHMe	> 10	7.2
28	NH*i*Pr	> 10	> 10
29	NHBn	> 10	> 10

[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

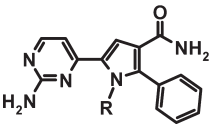
water were included in the binding site as they might play an important role in the binding of compound **11** and its close analogues.

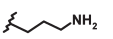
Having established the importance of a 2-phenyl substituent for the activity against Cdc7 kinase, we decided to investigate the role of the substitution pattern on the aromatic ring.

As illustrated in Table 2, a clear trend in terms of electronic influence does not emerge, and only the small fluorine atom seems to give an activity comparable to that of the unsubstituted derivative **11**, in particular for the ortho regioisomer **13**. This might suggest that the steric hindrance of the substituent might affect unfavorably the potency of the compound despite a potentially good contribution to the T-shaped interaction.

On the other hand, the good potency of most of these compounds in the biochemical assay was counterbalanced by a disappointing micromolar activity in the A2780 cellular assay, making them not appealing for additional studies.

Table 6. SAR: Variations of the Pyrrole *N*-Substituent (IC_{50}, μM)[a]



Cpd #	Cdc7	R	A2780[b]
18	0.022 ± 0.013	H	0.8
58	0.140 ± 0.093		2.3
67	0.040 ± 0.017		0.5
59	0.036 ± 0.022		3.5
60	0.456 ± 0.317		>10
64	0.530 ± 0.102		>10
65	0.793 ± 0.389		>10

[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

Another important site for exploration is ring A, which models suggest interacts with the hinge region of the ATP binding site. For this reason, we replaced ring A of compound **11** with other nitrogen containing heterocycles able to form or even improve the hydrogen bonding interaction with the hinge region.

Table 3 summarizes the biochemical data on Cdc7 kinase, antiproliferative activity against A2780 cell lines, and the main cross-reactivities against a panel of 51 tyrosine and serine−threonine kinases.

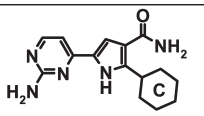
The addition of an amino group onto the pyridyl ring (compound **32**) able to form additional H-bond interactions, has a detrimental effect on the activity both in biochemical and cellular assay. On the contrary, the replacement of the pyridyl ring with an amino-pyrimidinyl heterocycle, as in compound **18**, has a minor impact on potency but provides submicromolar cellular potency in the proliferation assay. The introduction of a phenyl ring on the amino group (compound **19**) has instead a moderately negative effect on the biochemical and cellular potency and also affects selectivity, as GSK3β represents the main target affected in the double-digit nanomolar range.

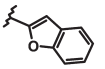
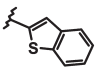
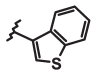
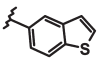
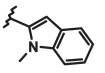
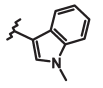
Addition of halogens on the heterocyclic ring in compounds **20**, **39**, **75**, and **76** generally leads to an improvement of potency and cellular activity, however, all these derivatives, except **20**, display a less satisfactory selectivity profile. The outstanding impact of the 2-aminopyrimidinyl residue on the cell based assay prompted us to maintain this residue in all subsequent derivatives.

Modifications of the central core B were also explored (Table 4). Whereas the halogen substituted derivatives **73** and **77** proved to still be active and very potent in A2780 cells, a vinyl group at that position is deleterious (compound **74**). When the central nucleus was replaced with either a furan or a thiophene ring (compounds **71** and **72**, respectively) a considerable loss of activity was observed both in the biochemical and in the cellular assay.

Next we focused our attention on the carboxamido group (Table 5). As already mentioned, we knew from our previous studies on the pyrrolopyridinone series that the lactamic moiety should participate in relevant interactions with the

Table 7. SAR: Variations of Aromatic Ring C (IC_{50}, μM)[a]



Cpd #	C	Cdc7	A2780[b]	Cpd #	C	Cdc7	A2780[b]
18		0.022 ± 0.013	0.8	**52**		0.658 ± 0.257	3.7
21		0.412 ± 0.294	1.8	**53**		0.114 ± 0.038	2.5
22		0.022 ± 0.008	0.26	**54**		0.068 ± 0.029	1.7
40		0.039 ± 0.011	0.5	**23**		0.082 ± 0.017	0.35
50		0.325 ± 0.094	3.6	**24**		0.090 ± 0.032	0.1
51		0.269 ± 0.164	2.7	**25**		0.068 ± 0.011	0.4

[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

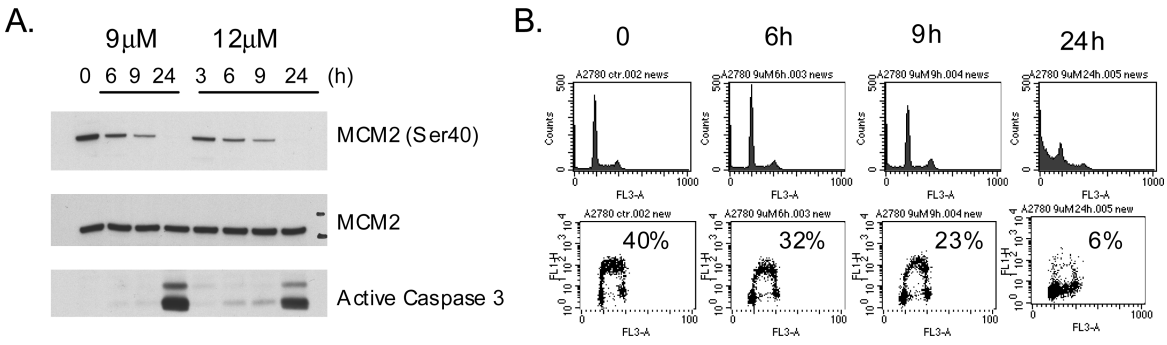


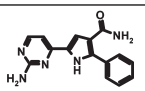
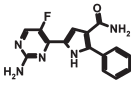
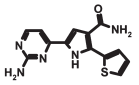
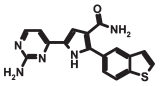
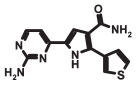
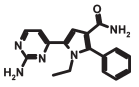
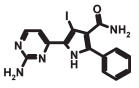
Figure 4. (A) In vitro mechanism of action (MoA) of compound **18**. A2780 cells were incubated for up to 24 h with 9 and 12 μM concentrations of **18**. Proteins were prepared and analyzed by Western blot. Phosphorylation status of MCM2 protein at Cdc7-dependent (Ser-40) phosphosite was assessed using specific antiphosphopeptide antibody. Detection of cleaved active caspase 3 indicates that cells are undergoing apoptotic cell death. (B) DNA synthesis and BrdU incorporation analysis in A2780 cells treated with compound **18**. Logarithmically growing A2780 cells were treated for the indicated times with 9 μM **18** and labeled with BrdU before fixation. DNA content and BrdU positive cells (%) were measured by FACS.

conserved lysine and aspartate residues. As expected, the lactamic ring-opening did not affect the activity on Cdc7 kinase in the case of the primary amide (compound **18**). However when secondary amides were tested (compounds **27**−**29**), a complete loss of activity has been observed likely as a result of the syn conformation adopted by the substituted amide bond with respect to the anti conformation of the lactam, thus hampering efficient H-bond interactions. The acid derivative **3** is still active against Cdc7 kinase in the nanomolar range, but it is devoid of cellular activity possibly due to poor cell permeability.

Further substitutions on the pyrrole nitrogen were considered (Table 6), in particular the alkylation of the pyrrole nitrogen. At first, the insertion of the small methyl group (compound **58**) was checked and found to be detrimental to Cdc7 kinase inhibitory activity. Not surprisingly, the ethyl derivative **67** performed much better both in the biochemical and in the cellular assay compared to **58**, enforcing the trend already observed with the pyrrolopyridinones class.[12] The trifluoroethyl derivative **59** still maintained a good activity on Cdc7 but was poorly active in cells, and variations of the ethyl group such as hydroxyethyl, aminoethyl, and aminopropyl substitutions in compounds **60**, **64**, and **65** were all unsuccessful in terms of biochemical and cellular activity.

Because the aminopyrimidinyl ring A, the 4-unsubstituted-pyrrolyl ring B, and the primary carboxamido group (Figure 1) emerged as promising structural moieties to achieve satisfactory biological activity, we maintained this core structure in undertaking further study of substituent R. In this work, we mainly focused on heteroaromatic groups. It is evident from the data in Table 7 that compounds **22**−**25** and **40** show a good combination of Cdc7 kinase inhibition and cellular

Table 8. In Vitro ADME Parameters of Selected Derivatives

Cpd	Structure	Solubility	Permeability	PPB	Cl int
#		pH 7 (μM)	PAMPA Papp [10^{-6}cm/s] (% in membrane)	(%)	(mL/min/Kg) rat hepatocytes
18		179	6.0 (3)	64	12
20		>225	4.7 (13)	68	19
22		>225	7.6 (2)	68	40
23		149	21.2 (25)	94	70
40		124	6.3 (22)	68	361
67		207	18.6 (6)	78	74
73		>225	8.5 (0)	77	186

activity. All other compounds displayed an unsatisfactory inhibitory activity on Cdc7 kinase and/or a poor cellular potency.

The biochemical data confirmed the importance of an aromatic substituent for good activity and a strong preference for phenyl bioisosters, in particular the thiophenyl derivatives **22** and **40**. The disappointing biochemical activity of the 2′-pyridinyl compound **21** is also in line with the previous observation on 4′-pyridinyl analogue **12**.

The study of the mechanism of action in A2780 cells of those compounds, which best performed in terms of biochemical potency, selectivity profile, and cellular activity, in particular compounds **18**, **20**, **22**−**25**, **40**, **67**, **73**, and **77**, permitted further prioritization. Therefore the capacity of these inhibitors to halt the cell cycle and DNA synthesis by bromodeoxyuridine (BrdU) incorporation block, to down-modulate the Ser40 phosphorylation of MCM2 substrate, and to induce cleaved caspase 3, was evaluated.[13]

Despite the good cellular activity of derivatives **24**, **25**, and **77**, their mechanism of action could not be clearly elucidated in vitro and thus they have not been investigated further. However, the antiproliferative activity of the other analogues was demonstrated to be correlated with the inhibition of cellular Cdc7 kinase, as exemplified by the data for compound **18** (Figure 4).

In Figure 4A, the inhibition of Ser40 phosphorylation of the MCM2 substrate was evaluated in a time-course experiment at different compound concentrations. Both at 9 μM and at 12 μM, the inhibition was complete at 24 h. In panel B, the cell cycle profile was studied on A2780 cells, using fluorescence-activated cell sorting. Cell population peaks showed a G1/S block and a strong decrease of bromodeoxyuridine incorporation (from 40% to 6%) indicated an impairment of DNA synthesis in the cells. Both caspase 3 activation and sub-G1 accumulation demonstrated that cells treated with compound **18** were undergoing apoptosis.

Solubility, permeability, plasma protein binding, and intrinsic clearance in rat hepatocytes data (in vitro ADME properties) of the most interesting compounds **18**, **20**, **22**, **23**, **40**, **67**, and **73** are summarized in Table 8.

Most compounds showed good to excellent solubility at neutral pH, moderate permeability in the PAMPA assay, and modest plasma protein binding. The intrinsic clearance, evaluated in rat hepatocytes, ranges in most cases from low to moderate but is clearly higher for compounds **40** and **73**, and these data were confirmed by their high in vivo clearance value. For all these compounds, in vitro profiles were considered acceptable and PK was evaluated in mice (Table 9).

Table 9 reports the main in vivo PK parameters of the previously described derivatives, measured after iv and per os administration. Among them, compounds **20**, **40**, and **73** were judged unsatisfactory. In particular, compound **20** shows very short per os half-life, low exposure, and modest bioavailability. Compound **73** is characterized by the worst clearance and exposure values, making it unsuitable for oral administration. Compound **40** also displays modest per os exposure and a

Table 9. In Vivo ADME Parameters of Selected Derivatives (Harlan nu/nu Mice)[a]

	PK data (iv), dose[b]: 10 mg/kg					PK data (per os), dose[b]: 10 mg/kg				
compd	C_{max} (μM)	AUC∞ (μM·h)	CL (mL/min/kg)	Vss (mL/kg)	$t_{1/2}$ (h)	C_{max} (μM)	T_{max} (h)	AUC∞ (μM·h)	$t_{1/2}$ (h)	F[c] (%)
18	30.0 ± 0.2	11.6 ± 0.7	50.0 ± 2.7	560.0 ± 33.0	0.16	5.2 ± 1.9	0.25	3.8 ± 1.1	0.8	31
20	24.7 ± 6.1	11.3 ± 3.3	33.5 ± 11.8	485.0 ± 143.0	0.18	4.5 ± 0.8	0.25	2.1 ± 0.6	0.2	18
22	58.4 ± 5.3	20.9 ± 1.9	27.3 ± 2.0	264.0 ± 22.4	0.15	8.9 ± 0.2	0.25	11.2 ± 1.4	0.7	51
23	25.6 ± 1.0	13.7 ± 2.2	31.5 ± 5.4	723.0 ± 43.0	0.31	4.7 ± 1.6	0.4	11.2 ± 2.7	0.9	65
40	31.0 ± 3.2	10.5 ± 1.3	58.3 ± 8.2	480.0 ± 40.0	0.14	4.6 ± 2.2	0.25	2.4 ± 1.0	0.5	22
67	96.4 ± 6.7	119.2 ± 22	4.8 ± 0.9	213.6 ± 23.5	0.79	37.4 ± 16	0.25	86.8 ± 31.7	1.2	73
73	1.4 ± 0.1	0.5 ± 0.1	122.3 ± 15.7	1035.0 ± 96.0	0.16	0.1 ± 0.0	0.25	0.1 ± 0.0		3

[a] $n = 6$ animals per study. [b] Dosed in 5% dextrose; iv = intravenous administration; per os = oral administration. [c] Bioavailability.

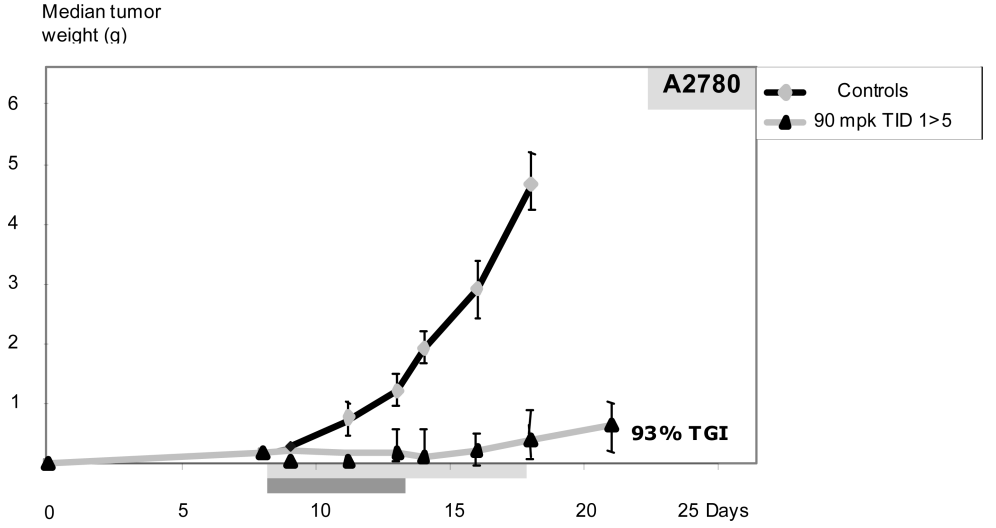


Figure 5. Compound **18** has antitumor activity in rodents. CDI nu/nu mice carrying subcutaneous A2780 human ovarian carcinoma were treated with either vehicle or **18** by oral administration. Curves indicate tumor growth in vehicle-treated (black line) or **18**-treated mice for 5 days (dark bar) at 90 mg/kg (triangles) three times a day. Data are represented as mean ± SEM.

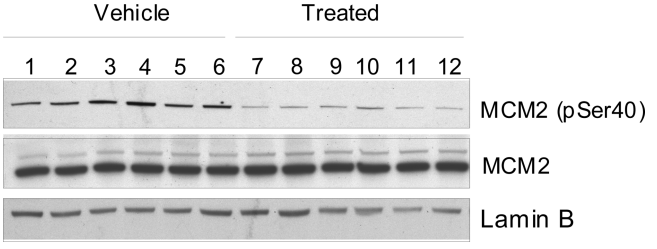


Figure 6. In vivo target modulation by compound **18**. A2780 xenografted mice were treated either with vehicle (lanes 1−6) or with 3×90 mg/kg of **18** (lanes 7−12) and sacrificed after 6 h. Tumors were explanted and analyzed by Western blot using antibodies against phosphorylated MCM2 at Ser40. Levels of total MCM2 and lamin B were also measured as loading control.

borderline bioavailability. The remaining four compounds, **18**, **22**, **23**, and **67**, are reasonably bioavailable, with very good F values for derivatives **23** and **67**. These data convinced us to pursue these four compounds further.

These four compounds were challenged in efficacy experiments to evaluate their potential for in vivo treatment. Thus derivatives **18**, **22**, **23**, and **67** were administered orally as a methocel suspension to nude mice carrying subcutaneous A2780 human ovarian carcinoma. From these preliminary results, compound **67** showed signs of toxicity at low dosages, while compounds **22** and **23** proved to be poorly efficacious in vivo. However, compound **18** displayed an excellent in vivo activity, exceeding 90% TGI (tumor growth inhibition) after three times per day administration (90 mg/kg) for five consecutive days (Figure 5).

Table 10. Selectivity Profile of Compound **18**[a]

kinase	IC_{50} (μM)	kinase	IC_{50} (μM)
Cdc7	0.022 ± 0.013	Cdk2/A	2.8
Cdk9/T	0.394 ± 0.114	Cdk1/B	3.1
TAO1	0.42 ± 0.15	JAK2	3.3
CK2	0.89 ± 0.02	PKCβ	3.7
GSK3β	1.39	IKK2	3.8
Cdk2/E	2.7	others[b]	> 10

[a] Where possible, IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$). [b] ABL, AKT1, ALK, AUR1, AUR2, BRK, Cdk4/D1, Cdk5/P25, CHK1, EEF2K, EGFR1, ERK2, FAK, FGFR1, FLT3, IGFR1, IKKi, IR, JAK3, KIT, LCK, MET, MK2, MPS1, MST4, NEK6, NIM1, P38α, P38β, PAK4, PDGFR, PDK1, PERK, PIM1, PKAα, PLK1, RET, SYK, TRKA, VEGFR3 and ZAP70.

The correlation of the in vivo antitumor activity with Cdc7 inhibition was evaluated by Western blot on A2780 tumors explanted from controls and animals treated with 3 × 90 mg/kg of **18** and sacrificed after 6 h (Figure 6).

The inhibition of Ser40 phosphorylation of MCM2 substrate was clearly observed in the tumors of treated animals.

A good antitumor efficacy (TGI = 68%) was also obtained in the xenograft colorectal cancer model HCT-116 with the compound **18** administered orally following the same schedule reported above. A lower but still significant antitumor activity (max TGI = 41%) was obtained in COLO-205 colorectal cancer xenograft model.

Compound **18** provided a clean selectivity profile when tested on a panel of 51 kinases, with just three kinases inhibited below the micromolar range (Cdk9/T, TAO1, and CK2) but with at least a 20-fold selectivity ratio (Table 10).

Table 11. Antiproliferative Activity of Compound **18**

			IC_{50} (μM)[a]		
cell line	origin	p53	5-FU	gemcitabine	**18**
A2780	ovary	+	14	0.035	0.8
HCT116	colon	+	12	0.006	1.8
HCT116-E6	colon p53-	−	50	0.5	2
HeLa	cervix	−	> 100	> 10	4
SW480	colon	−	57	1.7	5.7
COLO205	colon	−	90	3	2.5
K562	leukaemia	−	> 100	0.6	8.9
SF-268	astrocytoma	−	> 100	0.01	7.5
OVCAR-8	ovary	−	> 100	0.003	6.6
HCT-15	colon	+	48	0.01	5.9
Jurkat	leukaemia	−	87	0.03	7.7
MCF7	breast	+	64	0.08	3.7
NHDF	human fibroblasts	+	30	0.02	9.2
PC-3	prostate	−	30	0.003	7
SF-539	gliosarcoma	+	43	0.02	7.9
U2OS	osteosarcoma	+	16	0.18	5.8

[a] IC_{50} values are reported as the mean of 2−3 experiments with a coefficient of variation below 35%.

In addition, compound **18** demonstrated a good antiproliferative activity against a panel of several cell lines independently of the p53 status and in cellular models resistant to 5-FU and/or gemcitabine, well-known inhibitors of DNA replication elongation (Table 11).

Conclusions

Starting from our previous series of pyrrolopyridinone compounds, we have developed a new chemical class of Cdc7 kinase inhibitors, the 5-heteroaryl-3-carboxamido-2-substituted pyrrole derivatives. This class of compounds is amenable to straightforward diversification through both solution and solid phase synthesis, is characterized by good potency against the target, satisfactory activity in cells, and good in vitro ADME properties. From this expansion, a potent, selective, cellularly efficacious, and orally available derivative, **18**, was identified. It displays very good activity in a A2780 xenograft model with ex vivo target inhibition.

On the basis of these data, derivative **18** has emerged as a new promising lead compound worthy of further studies aimed at the selection of a potential candidate for clinical development.

Experimental Section

1. Chemistry. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers and used without further purification. All reactions involving air- or moisture-sensitive reagents were performed under an argon atmosphere. All final compounds were purified to > 95% purity as determined by high-performance liquid chromatography (HPLC).

Purity was routinely measured by HPLC on a Waters X Terra RP 18 (4.6 mm × 50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and Micromass model A ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was an ammonium acetate 5 mM buffer (pH 5.2 with acetic acid/acetonitrile 95:5), and mobile phase B was H_2O/acetonitrile (5:95). The following conditions were used: a gradient from 10 to 90% B in 8 min and held at 90% B for 2 min; UV detection at 220 and 254 nm; a flow rate of 1 mL/min; an injection volume of 10 μL; full scan, mass range from 100 to 800 amu. The capillary voltage was 2.5 kV; the source temperature was 120 °C; the cone was 10 V. Masses are given as an m/z ratio.

Column chromatography was conducted either under medium pressure on silica (Merck silica gel 40−63 μm) or on prepacked silica gel cartridges (Biotage) or on a Horizon system. When necessary, compounds were purified by preparative HPLC on a Waters XTerra Prep RP18 (19 mm × 100 mm, 5 μm) column using a Waters FractionLynx System equipped with a Waters 2996 PDA detector and a Waters ZQ single quadrupole mass spectrometer, with electro-spray ionization, in the positive mode, was used. Mobile phase A was water and 0.05% NH_4OH, in H_2O pH10/acetonitrile 95/5 and mobile phase B was acetonitrile. The following conditions were used: a gradient from 10 to 90% B in 8 min and held at 100% B for 2 min; a flow rate 20 mL/min.

^1H NMR spectra were acquired at 25 °C in DMSO-d_6 on a Varian Inova 400 spectrometer operating at 400 MHz and equipped with a 5 mm $^1H\{^{15}N-^{31}P\}$ Z-axis-PFG indirect detection probe and on a Varian Mercury 300 spectrometer operating at 300 MHz and equipped with a 5 mm $^{15}N-^{31}P\{^1H,^{19}F\}$ switchable probe. Residual not-deuterated solvent signal was used as reference with δ = 2.50 ppm for DMSO-d_5. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, bs = broad singlet, dd = doublet of doublet, td = triplet of doublet, m = multiplet), coupling constants, and number of protons.

Low-resolution mass spectral (MS) data were determined on a Finnigan MAT LCQ ion trap instrument, equipped with ESI. ESI(+) high-resolution mass spectra (HRMS) were obtained on a Waters Q-Tof Ultima directly connected with micro HPLC 1100 Agilent as previously described.[28]

Elemental analyses were performed on Carlo Erba EA1110 instrument, and C, H, and N values were within ±0.4% of theoretical values unless otherwise noted.

Thin-layer chromatography was performed on Merck silica gel 60 plates coated with 0.25 mm layer with fluorescent indicator. Components were visualized by UV light (λ = 254 and 366 nm) and iodine vapors.

Compounds **73**, **75**, **76**, and **77** were prepared as described in the literature.[25]

1-(2-Amino-5-fluoro-4-pyrimidinyl)-2-bromo-ethanone (2e). To a solution of 2,4-dichloro-5-fluoro-pyrimidine (1.23 g, 7.24 mmol) in *N*,*N*-dimethylformamide (14 mL), tributyl-(1-ethoxy-vinyl)-stannane (2.7 mL, 7.9 mmol) was added, followed by bis(triphenylphosphine) palladium(II) dichloride (0.103 g, 0.145 mmol). The mixture was heated at 70 °C for 1 h, cooled, a saturated aqueous solution of potassium fluoride was added, and the mixture was stirred at room temperature for 0.5 h. After dilution with water/diethylether and filtration through a Celite pad, the organic phases were washed thoroughly with water, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified with the Horizon system (25 mm column), eluting with *n*-hexane/EtOAc 95:5. 2-Chloro-4-(1-ethoxy-vinyl)-5-fluoro-pyrimidine was obtained (1.24 g, 84%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J = 6.95 Hz, 3H), 3.95 (q, J = 6.99 Hz, 2H), 4.88 (d, J = 2.80 Hz, 1H), 5.20 (d, J = 2.93 Hz, 1H), 8.90 (d, J = 3.17 Hz, 1H).ESI (+) MS: m/z 203 (MH^+).

A solution of the above obtained enol ether (15.52 g, 76.73 mmol) in absolute ethanol (25 mL) and 30% aqueous ammonia (50 mL) was warmed under shaking at 100 °C for 1.5 h in a Parr apparatus. After cooling, ethanol was removed and the compound was extracted with dichloromethane. The crude material was purified with the Horizon system, eluting with *n*-hexane/EtOAc 1:1. There was obtained 4-(1-ethoxy-vinyl)-5-fluoro-pyrimidin-2-ylamine (9.01 g, 64%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, J = 7.01 Hz, 3H), 3.87 (q, J = 6.95 Hz, 2H), 4.62 (d, J = 2.44 Hz, 1H), 4.91 (dd, J = 2.38, 0.55 Hz, 1H), 6.64 (bs, 2H), 8.28 (d, J = 3.54 Hz, 1H). ESI (+) MS: m/z 184 (MH^+).

To a solution of the above prepared amino derivative (0.521 g, 2.78 mmol) in tetrahydrofuran (25 mL), water (1.7 mL) was added followed by *N*-bromosuccinimide (0.512 mg, 2.87 mmol).

The mixture was stirred at room temperature for 1.5 h. The solvent was evaporated, and the residue was stirred thoroughly in methanol and filtered to obtain the title compound 1-(2-amino-5-fluoro-pyrimidin-4-yl)-2-bromo-ethanone (0.511 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.70 (s, 2H), 6.94 (bs, 2H), 8.50 (d, J = 2.93 Hz, 1H). ESI (+) MS: m/z 234−236 (MH^+).

2-Methyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide hydrochloride (4). A solution of 2-bromo-1-pyridin-4-ylethanone hydrobromide (**2a**) (3.00 g, 10.8 mmol) and methyl 3-aminocrotonate (1.84 g, 1.5 equiv) in anhydrous *N*,*N*-dimethylformamide (15 mL) was stirred for 15 h at room temperature. The reaction mixture was diluted with ethyl acetate and the precipitate filtered off. The mother liquor was basified with aqueous 10% potassium carbonate solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (ethyl acetate). The oily residue was dissolved in methanol and treated with excess 4 M HCl in dioxane. The precipitate was immediately filtered, washed with ethyl acetate, and dried, yielding 2-methyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid methyl ester hydrochloride as a white solid (0.752 g, 28% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.57 (s, 3H), 3.77 (s, 3H), 7.64 (d, J = 2.68 Hz, 1H), 8.15 (d, J = 6.95 Hz, 2H), 8.71 (d, J = 6.95 Hz, 2H), 12.56 (bs, 1H). ESI (+) MS: m/z 217 (MH^+).

The ester (0.175 g, 0.69 mmol), dissolved in 2 mL of ethanol and 1.5 M KOH in ethanol (2.3 mL), was refluxed for 15 h. The solution was cooled and neutralized with ammonium chloride. The yellow precipitate was filtered and washed with water to afford 0.114 g (80%) of 2-methyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (s, 3H), 7.09 (d, J = 2.80 Hz, 1H), 7.62 (d, J = 6.22 Hz, 2H), 8.50 (d, J = 6.22 Hz, 2H), 11.84 (bs, 2H). ESI (+) MS: m/z 203 (MH^+).

The acid (0.083 g, 0.4 mmol) was dissolved in anhydrous tetrahydrofuran (1.5 mL) and anhydrous *N*,*N*-dimethylformamide (1.5 mL) in the presence of DIEA (0.14 mL, 2 equiv). To the solution, cooled to 0 °C, EDC·HCl (0.152 g, 2 equiv) and HOBt·NH_3 (0.120 g, 2 equiv) were added. The reaction mixture was left overnight at room temperature. Water was added, and the slurry was extracted with ethyl acetate (×2). The organic layer was concentrated, and the residue was dissolved in ethanol and treated with 2 M aqueous HCl. The precipitate was filtered and dried to yield 0.041 g (42%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.55 (s, 3H), 6.94 (bs, 1H), 7.35 (bs, 1H), 7.65 (d, J = 2.56 Hz, 1H), 7.95 (d, J = 6.83 Hz, 2H), 8.68 (d, J = 6.95 Hz, 2H), 12.33 (bs, 1H). ESI (+) MS: m/z 202 (MH^+). HRMS (ESI): calcd for $C_{11}H_{11}N_3O + H^+$, 202.0975; found, 202.0971.

2-Aminomethyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide dihydrochloride (7). 4-*tert*-Butoxycarbonylamino-3-oxo-butyric acid ethyl ester (1.06 g, 4.08 mmol) and 0.410 g of sodium hydride (60% in mineral oil) dissolved in 20 mL of anhydrous tetrahydrofuran were stirred 1 h at room temperature and then cooled to 0 °C. A suspension of 1.22 g (4 mmol) of 2-bromo-1-pyridin-4-ylethanone hydrobromide (**2a**) in 10 mL of anhydrous tetrahydrofuran was added dropwise and the mixture stirred at 0 °C for 4 h. The resulting solution was concentrated, the residue was dissolved in 30 mL of ethanol/acetic acid 1:1, and 1.25 g of ammonium acetate was added. The solution was stirred for 5 h, the solvent was removed, and the raw product was dissolved in ethyl acetate, washed (×3) with brine, and dried over anhydrous sodium sulfate. The solvent was removed and the crude was purified by flash chromatography over silica gel, thus providing 0.463 g of 2-(*tert*-butoxycarbonylamino-methyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester (34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, J = 7.07 Hz, 3H), 1.41 (s, 9H), 4.22 (d, J = 7.07 Hz, 2H), 4.50 (d, J = 5.49 Hz, 2H), 6.91 (s, 1H), 7.15 (d, J = 2.68 Hz, 1H), 7.70 (dd, J = 4.63, 1.59 Hz, 2H), 8.52 (dd, J = 4.63, 1.59 Hz, 2H), 11.94 (s, 1H). ESI (+) MS: m/z 346 (MH^+). HRMS $(M + H)^+$ calcd for $C_{18}H_{23}N_3O_4 + H^+$, 346.1761; found, 346.1764.

To a solution of 2-(*tert*-butoxycarbonylamino-methyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester (0.345 g, 1 mmol) in 30 mL of ethanol/water 3:1, 1.05 g of sodium hydroxide was added. The solution was heated at 70 °C for 18 h, and then cooled. 2 N HCl was added to reach pH 6−7, and the precipitate was filtered, yielding 0.274 g (85%) of 2-(*tert*-butoxycarbonylamino-methyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (s, 9H), 4.47 (s, 2H), 7.04 (s, 1H), 7.19 (s, 1H), 7.67 (d, J = 5.86 Hz, 2H), 8.45 (d, J = 6.15 Hz, 2H), 12.06 (bs, 1H).

A solution of 2-(*tert*-butoxycarbonylamino-methyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid (26 mg, 0.081 mmol), HOBt (16 mg, 1.5 equiv), ammonium chloride (8 mg, 2 equiv), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP, 63 mg, 1.5 equiv), and DIEA (0.05 mL) in *N*,*N*-dimethylformamide (3 mL) was stirred at room temperature for 6 h. The reaction mixture was concentrated and purified by reverse phase flash chromatography. The obtained protected amide was treated with 4 M HCl in dioxane to yield the title compound (12 mg, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.22−4.29 (m, 2H), 7.52 (d, J = 9.63 Hz, 2H), 7.74 (s, 2H), 7.93 (s, 1H), 8.39 (s, 3H), 8.68 (d, J = 4.27 Hz, 2H), 12.70 (s, 1H). ESI (+) MS: m/z 217 (MH^+). HRMS $(M + H)^+$ calcd for $C_{11}H_{12}N_4O + H^+$, 217.1084; found, 217.1081.

2-Ethyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (5). To a cooled (0 °C) solution of ethyl 3-oxopentanoate (1.21 g, 8.3 mmol) in anhydrous tetrahydrofuran (200 mL), sodium hydride (60% in mineral oil, 0.923 g, 21 mmol) was added cautiously. After 5 min, 4-(bromoacetyl)pyridine hydrobromide **2a** (3.05 g, 10.8 mmol) was added and the thick solution was stirred at 0 °C for 5 h. The solvent was replaced with ethanol (120 mL), and ammonium acetate (1.93 g, 25 mmol) was added. The mixture was stirred at room temperature for 18 h. After concentration, ethyl acetate was added and the organic layer was washed first with saturated aqueous Na_2CO_3, then with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography (ethyl acetate), yielding 1.22 g (59%) of 2-ethyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 (t, J = 7.44, 3H), 1.30 (t, J = 7.07, 3H), 2.94 (q, J = 7.56, 2H), 4.21 (q, J = 7.07, 2H), 7.09 (d, J = 2.80 Hz, 1H), 7.64 (m, 2H), 8.50 (m, 2H), 11.83 (bs, 1H). ESI (+) MS: m/z 245 (MH^+). HRMS (ESI): calcd for $C_{14}H_{16}N_2O_2 + H^+$, 245.1284; found, 245.1283.

2-Ethyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester (1.22 g, 5 mmol), dissolved in 10 mL of 4 M aq NaOH and 10 mL of ethanol, was refluxed for 2 h. The solution was cooled and neutralized with acetic acid. The precipitate was filtered and washed with water and acetone to afford 0.756 g (70%) of 2-ethyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid (general structure **IIa**, R = Et) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (t, J = 7.50 Hz, 3H), 2.99 (q, J = 7.36 Hz, 2H), 7.59 (d, J = 2.68 Hz, 1H), 8.16 (d, J = 6.95 Hz, 2H), 8.70 (d, J = 6.95 Hz, 2H), 12.39 (bs, 1H). ESI (+) MS: m/z 217 (MH^+). HRMS (ESI): calcd for $C_{12}H_{12}N_2O_2 + H^+$, 217.0971; found, 217.0973

Acid (0.136 g, 0.63 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (5 mL) in the presence of DIEA (0.6 mL, 6 equiv). To the solution, cooled to 0 °C, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 0.412 g, 2 equiv) and HOBt·NH_3 (0.211 g, 2 equiv) were added. The reaction mixture was left overnight at room temperature and then poured into water. The aqueous solution was extracted (5 × 5 mL) with ethyl acetate, the combined organic layers were washed with 1 M aqueous NaOH, dried, and concentrated. The crude material was treated with ethyl ether and filtered, yielding 0.064 g (46%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, J = 7.44 Hz, 3H), 2.94 (q, J = 7.48 Hz, 2H), 6.68 (bs, 2H), 7.17 (d, J = 2.80 Hz,

1H), 7.50 (d, J = 6.22 Hz, 2H), 8.48 (d, J = 6.10 Hz, 2H), 11.54 (s, 1H). ESI (+) MS: m/z 216 (MH^+). HRMS $(M + H)^+$ calcd for $C_{12}H_{13}N_3O + H^+$, 216.1132; found, 216.1133.

Analogously the following compounds were obtained:

2-*iso*-Propyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (6). From 4-methyl-3-oxo-pentanoic acid ethyl ester and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 18% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (d, J = 7.07 Hz, 6H), 3.99 (qq, J = 6.99, 6.77 Hz, 1H), 7.14 (d, J = 2.56 Hz, 1H), 7.49 (s, 1H), 7.57 (d, J = 6.10 Hz, 2H), 8.48 (d, J = 5.98 Hz, 2H). ESI (+) MS: m/z 230 (MH^+). HRMS $(M + H)^+$ calcd for $C_{13}H_{15}N_3O + H^+$, 230.1288; found, 230.1286.

2-Benzyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (8). From 3-oxo-4-phenyl-butyric acid ethyl ester and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 13% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.39 (s, 2H), 6.97 (bs, 1H), 7.16 (m, 1H), 7.26 (m, 2H), 7.29−7.33 (m, 2H), 7.44 (bs, 1H), 7.63−7.71 (m, 1H), 7.86−8.03 (m, 2H), 8.68 (d, J = 6.58 Hz, 2H), 12.43 (bs, 1H). ESI (+) MS: m/z 278 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O + H^+$, 278.1288; found, 278.1287.

2-Cyclohexyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (9). From 3-cyclohexyl-3-oxo-propionic acid ethyl ester and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 13% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.62−1.84 (m, 10H), 3.59−3.71 (m, 1H), 6.67 (bs, 1H), 7.13 (d, J = 2.68 Hz, 1H), 7.21 (bs, 1H), 7.58 (d, J = 6.22 Hz, 2H), 8.48 (d, J = 6.10 Hz, 2H), 11.13 (bs, 1H). ESI (+) MS: m/z 270 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{19}N_3O + H^+$, 270.1601; found, 270.1602.

4-(3-Carbamoyl-5-pyridin-4-yl-1*H*-pyrrol-2-yl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (10). From 4-(2-ethoxycarbonyl-acetyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 15% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 9H), 1.67 (d, J = 12.32 Hz, 2H), 1.76−1.89 (m, 2H), 2.71 (bs, 2H), 3.81−3.91 (m, 1H), 4.12 (d, J = 11.10 Hz, 2H), 6.76 (bs, 1H), 7.18 (d, J = 2.56 Hz, 1H), 7.29 (bs, 1H), 7.59 (d, J = 6.22 Hz, 2H), 8.50 (d, J = 6.10 Hz, 2H), 11.22 (bs, 1H). ESI (+) MS: m/z 371 (MH^+). HRMS $(M + H)^+$ calcd for $C_{20}H_{26}N_4O_3 + H^+$, 371.2078; found, 371.2075.

2-Phenyl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (11). From 3-oxo-3-phenyl-propionic acid ethyl ester and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 22% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.90 (bs, 2H), 7.27 (d, J = 2.56 Hz, 1H), 7.37 (m, 1H), 7.44 (m, 2H), 7.67−7.71 (m, 4H), 8.53 (m, 2H), 11.82 (s, 1H). ESI (+) MS: m/z 264 (MH^+). HRMS $(M+H)^+$ calcd for $C_{16}H_{13}N_3O+H^+$, 264.1131; found, 264.1132.

2,5-Dipyridin-4-yl-1*H*-pyrrole-3-carboxamide (12). From ethyl isonicotinoylacetate and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 21% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.02 (bs, 2H), 7.29 (s, 1H), 7.71 (m, 4H), 8.56 (m, 4H), 12.01 (bs, 1H). ESI (+) MS: m/z 265(MH^+). HRMS $(M + H)^+$ calcd for $C_{15}H_{12}N_4O + H^+$, 265.1084; found, 265.1078.

2-(2-Fluoro-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (13). From ethyl (2-fluorobenzoyl)acetate and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 20% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.00 (bs, 1H), 7.29−7.34 (m, 2H), 7.36 (bs, 1H), 7.49−7.60 (m, 2H), 7.73 (d, J = 2.43 Hz, 1H), 8.11 (d, J = 6.59 Hz, 2H), 8.74 (d, J = 6.59 Hz, 2H), 12.56 (s, 1H). ESI (+) MS: m/z 282 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}FN_3O + H^+$, 282.1037; found, 282.1035.

2-(3-Fluoro-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (14). From ethyl (3-fluorobenzoyl)acetate and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 24% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.16 (bs, 2H), 7.29 (m, 2H), 7.52 (m, 2H), 7.74 (s, 1H), 8.23 (d, J = 5.80 Hz, 2H), 8.78 (d, J = 5.80 Hz, 2H), 12.42 (s, 1H). ESI (+) MS: m/z 282 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}FN_3O + H^+$, 282.1037; found, 282.1036.

2-(4-Fluoro-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (15). From ethyl (4-fluorobenzoyl)acetate and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 23% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.12 (bs, 2H), 7.32−7.39 (m, 4H), 7.70 (d, J = 2.43 Hz, 1H), 8.15 (d, J = 6.59 Hz, 2H), 8.72 (d, J = 6.59 Hz, 2H), 12.52 (s, 1H). ESI (+) MS: m/z 282 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}FN_3O + H^+$, 282.1037; found, 282.1044.

2-(3-Bromo-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (16). From ethyl (3-bromobenzoyl)acetate and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 18% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 (bs, 1H), 7.44 (t, J = 7.93 Hz, 1H), 7.51 (bs, 1H), 7.60−7.65 (m, 1H), 7.69 (d, J = 2.56 Hz, 1H), 7.71−7.75 (m, 1H), 7.93 (t, J = 1,83 Hz, 1H), 8.18 (d, J = 5.85 Hz, 2H), 8.76 (d, J = 6.83 Hz, 2H), 12.38 (bs, 1H). ESI (+) MS: m/z 342−344 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}BrN_3O + H^+$, 342.0236; found, 342.0233.

2-(4-Bromo-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid amide (17). From ethyl (4-bromobenzoyl)acetate and 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **2a** in 22% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.93 (bs, 1H), 7.28 (d, J = 2.68 Hz, 1H), 7.37 (bs, 1H), 7.62−7.67 (m, 4H), 7.69 (d, J = 6.22 Hz, 2H), 8.54 (d, J = 6.22 Hz, 2H), 11.86 (bs, 1H). ESI (+) MS: m/z 342−344 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}BrN_3O + H^+$, 342.0236; found, 342.0240.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxamide (18). From 3-oxo-3-phenyl-propionic acid ethyl ester and 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**), ethyl 5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylate (**61**) was obtained (46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, J = 7.13 Hz, 3H), 4.14 (q, J = 7.07 Hz, 2H), 6.45 (s, 2H), 7.10 (d, J = 5.24 Hz, 1H), 7.33 (d, J = 2.56 Hz, 1H), 7.40−7.49 (m, 3H), 7.61−7.65 (m, 2H), 8.23 (d, J = 5.24 Hz, 1H), 12.01 (bs, 1H). ESI (+) MS: m/z 309 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{16}N_4O_2+H^+$, 309.1346; found, 309.1342.

From ester **61**, 5-(2-amino-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid (**3**) was isolated as a white solid (quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.05 (bs, 2H), 7.22 (d, J = 5.73 Hz, 1H), 7.39−7.47 (m, 4H), 7.62−7.64 (m, 2H), 8.24 (d, J = 5.85 Hz, 1H), 11.99 (bs, 1H), 12.10 (bs, 1H). MS: m/z 279 [M − H]. HRMS $(M + H)^+$ calcd for $C_{15}H_{12}N_4O_2 + H^+$, 281.1033; found, 281.1043.

From acid **3** the title compound (**18**) was obtained as an orange powder in 43% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.36 (s, 2H), 6.82 (bs, 1H), 7.02 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.32 (br s, 1H), 7.32−7.37 (m, 1H), 7.37−7.44 (m, 2H), 7.64 (dd, J = 8.3, 1.3 Hz, 2H), 8.20 (d, J = 5.2 Hz, 1H), 11.63 (bs, 1H). ESI (+) MS: m/z 280 (MH^+). HRMS $(M + H)^+$ calcd for $C_{15}H_{13}N_5O + H^+$, 280.1193; found, 280.1189. Anal. ($C_{15}H_{13}N_5O$) C, H, N.

2-Phenyl-5-(2-phenylamino-pyrimidin-4-yl)-1*H*-pyrrole-3-carboxamide (19). From 3-oxo-3-phenyl-propionic acid ethyl ester and 2-bromo-1-[2-(phenylamino)-4-pyrimidinyl]-ethanone (**2d**), the title compound was obtained in 12% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.89 (bs, 1H), 6.95 (t, J = 7.33 Hz, 1H), 7.29−7.48 (m, 6H), 7.29 (d, J = 5.24 Hz, 1H), 7.66−7.68 (m, 2H), 7.85 (d, J = 7.68 Hz, 2H), 8.43 (d, J = 5.24 Hz, 1H), 9.40 (s, 1H), 11.75 (s, 1H). ESI (+) MS: m/z 356 (MH^+). HRMS $(M + H)^+$ calcd for $C_{21}H_{17}N_5O + H^+$, 356.1506; found, 356.1508.

5-(2-Amino-5-fluoro-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide (20). From 3-oxo-3-phenyl-propionic acid ethyl ester and 1-(2-amino-5-fluoro-4-pyrimidinyl)-2-bromo-ethanone **2e**, the title compound was obtained in 17% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.34 (s, 2H), 6.87 (bs, 1H), 7.27 (t, J = 2.80 Hz, 1H), 7.33−7.43 (m, 3H), 7.40 (s, 1H), 7.62−7.66 (m, 2H), 8.27 (d, J = 3.41 Hz, 1H), 11.49 (bs, 1H). ESI (+) MS: m/z 298 (MH^+). HRMS $(M + H)^+$ calcd for $C_{15}H_{12}FN_5O + H^+$, 298.1099; found, 298.1096. Anal. ($C_{15}H_{12}FN_5O$) C, H, N.

5-(2-Amino-pyrimidin-4-yl)-2-pyridin-2-yl-1*H*-pyrrole-3-carboxamide (21). From ethyl picolinoylacetate and 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**),, the title compound was obtained in 14% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.62 (bs, 2H), 7.03 (d, J = 5.12 Hz, 1H), 7.16 (bs, 1H), 7.33−7.40 (m, 2H), 7.89 (ddd, J = 8.05, 7.56, 1.83 Hz, 1H), 8.25 (d, J = 5.12 Hz, 1H), 8.28 (bs, 1H), 8.43 (d, J = 8.17 Hz, 1H), 8.64 (ddd, J = 4.08, 1.70, 1.00 Hz, 1H), 11.29 (s, 1H). ESI (+) MS: m/z 281 (MH^+). HRMS $(M + H)^+$ calcd for $C_{14}H_{12}N_6O + H^+$, 281.1146; found, 281.1145.

5-(2-Amino-pyrimidin-4-yl)-2-thiophen-2-yl-1*H*-pyrrole-3-carboxamide (22). From 3-oxo-3-thiophen-2-yl-propionic acid ethyl ester and 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**), the title compound was obtained in 10% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.46 (bs, 2H), 6.91 (bs, 1H), 7.04 (d, J = 5.24 Hz, 1H), 7.11 (dd, J = 5.12, 3.66 Hz, 1H), 7.30 (d, J = 2.56 Hz, 1H), 7.44 (bs, 1H), 7.57 (dd, J = 5.12, 1.22 Hz, 1H), 7.66 (dd, J = 3.66, 1.22 Hz, 1H), 8.23 (d, J = 5.24 Hz, 1H), 11.60 (bs, 1H). ESI (+) MS: m/z 286 (MH^+). HRMS $(M + H)^+$ calcd for $C_{13}H_{11}N_5OS + H^+$, 286.0757; found, 286.0758. Anal. ($C_{13}H_{11}N_5OS$) C, H, N, S.

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-5-yl-1*H*-pyrrole-3-carboxamide (23). A solution of 1-benzothiophene-5-carboxylic acid (9.71 g, 54.5 mmol) and 1,1′-carbonyldiimidazole (13.04 g, 80.1 mmol) in tetrahydrofuran (100 mL) was stirred at room temperature for 40 min. After addition of $MgCl_2$ (10.44 g, 109 mmol) and monoethylmalonate potassium salt (14.72 g, 87 mmol) in tetrahydrofuran (100 mL), the mixture was heated for 3 h at 45 °C under stirring. After solvent removal, the residue was dissolved in ethyl acetate and washed with 5% $KHSO_4$ aqueous solution, with saturated aqueous $NaHCO_3$ solution, and with brine. After drying over anhydrous sodium sulfate, ethyl 3-(1-benzothiophen-5-yl)-3-oxopropanoate (6.22 g, 45%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, J = 7.13 Hz, 3H), 4.14 (q, J = 7.07 Hz, 2H), 4.27 (s, 2H), 7.63 (d, J = 5.37 Hz, 1H), 7.89−7.92 (m, 1H), 7.92−7.93 (m, 1H), 8.18 (d, J = 8.54 Hz, 1H), 8.56 (d, J = 1.59 Hz, 1H). Anal. ($C_{17}H_{13}N_5OS$) C, H, N, S.

From ethyl 3-(1-benzothiophen-5-yl)-3-oxopropanoate and 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**), the title compound was obtained in 17% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.36 (bs, 2H), 6.84 (bs, 1H), 7.04 (d, J = 5.24 Hz, 1H), 7.31 (d, J = 2.56 Hz, 1H), 7.34 (bs, 1H), 7.50 (dd, J = 5.49, 0.49 Hz, 1H), 7.62 (dd, J = 8.41, 1.71 Hz, 1H), 7.80 (d, J = 5.49 Hz, 1H), 8.01 (d, J = 8.41 Hz, 1H), 8.13 (d, J = 1.34 Hz, 1H), 8.21 (d, J = 5.37 Hz, 1H), 11.75 (bs, 1H). ESI (+) MS: m/z 336 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{13}N_5OS + H^+$, 336.0914; found, 336.0918.

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1*H*-indol-2-yl)-1*H*-pyrrole-3-carboxamide (24). A solution of 1-methylindole-2-carboxylic acid (0.311 g, 1.71 mmol) and 1,1′-carbonyldiimidazole (0.360 g, 2.22 mmol mmol) in anhydrous tetrahydrofuran (10 mL) was stirred at room temperature for 1 h under argon atmosphere. In another flask, to a cooled (0 °C) solution of 3-ethoxy-3-oxopropanoic acid (0.522 g, 3.93 mmol) in anhydrous tetrahydrofuran (10 mL), under stirring and argon atmosphere, $Mg(OEt)_2$ (0.255 g, 2.22 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. To this solution, kept at 0 °C under stirring, the solution of imidazolide was added dropwise and stirred at 0 °C for 30 min. The mixture was heated to 50 °C and stirred at this temperature for 8 h and then for 18 h at room temperature. After solvent removal, the residue was dissolved in diethyl ether and washed with 1 N HCl, with saturated aqueous $NaHCO_3$ solution, and with brine. After drying over anhydrous sodium sulfate, ethyl 3-(1-methyl-1*H*-indol-2-yl)-3-oxopropanoate was isolated as a yellow oil (0.412 g, quant). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (t, J = 7.13 Hz, 3H), 4.02 (s, 3H), 4.14 (q, J = 6.99 Hz, 2H), 4.14 (s, 2H), 7.17 (ddd, J = 7.99, 6.95, 0.91 Hz, 1H), 7.42 (ddd, J = 8.41, 7.01, 1.16 Hz, 1H), 7.58 (d, J = 0.73 Hz, 1H), 7.59−7.62 (m, 1H), 7.75 (ddd, J = 8.02, 0.99 Hz, 1H).

From ethyl 3-(1-methyl-1*H*-indol-2-yl)-3-oxopropanoate and 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**), the title compound was obtained in 14% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.58 (s, 3H), 6.38 (bs, 2H), 6.61 (d, J = 0.61 Hz, 1H), 6.88 (bs, 1H), 7.00 (d, J = 5.24 Hz, 1H), 7.08 (t, J = 7.70 Hz, 1H), 7.20 (t, J = 7.70 Hz, 1H), 7.25 (bs, 1H), 7.41 (d, J = 2.44 Hz, 1H), 7.47 (d, J = 7.70 Hz, 1H), 7.59 (d, J = 7.70 Hz, 1H), 8.22 (d, J = 5.24 Hz, 1H), 11.98 (bs, 1H). ESI (+) MS: m/z 333 (MH^+). HRMS $(M + H)^+$ calcd for $C_{18}H_{16}N_6O + H^+$, 333.1459; found, 333.1460.

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1*H*-indol-3-yl)-1H-pyrrole-3-carboxamide (25). Ethyl 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanoate crude yellow oil (0.412 g, quant.) was obtained as described above for its regioisomer. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (t, J = 7.07 Hz, 3H), 3.89 (s, 3H), 3.95 (s, 2H), 4.13 (q, J = 7.15 Hz, 2H), 7.24−7.29 (m, 1H), 7.30−7.35 (m, 1H), 7.56 - 7.60 (m, 1H), 8.18 (ddd, J = 7.77, 1.37, 0.73 Hz, 1H), 8.39 (s, 1H).

From ethyl 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanoate and 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**), the title compound was obtained in 18% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.87 (s, 3H), 6.35 (bs, 2H), 6.73 (bs, 1H), 6.91 (bs, 1H), 6.98 (d, J = 5.24 Hz, 1H), 7.11 (ddd, J = 7.99, 7.07, 0.91 Hz, 1H), 7.22 (ddd, J = 8.17, 7.13, 0.91 Hz, 1H), 7.32 (d, J = 2.68 Hz, 1H), 7.50 (dt, J = 8.05, 0.85 Hz, 1H), 7.51 (dt, J = 8.32, 0.84 Hz, 1H), 7.80 (s, 1H), 8.17 (d, J = 5.24 Hz, 1H), 11.36 (bs, 1H).. ESI (+) MS: m/z 333 (MH^+). HRMS $(M + H)^+$ calcd for $C_{18}H_{16}N_6O + H^+$, 333.1459; found, 333.1463.

2-Piperidin-4-yl-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Dihydrochloride (26). Amide **10** (0.030 g, 0.08 mmol) was dissolved in methanol (5 mL), 2N HCl (1 mL) was added, and the clear solution was warmed at 50 °C under stirring for 5 h. The precipitate was filtered and washed with methanol, yielding the title compound as a white solid (0.025 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.96 (d, J = 13.05 Hz, 2H), 2.09−2.24 (m, 2H), 2.92−3.07 (m, 2H), 3.74−3.87 (m, 1H), 7.01 (bs, 1H), 7.49 (bs, 1H), 7.66 (s, 1H), 8.10 (bs, 2H), 8.56 (bs, 1H), 8.71 (d, J = 6.34 Hz, 2H), 8.83 (bs, 1H), 11.97 (bs, 1H). ESI (+) MS: m/z 271 (MH^+). HRMS $(M + H)^+$ calcd for $C_{15}H_{18}N_4O$, 271.1554; found, 271.1550.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic Acid Methylamide Hydrochloride (27). To a solution of 5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid **3** (0.023 g, 0.07 mmol) in anhydrous *N*,*N*-dimethylformamide, 1,1′-carbonyldiimidazole (0.025 g, 0.14 mmol) was added and the mixture stirred at 45 °C for 1 h. After cooling to room temperature, the solution was treated with 0.5 mL of 33% methylamine in ethanol. The mixture was stirred overnight, filtered, and the filtrate was poured into water. After extraction with ethyl acetate (×2), the organic layer was concentrated, dissolved in ethanol, and treated with excess 1.25 M HCl in methanol. Diethyl ether was added, and the yellow crystalline solid was filtered, washed with diethyl ether, and recovered. The title compound was obtained (8 mg, 37% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.70 (d, J = 4.63 Hz, 3H), 7.36 (d, J = 6.58 Hz, 1H), 7.39−7.49 (m, 3H), 7.53 (d, J = 2.44 Hz, 1H), 7.64−7.70 (m, 2H), 7.84 (bs, 3H), 8.02 (q, J = 4.51 Hz, 1H), 8.29 (d, J = 6.46 Hz, 1H), 12.20 (bs, 1H). ESI (+) MS: m/z 294 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{15}N_5O + H^+$, 294.1349; found, 294.1345.

Analogously the following compounds were prepared:

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic Acid Isopropylamide (28). Yield 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (d, J = 6.58 Hz, 6H), 3.93−4.06 (m, 1H), 6.36 (bs, 2H), 7.04 (d, J = 5.24 Hz, 1H), 7.23 (d, J = 2.44 Hz, 1H), 7.30−7.43 (m, 3H), 7.59−7.67 (m, 3H), 8.21 (d, J = 5.24 Hz, 1H), 11.61 (bs, 1H). ESI (+) MS: m/z 322 (MH^+).

HRMS $(M + H)^+$ calcd for $C_{18}H_{19}N_5O + H^+$, 322.1662; found, 322.1667.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic Acid Benzylamide (29). Yield 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.37 (d, J = 6.10 Hz, 2H), 6.37 (bs, 2H), 7.05 (d, J = 5.24 Hz, 1H), 7.18−7.44 (m, 9H), 7.64 (d, J = 8.30 Hz, 2H), 8.21 (d, J = 5.24 Hz, 1H), 8.48 (t, J = 6.10 Hz, 1H), 11.70 (bs, 1H). ESI (+) MS: m/z 370 (MH^+). HRMS $(M + H)^+$ calcd for $C_{22}H_{19}N_5O + H^+$, 370.1662; found, 370.1668.

5-(2-Amino-pyridin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide (32). To a solution of 3-oxo-3-phenyl-propionic acid ethyl ester (0.351 g, 2 mmol) in THF (45 mL) at 0 °C, NaH (60% in oil, 0.182 g, 4.5 mmol) was added and the mixture was stirred for 20 min at 0 °C. 2-Bromo-1-(2-chloro-4-pyridinyl)-ethanone hydrobromide **2f** (0.635 g, 2 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h, then at room temperature for 2 h. After solvent removal, absolute ethanol (25 mL) and ammonium acetate (0.505 g, 6.5 mmol) were added and the mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was taken up with ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and purified by flash chromatography (dichloromethane/methanol 95:5), affording 5-(2-chloro-pyridin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (**30**, 0.342 g, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.19 (t, J = 7.07 Hz, 3H), 4.14 (q, J = 7.07 Hz, 2H), 7.38−7.52 (m, 4H), 7.62−7.68 (m, 2H), 7.80 (d, J = 5.37, 1H), 7.97 (s, 1H), 8.33 (d, J = 5.37 Hz, 1H), 12.37 (bs, 1H). ESI (+) MS: m/z 327 (MH^+). HRMS $(M + H)^+$ calcd for $C_{18}H_{15}ClN_2O_2 + H^+$, 327.0895; found, 327.0900.

A mixture of **30** (0.122 g, 0.37 mmol), *t*-butyl carbamate (0.215 g, 1.84 mmol), Xantphos (0.016 g, 0.028 mmol), palladium diacetate (0.004 g, 0.018 mmol), and cesium carbonate (0.242 g, 0.73 mmol) in dioxane (3 mL) was stirred at 140 °C in a microwave cavity for 20 min. The crude material was taken up with methanol, filtered through Celite, treated with ethyl acetate and water, dried, and concentrated. The residue was purified by flash chromatography (dichloromethane/methanol 95:5) affording 5-(2-amino-pyridin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (**31**, 0.045 g, 40%). ESI (+) MS: m/z 308 (MH^+).

A solution of **31** (0.042 g, 0.15 mmol) in ethanol (0.5 mL) and 4 N NaOH (0.5 mL) was warmed at reflux for 2 h. The mixture was acidified with acetic acid and stripped under reduced pressure. The residue was dissolved in *N*,*N*-dimethylformamide (2 mL) and treated with HOBt·NH_3 (0.042 g, 0.27 mmol), EDC·HCl (0.052 g, 0.27 mmol), and DIEA (0.12 mL) for 3 days at room temperature (two more additions of the same amount of reagents after one and two days). After concentration and aqueous workup with ethyl acetate, the residue was purified by reverse phase flash chromatography, affording the title compound (0.033 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.37 (bs, 2H), 6.83 (bs, 1H), 7.02 (d, J = 5.78 Hz, 1H), 7.28 (d, J = 2.68 Hz, 1H), 7.32 (bs, 1H), 7.31−7.46 (m, 3H), 7.65 (d, J = 8.17 Hz, 2H), 7.90 (d, J = 5.78 Hz, 1H), 11.64 (bs, 1H). ESI (+) MS: m/z 279 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{14}N_4O + H^+$, 279.1241; found, 279.1245.

2-Bromo-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic Acid Amide (36a). Ethylcyanoacetate (0.79 mL, 7.4 mmol) was added to a suspension of sodium metal (0.17 g, 7.4 mmol) in 25 mL of anhydrous ethanol at 0 °C. The solution was stirred until sodium dissolved completely. The solvent was evaporated, and the solid was added to a solution of 2-bromo-1-(4-pyridinyl)-ethanone (2.08 g, 7.4 mmol) and DIEA (1.29 mL, 7.4 mmol) in 45 mL of anhydrous tetrahydrofuran. The mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was suspended in water and extracted with dichloromethane. The organic extracts were dried over anhydrous Na_2SO_4, and the crude material was purified by flash chromatography (dichloromethane/methanol 95:5) to afford 2-cyano-4-(pyridin-4-yl)-4-oxo-butyric acid ethyl ester (**33a**) as an oil (1.03 g, 4.4 mmol, 60%). ^{1}H NMR (DMSO-d_6/400 MHz) δ ppm 1.23 (t, J = 7.07 Hz, 3H), 3.87 (m, 2H), 4.22 (q, J = 7.07 Hz, 2H), 4.64 (t, J = 5.37 Hz, 1H), 7.88 (m, 2H), 8.86 (m, 2H). ESI (+) MS: m/z 233(MH^+). HRMS $(M + H)^+$ calcd for $C_{12}H_{12}N_2O_3 + H^+$, 233.0921; found, 233.0922.

A solution of cyanoester **33a** (1.02 g, 4.3 mmol), dissolved in diethyl ether and dichloromethane, was added dropwise to a solution of HBr (33% in acetic acid, 13 mL, 43.1 mmol) at 0 °C. The reaction mixture was left for 20 min at 0 °C and then at room temperature until disappearance of the starting material (2.5 h). The solid was filtered and washed with acetone and methanol. The pyridinium salt was neutralized with 7N NH_3 in methanol. The solid was purified by flash chromatography (dichloromethane/methanol 95:5) to give 0.805 g (62%) of 2-bromo-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester (**34a**) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, J = 7.12 Hz, 3H), 4.24 (q, J = 7.12 Hz, 2H), 7.26 (s, 1H), 7.71 (d, J = 6.22 Hz, 2H), 8.54 (d, J = 6.22 Hz, 2H), 12.85 (s, 1H). ESI (+) MS: m/z 295−297 (MH^+). HRMS (ESI): calcd for $C_{12}H_{11}BrN_2O_2 + H^+$, 295.0077; found, 295.0078.

Ester **34a** (1.10 g, 3.74 mmol), dissolved in 8 mL of 4 M aqueous NaOH and 8 mL of ethanol, was refluxed for 4 h. The solution was cooled and neutralized with acetic acid. The precipitate was filtered and washed with water and acetone to afford 0.850 g (85%) of 2-bromo-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.33 (s, 1H), 7.83 (d, J = 6.00 Hz, 2H), 8.58 (d, J = 6.00 Hz, 2H), 12.37 (bs, 1H), 12.91 (s, 1H). MS: m/z 265−267 [M − H].

The acid (0.450 g, 1.68 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) in the presence of DIEA (1.27 mL, 7.30 mmol). To the solution, cooled to 0 °C, EDC·HCl (1.03 g, 5.5 mmol) and HOBt·NH_3 (0.810 g, 5.34 mmol) were added. The reaction mixture was left overnight at room temperature. The solvent was evaporated, water was added, and the slurry was extracted with dichloromethane. The crude was purified by flash-chromatography (dichloromethane/methanol 95:5) to yield 0.153 g (33%) of the title compound as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.02 (s, 2H), 7.29 (s, 1H), 7.59 (d, J = 6.25 Hz, 2H), 8.52 (d, J = 6.25 Hz, 2H), 12.54 (s, 1H). ESI (+) MS: m/z 266−268 (MH^+). HRMS (ESI): calcd for $C_{10}H_8BrN_3O + H^+$, 265.9923; found, 265.9935.

5-(3-Fluoro-pyridin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (39). Ethylcyanoacetate (715 μL, 6.7 mmol) was added to a suspension of sodium metal (0.154 g, 6.7 mmol) in 20 mL of anhydrous ethanol at 0 °C. The solution was stirred until sodium dissolved completely. The solvent was evaporated, and the solid was added to a solution of 2-bromo-1-(3-fluoro-4-pyridinyl)-ethanone (2.04 g, 6.7 mmol) and DIEA (1.16 mL, 6.7 mmol) in 40 mL of anhydrous tetrahydrofuran. The mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was suspended in water and extracted with dichloromethane. The organic extracts were dried over anhydrous sodium sulfate, and the crude material was purified by flash chromatography (dichloromethane/methanol 98:2) to afford 2-cyano-4-(3-fluoro-pyridin-4-yl)-4-oxo-butyric acid ethyl ester (**33b**) as an oil (1.05 g, 4 mmol, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 (t, J = 7.07 Hz, 3H), 3.78 (m, 2H), 4.20 (q, J = 7.07 Hz, 2H), 4.61 (t, J = 5.37 Hz, 1H), 7.81 (m, 1H), 8.64 ((dd, J = 5.00, 1.22 Hz, 1H), 8.82 (d, J = 2.56 Hz, 1H). ESI (+) MS: m/z 251(MH^+). HRMS $(M + H)^+$ calcd for $C_{12}H_{11}FN_2O_3 + H^+$, 251.0826; found, 251.0816.

A solution of **33b** (1.05 g, 4 mmol) in anhydrous diethyl ether (3 mL) and dichloromethane (2 mL) was added to 33% HBr in acetic acid (12 mL), cooled at 0 °C. The reaction mixture was stirred for 3 h, the precipitate was filtered, washed with acetone and methanol, and neutralized with 7 N NH_3 in methanol. The solvent was evaporated to give 1.03 g (80%) of 2-bromo-5-(3-fluoro-pyridin-4-yl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (**34b**) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26

(t, J = 7.07 Hz, 3H), 4.20 (q, J = 7.07 Hz, 2H), 7.08 (d, J = 3.53 Hz, 1H), 7.30 (bs, 1H), 7.83 (m, 1H), 8.39 (dd, J = 5.12, 0.85 Hz, 1H), 8.55 (d, J = 3.41 Hz, 1H). ESI (+) MS: m/z 313−315 (MH^+). HRMS $(M + H)^+$ calcd for $C_{12}H_{10}BrFN_2O_2 + H^+$, 312.9982; found, 312.9976.

The ester **34b** (1.0 g, 3.2 mmol) was dissolved in 8 mL of ethanol and 8 mL of 1 M aq NaOH and heated at 100 °C for 6 h. The product was precipitated with acetic acid, and the solid was filtered and washed with acetone to afford 0.722 g (77%) of 2-bromo-5-(3-fluoro-pyridin-4-yl)-1*H*-pyrrole-3-carboxylic acid (**35b**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.98 (d, J = 5.12 Hz, 1H), 7.81 (q, J = 5.12 Hz, 1H), 8.13 (d, J = 5.60 Hz, 1H), 8.25 (d, J = 4.02 Hz, 1H). MS: m/z 283−285 [M − H]. HRMS $(M + H)^+$ calcd for $C_{10}H_6BrFN_2O_2 + H^+$, 284.9669; found, 284.9670.

The acid **35b** (1.68 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) in the presence of DIEA (1.27 mL, 7.30 mmol). To the solution, cooled to 0 °C, EDC·HCl (1.03 g, 5.5 mmol) and HOBt·NH_3 (0.81 g, 5.34 mmol) were added. The reaction mixture was left overnight at room temperature. The solvent was evaporated, water was added, and the slurry was extracted with dichloromethane. The crude was purified by flash chromatography (dichloromethane/methanol 98:2) to yield 2-bromo-5-(3-fluoro-pyridin-4-yl)-1*H*-pyrrole-3-carboxamide (**36b**) as a yellow solid (48% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.09 (s, 2H), 7.35 (s, 1H), 7.98 (d, J = 4.83 Hz, 1H), 8.47 (d, J = 4.84 Hz, 1H), 8.61 (d, J = 0.91 Hz, 1H), 12.05 (s, 1H). ESI (+) MS: m/z 284−286 (MH^+). HRMS $(M + H)^+$ calcd for $C_{10}H_7BrFN_3O + H^+$, 283.9829; found, 283.9832.

To a solution of **36b** (0.227 g, 0.8 mmol) in deoxygenated toluene/ethanol 1:1 (10 mL), deoxygenated 1 M aqueous Na_2CO_3 (2.2 mL, 2.2 mmol), LiCl (2.7 mmol), phenyl boronic acid (1.4 mmol), and $(Ph_3P)_2PdCl_2$ (0.006 g) were added and the mixture was stirred at 100 °C until disappearance of the starting material. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography (eluant: dichloromethane/methanol 95:5). When required, the product was dissolved in ethanol and treated with 2N HCl in diethyl ether until precipitation of the hydrochloride salt occurred. The precipitate was filtered, affording 0.188 g of the title compound (74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.95 (bs, 2H), 7.34 (m, 4H), 7.69 (m, 2H), 8.10 (m, 1H), 8.5 (d, J = 5.37 Hz, 1H), 8.71 (d, J = 4.02 Hz, 1H), 12.01 (bs, 1H). ESI (+) MS: m/z 282 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}FN_3O + H^+$, 282.1037; found, 282.1033.

Analogously the following compounds were prepared:

2-(2-Methoxy-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (37). From 2-bromo-1-pyridin-4-yl-ethanone hydrobromide (**2a**, 32% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.76 (s, 3H), 6.95 (bs, 2H), 7.06 (t, J = 8.05 Hz, 1H), 7.16 (d, J = 8.05 Hz, 1H), 7.40 (dd, J = 7.44, 1.71 Hz, 1H), 7.46 (m, 1H), 7.73 (s, 1H), 8.15 (d, J = 7.00 Hz, 2H), 8.71 (d, J = 7.00 Hz, 2H), 12.42 (s, 1H). ESI (+) MS: m/z 294 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O_2 + H^+$, 294.1237; found, 294.1233.

2-(4-Methoxy-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide Hydrochloride (38). From 2-bromo-1-pyridin-4-yl-ethanone hydrobromide (**2a**, 42% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.84 (s, 3H), 7.07 (d, J = 8.90 Hz, 2H), 7.33 (bs, 2H), 7.67 (d, J = 8.90 Hz, 2H), 7.73 (s, 1H), 8.22 (d, J = 6.50 Hz, 2H), 8.72 (d, J = 6.50 Hz, 2H), 12.28 (s, 1H). ESI (+) MS: m/z 294 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O_2 + H^+$, 294.1237; found, 294.1234.

5-(2-Amino-pyrimidin-4-yl)-2-thiophen-3-yl-1*H*-pyrrole-3-carboxamide (40). From 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide (**2c**, 27% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.36 (bs, 2H), 6.87 (bs, 2H), 7.01 (d, J = 5.24 Hz, 1H), 7.26 (d, J = 2.44 Hz, 1H), 7.54 (dd, J = 5.00, 2.93 Hz, 1H), 7.65 (dd, J = 5.00, 1.22 Hz, 1H), 8.11 (dd, J = 2.93, 1.22 Hz, 1H), 8.20 (d, J = 5.24 Hz, 1H), 11.52 (bs, 1H). ESI (+) MS: m/z 286 (MH^+). HRMS $(M + H)^+$ calcd for $C_{13}H_{11}N_5OS + H^+$, 286.0757; found, 286.0753. Anal. ($C_{13}H_{11}N_5OS$) C, H, N, S.

5-Pyridin-4-yl-2-*p*-tolyl-1*H*-pyrrole-3-carboxamide (43). Acid **35a** (0.503 g, 1.87 mmol) was loaded on Rink amide MBHA resin (1.38 g, 0.935 mmol, theoretical loading 0.68 mmol/g) by stirring with DIEA (0.65 mL, 3.74 mmol), EDC·HCl (0.537 g, 2.8 mmol), and HOBt (0.379 g, 2.8 mmol) in 20 mL of *N*,*N*-dimethylformamide at room temperature overnight. The substitution rate was 78%, and the resin had been previously cleaved with 20% piperidine in *N*,*N*-dimethylformamide. The supported amide (0.112 g, 0.052 mmol) was heated at 100 °C overnight with 4-methylphenylboronic acid (0.035 g, 0.26 mmol), LiCl (0.011 g, 0.26 mmol), Cs_2CO_3 (0.085 g, 0.26 mmol), and $(PhP_3)_2PdCl_2$ (0.007 g, 0.01 mmol) in 2 mL of deoxygenated *N*,*N*-dimethylformamide and 0.1 mL of deoxygenated water. The Rink amide was cleaved with trifluoroacetic acid/dichloromethane 95:5 at room temperature. The solution was concentrated and the crude was purified by preparative HPLC to afford the title compound (yield: 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (s, 3H), 7.00 (bs, 2H), 7.25 (d, J = 8.00 Hz, 2H), 7.34 (d, J = 2.56 Hz, 1H), 7.58 (d, J = 8.00 Hz, 2H), 7.79 (d, J = 6.22 Hz, 2H), 8.56 (d, J = 6.22 Hz, 2H), 11.85 (s, 1H). ESI (+) MS: m/z 278 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O + H^+$, 278.1288; found, 278.1289.

Analogously the following compounds were prepared:

5-Pyridin-4-yl-2-*m*-tolyl-1*H*-pyrrole-3-carboxamide (42). Yield 52%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 6.90 (bs, 2H), 7.20−7.40 (m, 5H), 7.70 (d, J = 6.00 Hz, 2H), 8.55 (d, J = 6.00 Hz, 2H), 11.88 (s, 1H). ESI (+) MS: m/z 278 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O + H^+$, 278.1288; found, 278.1294.

2-(3-Methoxy-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (44). Yield 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.83 (s, 3H), 6.66 (bs, 2H), 7.28 (m, 3H), 7.40 (m, 2H), 8.24 (d, J = 6.82 Hz, 2H), 9.11 (d, J = 6.82 Hz, 2H), 12.32 (s, 1H). ESI (+) MS: m/z 294 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O_2 + H^+$, 294.1237; found, 294.1238.

2-(2-Nitro-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (45). Yield 50%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.96 (bs, 2H), 7.37 (s, 1H), 7.58−7.65 (m, 4H), 7.79 (m, 1H), 8.07 (dd, J = 8.17, 1.22 Hz, 1H), 8.55 (d, J = 6.22 Hz, 2H), 12.19 (s, 1H). ESI (+) MS: m/z 309 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}N_4O_3 + H^+$, 309.0982; found, 309.0980.

2-(3-Nitro-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (46). Yield 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.30 (bs, 2H), 7.35 (d, J = 2.69 Hz, 1H), 7.76 (m, 3H), 8.15 (m, 1H), 8.22 (m, 1H), 8.58 (dd, J = 4.63, 1.58 Hz, 2H), 8.61 (t, J = 1.81 Hz, 1H), 12.07 (s, 1H). ESI (+) MS: m/z 309 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}N_4O_3 + H^+$, 309.0982; found, 309.0978.

2-(4-Nitro-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (47). Yield 35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (bs, 2H), 7.70 (s, 1H), 8.02 (d, J = 8.78 Hz, 2H), 8.19 (d, J = 6.20 Hz, 2H), 8.32 (d, J = 8.78 Hz, 2H), 8.77 (d, J = 6.20 Hz, 2H), 12.57 (bs, 1H). ESI (+) MS: m/z 309 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{12}N_4O_3 + H^+$, 309.0982; found, 309.0981.

2-(2-Cyano-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (48). Yield 44%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.88 (bs, 2H), 7.39 (s, 1H), 7.59 (m, 1H), 7.64 (m, 3H), 7.75 (t, J = 7.19 Hz, 1H), 7.88 (d, J = 7.08 Hz, 1H), 8.56 (d, J = 4.75 Hz, 2H), 12.21 (s, 1H). ESI (+) MS: m/z 289 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{12}N_4O + H^+$, 289.1084; found, 289.1085.

2-(3-Cyano-phenyl)-5-pyridin-4-yl-1*H*-pyrrole-3-carboxamide (49). Yield 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.99 (bs, 2H), 7.32 (d, J = 2.56 Hz, 1H), 7.64 (t, J = 7.56 Hz, 1H), 7.69 (d, J = 6.10 Hz, 2H), 7.82 (m, 2H), 8.03 (m, 2H), 8.14 (m, 1H), 8.56 (d, J = 6.10 Hz, 2H), 11.95 (s, 1H). ESI (+) MS: m/z 289 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{12}N_4O + H^+$, 289.1084; found, 289.1082.

5-(2-Amino-pyrimidin-4-yl)-2-naphthalen-1-yl-1*H*-pyrrole-3-carboxamide (50). Yield 42%. ^{1}H NMR (400 MHz, DMSO-d_6)

δ ppm 6.33 (bs, 2H), 6.65 (bs, 2H), 6.96 (d, J = 5.27 Hz, 1H), 7.40−7.60 (m, 5H), 7.98 (m, 2H), 8.17 (d, J = 5.27 Hz, 1H), 11.95 (bs, 1H). ESI (+) MS: m/z 330 (MH^+). HRMS $(M + H)^+$ calcd for $C_{19}H_{15}N_5O + H^+$, 330.1349; found, 330.1349.

5-(2-Amino-pyrimidin-4-yl)-2-naphthalen-2-yl-1*H*-pyrrole-3-carboxamide (51). Yield 47%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.37 (bs, 2H), 6.87 (bs, 1H), 7.05 (d, J = 5.24 Hz, 1H), 7.32 (d, J = 2.32 Hz, 1H), 7.39 (bs, 1H), 7.51−7.59 (m, 2H), 7.78 (dd, J = 8.41, 1.71 Hz, 1H), 7.88−7.97 (m, 3H), 8.16 (d, J = 1.22 Hz, 1H), 8.23 (d, J = 5.24 Hz, 1H), 11.80 (bs, 1H). ESI (+) MS: m/z 330 (MH^+). HRMS $(M + H)^+$ calcd for $C_{19}H_{15}N_5O + H^+$, 330.1349; found, 330.1350.

5-(2-Amino-pyrimidin-4-yl)-2-benzofuran-2-yl-1*H*-pyrrole-3-carboxamide (52). Yield 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.53 (bs, 2H), 7.07 (bs, 1H), 7.11 (d, J = 5.12 Hz, 1H), 7.27 (td, J = 7.56, 0.98 Hz, 1H), 7.34 (td, J = 7.56, 0.98 Hz, 1H), 7.42 (s, 1H), 7.61 (dd, J = 7.56, 0.98 Hz, 1H), 7.65 (bs, 1H), 7.70 (dd, J = 7.56, 0.98 Hz, H), 7.87 (d, J = 0.98 Hz, 1H), 8.26 (d, J = 5.12 Hz, 1H), 11.61 (bs, 1H). ESI (+) MS: m/z 320 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{13}N_5O_2 + H^+$, 320.1142; found, 320.1142.

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-2-yl-1*H*-pyrrole-3-carboxamide (53). Yield 47%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.42 (bs, 2H), 6.99 (bs, 1H), 7.08 (d, J = 5.12 Hz, 1H), 7.32 (s, 1H), 7.33−7.41 (m, 2H), 7.56 (bs, 1H), 7.84 (bs, 1H), 7.91−8.03 (m, 2H), 8.25 (d, J = 5.12 Hz, 1H), 11.82 (bs, 1H). ESI (+) MS: m/z 336 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{13}N_5OS + H^+$, 336.0914; found, 336.0918.

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-3-yl-1*H*-pyrrole-3-carboxamide (54). Yield 52%. ^{1}H NMR ((400 MHz, DMSO-d_6) δ ppm 6.35 (bs, 2H), 6.76 (bs, 1H), 6.99 (d, J = 5.24 Hz, 1H), 7.20 (s, 1H), 7.35−7.42 (m, 3H), 7.51−7.57 (m, 1H), 7.90 (s, 1H), 8.00−8.06 (m, 1H), 8.20 (d, J = 5.24 Hz, 1H), 11.91 (bs, H). ESI (+) MS: m/z 336 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{13}N_5OS + H^+$, 336.0914; found, 336.0910.

5-Pyridin-4-yl-1*H*-pyrrole-3-carboxylic Acid Amide (57). To a suspension of sodium (0.081 g, 3.5 mmol) in 10 mL of anhydrous ethanol, ethyl cyanoacetate (0.37 mL, 3.5 mmol) was added at 0 °C. The solution was stirred until sodium was completely dissolved. The solvent was evaporated to obtain a white solid that was added portionwise to a stirred solution of 4-(bromoacetyl)pyridine hydrobromide **2a** (1.04 g, 3.5 mmol) in anhydrous tetrahydrofuran (20 mL) and DIEA (0.6 mL, 3.5 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed, and the residue was suspended in water and extracted with dichloromethane. The organic extracts were combined, dried (anhydrous sodium sulfate), and concentrated. The crude product was purified by flash chromatography (dichloromethane/methanol 95:5) to give 0.710 g (87%) of 2-cyano-4-oxo-4-pyridin-4-yl-butyric acid ethyl ester **33a** as a reddish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (t, J = 7.07 Hz, 3H), 3.88 (d, J = 5.25 Hz, 2H), 4.21 (q, J = 7.07 Hz, 2H), 4.64 (t, J = 5.25 Hz, 1H), 7.89 (d, J = 6.00 Hz, 2H), 8.85 (d, J = 6.00 Hz, 2H). ESI (+) MS: m/z 233 (MH^+). HRMS (ESI): calcd for $C_{12}H_{12}N_2O_3 + H^+$, 233.0921; found, 233.0921.

To a solution of **33a** (0.550 g, 2.37 mmol) in diethyl ether (1 mL) at 0 °C, 4 N HCl in dioxane (6 mL, 23.7 mmol) was added dropwise. The reaction mixture was left for 10 min at 0 °C and then stirred at room temperature for 6 h. The solid was filtered and washed with diethyl ether to yield 0.510 g (84%) of 2-chloro-5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester hydrochloride **55** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, J = 7.07 Hz, 3H), 4.27 (q, J = 7.07 Hz, 2H), 7.73 (s, 1H), 8.25 (d, J = 5.61 Hz, 2H), 8.78 (m, 2H), 13.5 (bs, 1H). ESI (+) MS: m/z 251 (MH^+). HRMS (ESI): calcd for $C_{12}H_{11}ClN_2O_2 + H^+$, 251.0582; found, 251.0581.

A mixture of **55** (0.630 g, 2.2 mmol) in 30 mL of methanol, ammonium formate (1.26 g, 19.8 mmol), and 10% Pd/C (0.633 g) was stirred at room temperature until disappearance of the starting material. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated. Saturated aqueous $NaHCO_3$ was added, and the slurry was extracted with ethyl acetate, affording 0.310 g (63%) of 5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid ethyl ester **56** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, J = 7.07 Hz, 3H), 4.24 (q, J = 7.07 Hz, 2H), 7.20 (m, 1H), 7.63 (m, 1H), 7.68 (m, 2H), 8.52 (m, 2H), 12.27 (bs, 1H). ESI (+) MS: m/z 217 (MH^+). HRMS (ESI): calcd for $C_{12}H_{12}N_2O_2 + H^+$, 217.0971; found, 217.0972.

Ester **56** (0.200 g, 0.92 mol) in 4 M aq NaOH (4.6 mL) and ethanol (4 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to 0 °C, and the product was precipitated by adding concentrated HCl. The solid was filtered to obtain 0.160 g (78%) of 5-pyridin-4-yl-1*H*-pyrrole-3-carboxylic acid hydrochloride as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.60 (m, 1H), 7.81 (m, 1H), 8.14 (m, 2H), 8.72 (m, 2H), 12.70 (s, 1H). MS: m/z 187 [M − H].

To a solution of the acid (0.137 g, 0.61 mmol) in DIEA (213 μL, 1.22 mmol) and anhydrous tetrahydrofuran (8 mL), cooled at 0 °C, EDC·HCl (0.175 g, 0.9 mmol) and HOBt·NH_3 (0.137 g, 0.9 mmol) were added and the solution was stirred overnight at room temperature. The solution was concentrated, water was added, and the product was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give a solid that was triturated with diethyl ether and filtered to afford 0.052 g (44%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.98 (bs, 2H), 7.61 (bs, 1H), 7.79−7.82 (m, 1H), 8.06 (d, J = 6.58 Hz, 2H), 8.71 (d, J = 6.83 Hz, 2H), 12.57 (s, 1H). ESI (+) MS: m/z 188 (MH^+). HRMS (ESI): calcd for $C_{10}H_9N_3O + H^+$, 188.0818; found, 188.0820.

5-(2-Amino-pyrimidin-4-yl)-1-methyl-2-phenyl-1*H*-pyrrole-3-carboxamide (58). Methyl iodide (0.015 g, 0.107 mmol) was added to a solution of 5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide **18** (0.030 g, 0.107 mmol) and Cs_2CO_3 (0.070 g, 0.215 mmol) in dry *N*,*N*-dimethylformamide (0.5 mL), and the reaction mixture was stirred at room temperature for 24 h. To achieve completion, a further addition of methyl iodide (0.009 g, 0.064 mmol) was required and the reaction mixture was stirred at 80 °C for 12 h. The solvent was removed under reduced pressure and the residue was taken up into dichloromethane (2 mL, with 2% methanol), which was washed with a saturated solution of sodium bicarbonate (2 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated to dryness to give the crude product, which was purified by flash chromatography over silica gel (dichloromethane/methanol/33% ammonium hydroxide 95/0.5/0.1), affording the title compound as a white solid (0.020 g, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.70 (s, 3H), 6.53 (s, 2H), 6.73 (bs, 1H), 6.81 (bs, 1H), 6.83 (d, J = 5.40 Hz, 1H), 7.25 (s, 1H), 7.35−7.40 (m, 2H), 7.41−7.51 (m, 3H), 8.20 (d, J = 5.20 Hz, 1H). ESI (+) MS: m/z 294 (MH^+). HRMS $(M + H)^+$ calcd for $C_{16}H_{15}N_5O + H^+$, 294.1350; found, 294.1348.

5-(2-Amino-pyrimidin-4-yl)-1-trifluoroethyl-2-phenyl-1*H*-pyrrole-3-carboxamide (59). To a solution of **18** (0.063 g, 0.215 mmol) in acetonitrile (6 mL), 18-crown-6 (0.085 g, 0.322 mmol), K_2CO_3 (0.059 g, 0.403 mmol), and 2,2,2-trifluoroethyl trifluoromethanesulfonate (46 μL, 0.320 mmol) were added and the suspension was heated at 80 °C for 5 h. The reaction mixture was taken up in water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. After preparative HPLC, the title compound was obtained as a white solid (70 mg, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.49 ppm (bs, 2H), 6.66 (s, 2H), 6.86 (d, J = 5.20 Hz, 1H), 6.89 (bs, 1H), 6.97 (bs, 1H), 7.33−7.40 (m, 3H), 7.43−7.53 (m, 3H), 8.24 (d, J = 5.20 Hz, 1H). ESI (+) MS: m/z 362 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{14}F_3N_5O + H^+$, 362.1223; found, 362.1228.

5-(2-Aminopyrimidin-4-yl)-1-(2-hydroxyethyl)-2-phenyl-1*H*-pyrrole-3-carboxamide (60). To a solution of 5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide **18** (0.162 g, 0.57 mmol) in 5 mL of dry *N*,*N*-dimethylformamide, cesium carbonate (0.741 g, 2.28 mmol) and iodoethanol tetrahydropyranylether (0.292 g, 1.14 mmol) were added under stirring. The mixture was heated at 80 °C for 8 h. The solvent was then removed under reduced pressure, the residue taken up with water, and the product extracted with dichloromethane and dried over anhydrous sodium sulfate. By trituration with diethyl ether 5-(2-aminopyrimidin-4-yl)-2-phenyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrrole-3-carboxamide (0.163 g; 69%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20−1.70 (m, 6H), 3.21−3.58 (m, 4H), 4.28 (t, J = 2.93 Hz, 1H), 4.49−4.66 (m, 2H), 6.52 (s, 2H), 6.73 (s, 2H), 6.84 (d, J = 5.24 Hz, 1H), 7.29 (s, 1H), 7.35−7.49 (m, 5H), 8.20 (d, J = 5.36 Hz, 1H). ESI (+) MS: m/z 408 (MH^+). HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_5O_3 + H^+$, 408.2030; found, 408.2033.

To a solution of 5-(2-aminopyrimidin-4-yl)-2-phenyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrrole-3-carboxamide (0.158 g, 0.39 mmol) in 5 mL of dry dichloromethane, 2 mL of trifluoroacetic acid were added. The solution was stirred at room temperature for 5 h in a closed bottle. After solvent evaporation, the residue was taken up with water, neutralized with saturated aqueous $NaHCO_3$, extracted with dichloromethane, and dried over anhydrous sodium sulfate. The crude product was then purified by flash chromatography on a silica gel column (dichloromethane/methanol 9:1) and afforded 0.123 g (95%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.32 (m, 2H), 4.35 (t, J = 6.58 Hz, 2H), 4.66 (t, J = 5.85 Hz, 1H), 6.54 (s, 2H), 6.62−6.75 (m, 2H), 6.85 (d, J = 5.24 Hz, 1H), 7.29 (s, 1H), 7.35−7.40 (m, 2H), 7.45−7.49 (m, 3H), 8.20 (d, J = 5.24 Hz, 1H). ESI (+) MS: m/z 324 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{17}N_5O_2 + H^+$, 324.1455; found, 324.1450.

1-(2-Aminoethyl)-5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide Dihydrochloride (64). Cesium carbonate (1.03 g, 3.25 mmol) and *tert*-butyl (2-bromoethyl)carbamate (0.364 g, 1.63 mmol) were added to a solution of ethyl 5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylate **61** (0.25 g, 0.81 mmol) in 5 mL of dry *N*,*N*-dimethylformamide. The mixture was stirred at 85 °C for 6 h. The solvent was removed in vacuo and the residue taken up with dichloromethane and washed with water. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was crystallized from di-*iso*-propyl ether to yield 0.363 g (98%) of ethyl 5-(2-aminopyrimidin-4-yl)-1-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-2-phenyl-1*H*-pyrrole-3-carboxylate **62a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (t, J = 7.07 Hz, 3H), 1.32 (s, 9H), 1.55−1.68 (m, 2H), 2.61−2.73 (m, 2H), 3.98 (q, J = 6.99 Hz, 2H), 4.19−4.34 (m, 2H), 6.56 (bs, 2H), 6.63 (t, J = 5.79 Hz, 1H), 6.97 (d, J = 5.37 Hz, 2H), 7.23 (s, 1H), 7.33−7.38 (m, 2H), 7.44−7.52 (m, 3H), 8.20 (d, J = 5.24 Hz, 2H). ESI (+) MS: m/z 452 (MH^+). HRMS $(M + H)^+$ calcd for $C_{24}H_{29}N_5O_4 + H^+$, 452.2293; found, 452.2305.

To a solution of ester **62a** (0.363 g, 0.80 mmol) in a mixture of tetrahydrofuran/methanol/water 8/1/1, lithium hydroxide monohydrate (0.268 g, 6.4 mmol) was added under stirring. The reaction was heated at 80 °C for 16 h. The solvent was then evaporated under reduced pressure and the residue taken up with water and neutralized with 5% $KHSO_4$ aqueous solution. The resulting precipitate was collected by filtration and washed with water and acetone, giving 0.262 g (77%) of 5-(2-aminopyrimidin-4-yl)-1-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-2-phenyl-1*H*-pyrrole-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 9H), 3.12−3.22 (m, 2H), 4.19 (t, J = 6.89 Hz, 2H), 6.46 (s, 2H), 6.80 (bs, 1H), 6.83 (d, J = 5.37 Hz, 1H), 7.06 (s, 1H), 7.27−7.39 (m, 5H), 8.08 (d, J = 5.49 Hz, 1H). ESI (+) MS: m/z 424 (MH^+). HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_5O_4 + H^+$, 424.1980; found, 424.1982.

To a suspension of the acid (0.142 g, 0.33 mmol) in 6 mL of dimethylacetamide and diisopropylethylamine (338 μL, 1.98 mmol), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (0.138 g, 0.43 mmol) and ammonium chloride (0.106 g, 1.98 mmol) were added to the mixture. The reaction was heated at 80 °C for 16 h. The solvent was then removed under reduced pressure, and the residue was dissolved with dichloromethane and washed with $NaHCO_3$ saturated aqueous solution. The organic layer was then dried over anhydrous sodium sulfate and evaporated to dryness. The crude material was purified by flash chromatography on a silica gel column (dichloromethane/methanol 95:5), giving 0.065 g (47%) of *tert*-butyl {2-[5-(2-aminopyrimidin-4-yl)-3-carbamoyl-2-phenyl-1*H*-pyrrol-1-yl]ethyl}carbamate (**63a**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (s, 9H), 3.17 (q, J = 6.06 Hz, 2H), 4.22 (t, J = 6.83 Hz, 2H), 6.58 (s, 2H), 6.61 (bs, 1H), 6.71 (bs, 1H), 6.83 (t, J = 5.97 Hz, 1H), 6.86 (d, J = 5.37 Hz, 1H), 7.34 (s, 1H), 8.18 (d, J = 5.37 Hz, 1H). ESI (+) MS: m/z 423 (MH^+). HRMS $(M + H)^+$ calcd for $C_{22}H_{26}N_6O_3 + H^+$, 423.2139; found, 423.2138.

To a solution of carbamate **63a** (0.065 g, 0.15 mmol) in 15 mL of dry dioxane, 4 mL of 4 M HCl in dioxane were added. The resulting solution was stirred at room temperature in a closed bottle overnight. The solvent was removed under reduced pressure, and toluene was added and evaporated again, giving a residue that was triturated with diethyl ether then collected by filtration, giving 0.050 g (86%) of the title compound **64**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.55 (t, J = 7.32 Hz, 2H), 6.83 (bs, 1H), 6.94 (bs, 1H), 7.18 (d, J = 6.46 Hz, 1H), 7.88 (s, 1H), 8.08 (bs, 3H), 8.23 (d, J = 6.58 Hz, 1H). ESI (+) MS: m/z 323 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{18}N_6O + H^+$, 323.1615; found, 323.1614.

1-(3-Aminopropyl)-5-(2-aminopyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxamide Dihydrochloride (65). As reported for the synthesis of **64**, ethyl 5-(2-aminopyrimidin-4-yl)-1-{3-[(*tert*-butoxycarbonyl)amino]propyl}-2-phenyl-1*H*-pyrrole-3-carboxylate **62b** was prepared (98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (t, J = 7.07 Hz, 3H), 1.32 (s, 9H), 1.54−1.69 (m, 2H), 2.63−2.71 (m, 2H), 3.98 (q, J = 6.99 Hz, 2H), 4.19−4.37 (m, 2H), 6.56 (bs, 2H), 6.63 (t, J = 5.55 Hz, 1H), 6.97 (d, J = 5.37 Hz, 1H), 7.23 (s, 1H), 7.31−7.40 (m, 2H), 7.42−7.53 (m, 3H), 8.20 (d, J = 5.24 Hz, 1H). ESI (+) MS: m/z 466 (MH^+). HRMS $(M + H)^+$ calcd for $C_{25}H_{31}N_5O_4 + H^+$, 466.2449; found, 466.2444.

As reported for the synthesis of **64**, 5-(2-aminopyrimidin-4-yl)-1-{3-[(*tert*-butoxycarbonyl)amino]propyl}-2-phenyl-1*H*-pyrrole-3-carboxylic acid was prepared similarly (37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 9H), 1.55−1.66 (m, 2H), 2.62−2.71 (m, 2H), 4.23 (t, J = 7.44 Hz, 2H), 6.53 (bs, 2H), 6.62 (t, J = 5.91 Hz, 1H), 6.94 (d, J = 5.24 Hz, 1H), 7.20 (s, 1H), 7.32−7.48 (m, 5H), 8.19 (d, J = 5.37 Hz, 0H), 11.48 (s, 1H). ESI (+) MS: m/z 438 (MH^+). HRMS $(M + H)^+$ calcd for $C_{23}H_{27}N_5O_4 + H^+$, 438.2136; found, 438.2137.

In parallel to the synthesis of **64**, *tert*-butyl {3-[5-(2-aminopyrimidin-4-yl)-3-carbamoyl-2-phenyl-1*H*-pyrrol-1-yl]propyl}-carbamate **63b** was prepared (68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 9H), 1.59 (quin, J = 7.50 Hz, 2H), 2.66 (q, J = 6.50 Hz, 2H), 4.21 (t, J = 7.19 Hz, 2H), 6.52 (bs, 2H), 6.61 (t, J = 5.49 Hz, 1H), 6.71 (bs, 2H), 6.84 (d, J = 5.37 Hz, 1H), 7.29 (s, 1H), 8.20 (d, J = 5.37 Hz, 1H). ESI (+) MS: m/z 437 (MH^+). HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_6O_3 + H^+$, 437.2296; found, 437.2300.

Similarly, the title compound **65** was prepared (81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.78 (quin, J = 7.70 Hz, 2H), 2.53−2.62 (m, 2H), 4.37 (t, J = 7.38 Hz, 2H), 6.89 (bs, 2H), 7.14 (d, J = 6.46 Hz, 1H), 7.74 (bs, 3H), 7.78 (bs, 1H), 7.95 (bs, 3H), 8.24 (d, J = 6.46 Hz, 1H). ESI (+) MS: m/z 337 (MH^+). HRMS $(M + H)^+$ calcd for $C_{18}H_{20}N_6O + H^+$, 337.1772; found, 337.1771.

5-(2-Amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1*H*-pyrrole-3-carboxamide (67). To a solution of ethyl benzoylacetate (1.34 g, 7 mmol) in anhydrous tetrahydrofuran (100 mL) at 0 °C, sodium

hydride (60% in mineral oil, 0.711 g, 17.5 mmol) was added under argon with stirring. After 5 min, 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide **2c** (2.52 g, 8.4 mmol) was added and the mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the residue was dissolved in acetic acid (30 mL) and 2 M ethylamine in tetrahydrofuran (8.7 mL, 17.5 mmol). The mixture was subjected to microwave irradiation at 170 °C for 5 min, then diluted with ethyl acetate and washed with $NaHCO_3$ saturated aqueous solution. The water layer was extracted with ethyl acetate, and the combined organic layers were washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (dichloromethane/ethanol/acetone 96:2:2), thus affording 0.723 g of 5-(2-amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (**66**, 29% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.97−1.04 (m, 6H), 3.97 (q, J = 7.07 Hz, 2H), 4.38 (q, J = 6.95 Hz, 2H), 6.56 (s, 2H), 6.97 (d, J = 5.37 Hz, 1H), 7.23 (s, 1H), 7.34−7.41 (m, 2H), 7.46−7.54 (m, 3H), 8.20 (d, J = 5.37 Hz, 1H). ESI (+) MS: m/z 337 (MH^+), HRMS $(M + H)^+$ calcd for $C_{19}H_{20}N_4O_2 + H^+$, 337.1659; found, 337.1664.

To a suspension of the ester **66** (0.711 g, 2.08 mmol) in 95% ethanol (8 mL), 4 M aq NaOH (8 mL) was added and the mixture was stirred for 1 h at 100 °C. The solvent was removed under vacuum, and the aqueous residue, when acidified with 37% HCl to pH 5, led to precipitation of the product. The mixture was filtered, the solid was washed with a little cold water and dried, thus affording 0.662 g of 5-(2-amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid that was used in the next step without further purification. MS: m/z 307 [M − H]. To a suspension of the acid (0.413 g, 1.31 mmol) in 10 mL of tetrahydrofuran and 600 μL of DIEA (3.52 mmol), cooled in an ice bath, 0.336 g of EDC·HCl (1.75 mmol) and 0.267 g of HOBt·NH_3 (1.75 mmol) were added and the mixture was stirred overnight at room temperature. Ethyl acetate and water were added and the organic layer was washed with 1 M aqueous NaOH and water and then dried over anhydrous sodium sulfate and concentrated. Flash chromatography (dichloromethane/methanol/acetone 90:5:5) afforded 0.343 g (83% yield) of the desired amide **67**. ^{1}H NMR (400 MHz, DMSO-d_6) 0.89 (t, J = 7.14 Hz, 3H), 4.30 (q, J = 7.14, 2H), 6.51 (s, 2H), 6.66 (s, 1H), 6.77 (d, J = 5.09 Hz, 1H), 6.78 (s, 2H), 7.08 (m, 2H), 7.42 (tt, J = 6.83, 1.64 Hz, 1H), 7.55 (m, 2H), 8.18 (d, J = 5.09 Hz, 1H). ESI (+) MS: m/z 308 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{17}N_5O + H^+$, 308.1506; found, 308.1508. Anal. ($C_{17}H_{17}N_5O$) C, H, N.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxamide (71). To a stirred solution of 3-oxo-3-phenyl-propionic acid ethyl-ester (2.10 g, 10 mmol) and sodium hydride (60% in mineral oil, 1.03 g, 25 mmol) in dry tetrahydrofuran (200 mL) at 0 °C, 1-(2-amino-4-pyrimidinyl)-2-bromo-ethanone hydrobromide **2c** (3.56 g, 12 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, then additional ethanone **62c** (1.48 g) was added and the reaction mixture was stirred at room temperature overnight. After solvent removal, the residue was diluted in dichloromethane and washed with brine and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure to give 4-(2-amino-pyrimidin-4-yl)-2-benzoyl-4-oxo-butyric acid ethyl ester (**68**, 3.27 g, 97%). ESI (+) MS: m/z 328 (MH^+).

A mixture of **68** (3.25 g, 10 mmol) and Lawesson's reagent (2.43 g, 6 mmol) in toluene (100 mL) were refluxed under argon for 4 h. After solvent removal, the residue was taken up in dichloromethane, filtered, and purified by flash chromatography (dichloromethane/methanol 99:1) to give the furan derivative **69** (0.236 g, 8%) and the thiophene derivative **70** (0.255 g, 8%) as yellow solids.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxylic acid ethyl ester (**69**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.29 (t, J = 7.1 Hz, 3H), 4.27 (q, J = 7.1 Hz, 2H), 6.76 (bs, 2H), 7.07 (d, J = 5.2 Hz, 1H), 7.52 (m, 4H), 8.03 (m, 2H), 8.34 (d, J = 5.2 Hz, 1H). ESI (+) MS: m/z 310 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O_3 + H^+$, 310.1186; found, 310.1177.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid ethyl ester (**70**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.14 (t, J = 7.1 Hz, 3H), 4.16 (q, J = 7.1 Hz, 2H), 6.73 (bs, 2H), 7.20 (d, J = 5.2 Hz, 1H), 7.43−7.55 (m, 5H), 8.18 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H). ESI (+) MS: m/z 326 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{15}N_3O_2S + H^+$, 326.0958; found, 326.0965.

To a solution of ester **69** (0.225 g, 0.71 mmol) in water/ethanol 1:1 (9 mL), 4 M aqueous NaOH (10 equiv) was added and the reaction mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the solution was acidified with 2 M HCl, yielding 5-(2-amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxylic acid as a white solid which was filtered, washed with water, and dried under reduced pressure (quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.75 (bs, 2H), 7.06 (d, J = 5.2 Hz,1H), 7.51 (m, 3H), 8.0 (m, 2H), 8.33 (d, J = 5.2 Hz,1H), 13.00 (bs, 1H). ESI (−) MS: m/z 280 [M − H]. HRMS $(M + H)^+$ calcd for $C_{15}H_{11}N_3O_3 + H^+$, 282.0873; found, 282.0872.

To a mixture of the acid (0.172 g, 0.61 mmol) and DIEA (213 μL, 1.22 mmol) in dry tetrahydrofuran (4 mL), EDC·HCl (0.143 g, 0.92 mmol) and HOBt·NH_3 (0.145 g, 0.92 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature overnight. After solvent evaporation, the residue was taken up with dichloromethane and washed with water. The aqueous phase was extracted with ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound 5-(2-amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxamide (**71**) as a yellow solid (0.083 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.69 (bs, 2H), 7.01 (d, J = 5.2 Hz, 1H), 7.41−7.48 (m, 4H), 7.53 (s, 1H), 7.92 (bs, 1H), 8.05 (m, 2H), 8.33 (d, J = 5.2 Hz,1H). ESI (+) MS: m/z 281 (MH^+). HRMS $(M+H)^+$ calcd for $C_{15}H_{12}N_4O_2 + H^+$, 281.1033; found, 281.1035.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxamide (72). Analogously to the previously reported synthesis, from ester **70**, 5-(2-amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid was obtained in 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.04 (bs, 2H), 7.28 (d, J = 5.2 Hz, 1H), 7.43−7.48 (m, 3H), 7.54−7.58 (m, 2H), 8.25 (s, 1H), 8.31 (d, J = 5.2 Hz, 1H), 12.86 (bs, 1H). ESI (−) MS: m/z 296 [M − H]. HRMS $(M + H)^+$ calcd for $C_{15}H_{11}N_3O_2S + H^+$, 298.0645; found, 298.0643.

From the carboxylic acid, the corresponding 5-(2-amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxamide (**72**) was prepared (48% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.69 (bs, 2H), 7.10 (d, J = 5.2 Hz,1H), 7.38−7.44 (m, 4H), 7.56 (m, 2H), 7.71 (bs, 1H), 8.01 (s, 1H), 8.29 (d, J = 5.2 Hz,1H). ESI (+) MS: m/z 297 (MH^+). HRMS $(M + H)^+$ calcd for $C_{15}H_{12}N_4OS + H^+$, 297.0805; found, 297.0804.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-4-vinyl-1*H*-pyrrole-3-carboxamide (74). To a stirred solution of 5-(2-amino-pyrimidin-4-yl)-4-iodo-2-phenyl-1*H*-pyrrole-3-carboxamide (**73**) (0.052 g, 0.125 mmol) in dioxane (5 mL) and *N*,*N*-dimethylformamide (0.5 mL), 2,6-dimethyl-4-*tert*-butyl phenol (0.005 g), palladium tetrakis (0.005 g), and tributylvinyl stannane (145 μL) were added. The mixture was warmed at 110 °C for 8 h, cooled and concentrated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane/methanol 20:1) affording the title compound as a pale-yellow solid (24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.15 (dd, J = 11.46, 1.95 Hz, 1H), 5.64 (dd, J = 17.93, 1.95 Hz, 1H), 6.49 (bs, 2H), 6.97 (d, J = 5.24 Hz, 1H), 7.31 (bs, 1H), 7.34 (m, 1H), 7.44 (m, 2H), 7.51 (dd, J = 17.95, 11.50 Hz, 1H),7.63 (bs, 1H), 7.69 (m, 1H), 8.23 (d, J = 5.24 Hz, 1H), 11.40 (bs, 1H). ESI (+) MS: m/z 306 (MH^+). HRMS $(M + H)^+$ calcd for $C_{17}H_{17}N_5O + H^+$, 306.1349; found, 306.1353.

2. Kinase Assays. Kinase assays were performed as previously described.[12]

3. High-Throughput Solubility. Solubility at pH 7 was performed as previously described.[29]

4. Cell Permeability. PAMPA cell permeability assays were performed as previously described.[30]

5. Plasma Protein Binding. Plasma protein binding was performed as previously described.[29]

6. In Vivo Pharmacokinetics. The pharmacokinetic profile of the compounds was investigated in nu/nu mice as previously described.[13] Pharmacokinetic parameters were derived as previously described.[13]

7. Inhibition of Cell Proliferation. Inhibition of cell proliferation was performed as previously described.[12]

8. Cell Cycle Analysis and BrdU Determination. Data were derived as previously reported.[13]

9. Western Blot Analysis. Data were obtained as previously reported.[13]

10. In Vivo Pharmacology. Evaluation of antitumor efficacy was performed as previously described.[13]

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Note Added after ASAP Publication. This manuscript was released ASAP on September 27, 2010 with incorrect numbering of compounds in Tables 1, 3, 4, 6, 7, and 8. The correct version was posted on October 1, 2010.

Supporting Information Available: Elemental analyses results of compounds **18**, **20**, **22**, **23**, **40**, **67**, and **73**. This material is available free of charge via the Internet at http://pubs.acs.org.

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