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Cell Division Cycle 7 Kinase Inhibitors: 1*H*-Pyrrolo[2,3-*b*]pyridines, Synthesis and Structure−Activity Relationships

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Cdc7 kinase has recently emerged as an attractive target for cancer therapy and low-molecular-weight inhibitors of Cdc7 kinase have been found to be effective in the inhibition of tumor growth in animal models. In this paper, we describe synthesis and structure−activity relationships of new 1*H*-pyrrolo[2,3-*b*]pyridine derivatives identified as inhibitors of Cdc7 kinase. Progress from (*Z*)-2-phenyl-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (**1**) to [(*Z*)-2-(benzylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-1,3-thiazol-4(5*H*)-one] (**42**), a potent ATP mimetic inhibitor of Cdc7 kinase with IC_{50} value of 7 nM, is also reported.

Introduction

DNA replication is a fundamental process for cell proliferation. Mechanisms that control entry in the S-phase and proper execution of DNA synthesis are often altered in malignant cells and at the same time are attractive targets for the development of antitumor agents. DNA replication is a two-step process: first, during the initiation reaction, proteins bound to origin DNA are activated by phosphorylation in order to assemble replication forks, and second, during elongation, DNA polymerases with accessory factors synthesize new DNA strands. Cdc7[a] kinase, a key cell cycle regulator, is an evolutionary conserved serine−threonine kinase that plays a pivotal role in linking cell cycle regulation to genome duplication. In the S-phase, Cdc7 kinase promotes initiation of DNA replication by phosphorylating proteins previously recruited at the origin sequences during the G1-phase. Cdc7-dependent phosphorylation is therefore essential for converting a dormant prereplicative complex into two active replication forks.[1]

The Cdc7 kinase, in the same way as cyclin-dependent kinases, is activated by the binding of alternative regulatory subunits, Dbf4 and Drf1.[2,3] Cdc7, Dbf4, and Drf1 mRNA are overexpressed in several tumor cell lines.[2−5]

Cdc7 kinase is therefore a good inhibitory target for the development of anticancer drugs. Cdc7 kinase function is in fact essential for DNA replication and cell proliferation of human cells: microinjection of specific anti-Cdc7 antibodies prevents DNA replication,[6] and genetic down-regulation of Cdc7 kinase by siRNA blocks DNA synthesis, leading to a p53 independent cell death in several cancer cell lines.[7]

Furthermore, Cdc7 kinase inhibition abolishes the phosphorylation of a relevant cellular substrate, Mcm2 protein, at specific phosphorylation sites.[8,9] Inhibition of Cdc7 kinase by small interfering RNAs[6] blocks DNA synthesis in human cell lines.[7] As a consequence, tumor cells are funneled into the apoptotic pathway in a p53 independent manner; whereas, normal cells are arrested in their progression through the cell cycle and are capable of surviving Cdc7 kinase inhibition for long periods of time.[7] These findings support the notion that the pharmacological inhibition of Cdc7 kinase can be an effective novel strategy for the development of oncologic therapeutics as exemplified by a few small-molecule inhibitors of Cdc7 kinase shown to be effective in animal models.

We have recently published the discovery of pyrrolopyridinones as the first class of potent Cdc7 kinase inhibitors.[10] These compounds supported the principle that pharmacological inhibition of Cdc7 kinase delays tumor growth in preclinical cancer models.[11,12] Although there is currently a small number of known Cdc7 kinase inhibitors,[13−16] their number will likely increase in the near future.

In addition to pyrrolopyridinones, we explored other chemical classes employing molecular modeling and medicinal chemistry techniques with the aim to obtain molecules having biological activity, selectivity profile, and pharmaceutical properties suitable for development. We herein report on a new class of novel azaindolylidene-imidazolones and azaindolylidene-thiazolones.[17] The screening of a number of Cdk family inhibitors, available in-house, led to the discovery of (*Z*)-2-phenyl-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (**1** Figure 1), as a potent ATP competitive inhibitor of Cdc7 kinase with an IC_{50} of 30 nM in a Cdc7 kinase assay (using a complex Cdc7FL/Dbf4FL)[3] and greater than 10-fold selectivity versus Cdk2/A kinase.

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[a] Cdc7, cell division cycle 7 kinase; Cdk, cyclin-dependent kinase; GSK, glycogen synthase kinase; PKA, cAMP-dependent kinase; VEGFR, vascular endothelial growth factor receptor; CK, casein kinase.

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SAR studies, designed to identify modifications and/or substituents that might increase the potency against Cdc7 kinase, were carried out on a series of analogues of **1**, which were predominantly modified at position 2. Their synthesis and biological activity are herein reported. The inhibitory activity of putative Cdc7 kinase inhibitors was determined by a ^{33}P-γ-ATP transphosphorylation assay previously described.[10] Selectivity toward other protein kinases was evaluated against a panel of about 35 Tyr and Ser-Thr kinases.[18] The Cdk2 and GSK3β kinases, consistent with their similarity in their ATP binding pockets,[19,20] exhibited greater inhibition, while PKAα, VEGFR3, and CK2 kinases were generally inhibited to a lesser extent.

Some of these compounds demonstrate some inhibitory effect also against Cdk9 (Table 3), a kinase involved in transcriptional regulation.[21,22] The combined inhibition of cell cycle progression and transcription could potentially increase the cytotoxic effect of the compound against tumoral cells as has been previously demonstrated for Cdks inhibitors.[23]

Chemistry. The preparation of the reported compounds is based on the described protocols and the largely predominant (>85% by NMR) stereochemistry of the exocyclic double bond is (*Z*), unless otherwise stated.

1. The condensation between 7-azaindole-3-carboxaldehyde and hyppuric acid derivatives **A** provides azlactones **B**[24] that are transformed into the imidazolones **1**, **3**−**5** upon treatment with aqueous ammonia and sodium carbonate in refluxing methanol (Scheme 1).[25]

2. The condensation between 7-azaindole-3-carboxaldehyde and thiohydantoin or rhodanine, obtained by refluxing in acetic acid and sodium acetate, yields imidazolidinone **C** and thiazolidinone **D**, respectively (Scheme 2). Alternatively, imidazolidinone **C1** was obtained from the condensation between thiohydantoin and 3-acetyl-7-azaindole in the presence of boron trifluoride etherate at room temperature.

Intermediates **C**, **C1**, and **D** are in turn transformed into the corresponding methylsulfanyl derivatives **E**, **E1**, and **F** by alkylation with methyl iodide in basic medium, and these are subsequently converted into compounds **6**−**34** and **42**−**45**, respectively, by nucleophilic substitution of the methylsulfanyl group with amines.[26]

Alternatively, 2-thioxo imidazolidinone **C** produces imidazolone **41** by alkylation with benzyl bromide in basic medium. The benzylsulfanyl group of compound **41** can be also replaced by amines. For instance, derivative **17** was obtained upon heating with (*S*)-(−)-1-phenylethylamine.

3. The synthesis of derivatives carrying nitrogen at position 5 is presented in Scheme 3. Stereoisomers **36** and **37** are obtained by chromatographic separation of the (*E*,*Z*) mixture **35** (Scheme 3), in turn obtained from 3-formyl-5-nitro-7-azaindole via the standard protocol previously shown. Formylation of 5-nitro-7-azaindole to 3-formyl-5-nitro-7-azaindole is obtained with the Duff reaction by refluxing with hexamethylenetetramine in acetic acid. Reduction of the nitro group of derivative **35** by catalytic hydrogenation, followed by chromatographic separation of the (*E*,*Z*) mixture **38**, yields 5-amino-7-azaindole **39**. Access to acetamide **40** is obtained from 5-acetylamino-7-azaindole through the sequence of reactions already used for compound **35**.

Results and Discussion

First, we undertook the screening of our internal collection of Cdk inhibitors, a choice driven by the close sequence similarity of the two kinases and by well-established in-house protocols for screening Cdk inhibitors. This strategy led to the prompt discovery of (*Z*)-2-phenyl-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (**1**), a potent Cdc7 kinase inhibitor and a promising starting scaffold for SAR. As a result, a synthetic chemistry program was initiated.

Two main sets of imidazolones with different substitutions at position 2 were prepared: one with a cyclic moiety directly linked to imidazolone and another with substituents tethered through an amino group. Most of the SAR evaluations were done on the latter derivatives based on their synthetic flexibility and potential for structural elaboration. The two sets were first evaluated by molecular modeling. A homology model of Cdc7 kinase[10] was utilized for exploring the possible binding mode in the ATP active site of **1** (taken as reference of the first set) and **10**, as representative of the second set. Under this model, the nitrogen atoms of the 7-azaindole ring in compound **1** are bound with two hydrogen bonds to the hinge region of the Cdc7 kinase. The carbonyl of imidazol-4-one forms a hydrogen bond with the conserved lysine residue, while the NH of the same ring is connected with the conserved aspartate via electrostatic interaction (Figure 2). The docking in the Cdc7 kinase model of compound **10** is less straightforward, owing to different binding mode possibilities for the benzylamino group. The best hypothesis proposes that there is a difference in the interaction of the phenyl group of compound **10** with the highly flexible glycine loop (Figure 3) in contrast to compound **1**.

The SAR analyses examine the 7-azaindole ring, the exocyclic double bond, the central five-membered ring and the substituents linked to it. First, we investigated if the 7-azaindole ring could be conveniently replaced by the indole

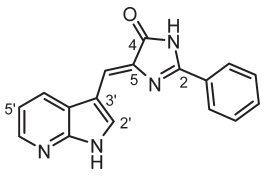
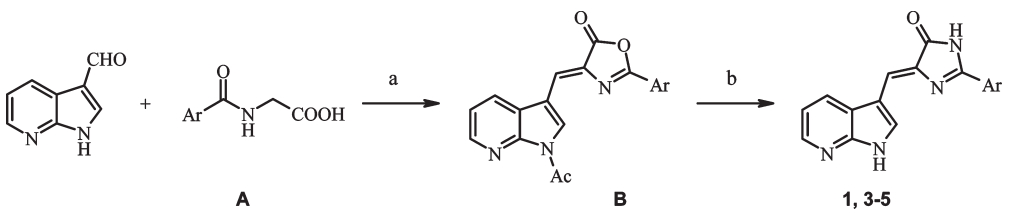


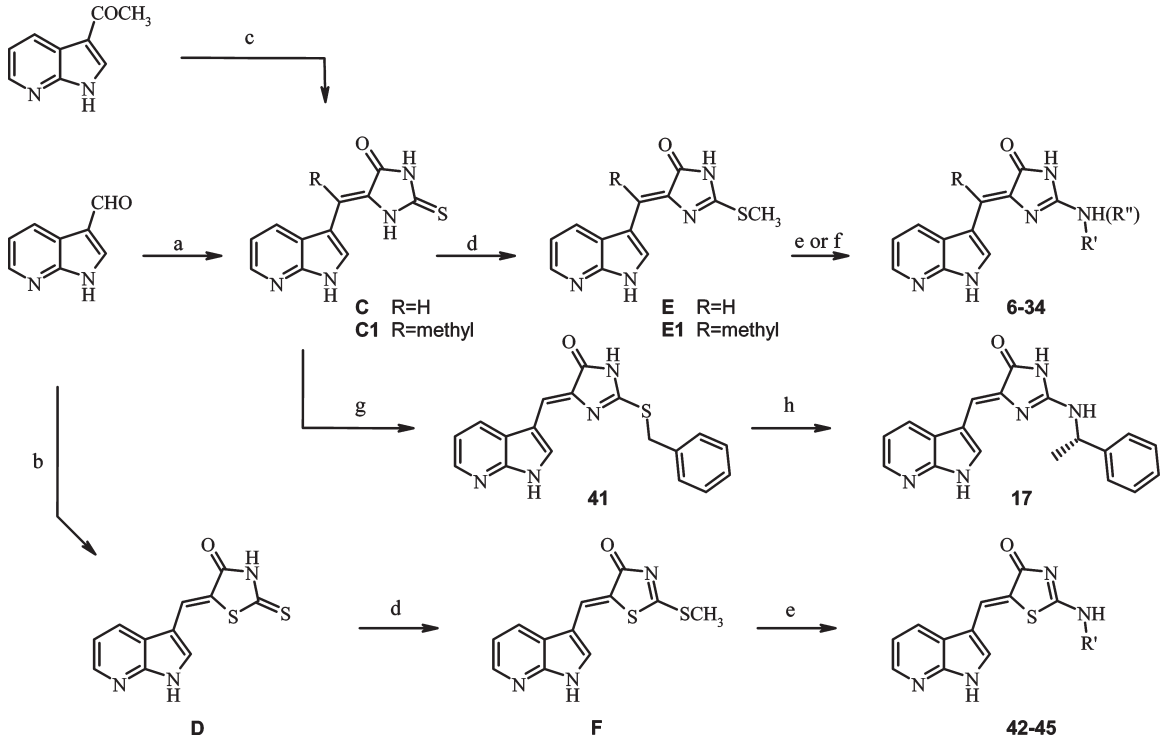
Figure 1. Structure of azaindole **1**.

Scheme 1. Synthesis of Arylimidazolones[a]



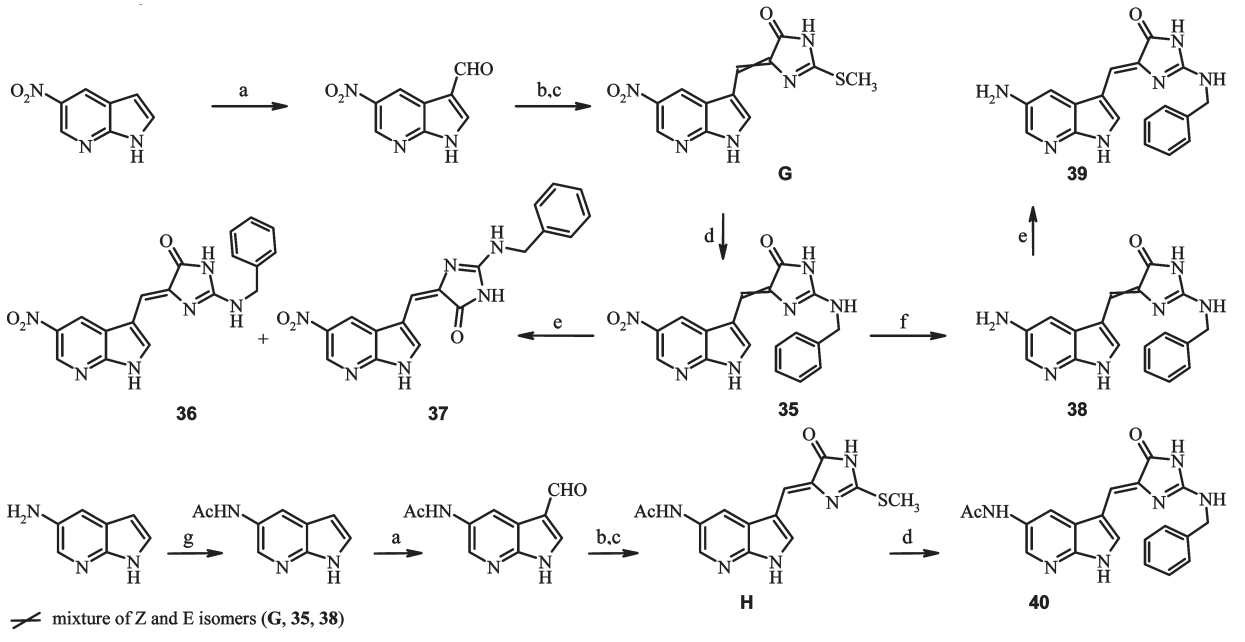
[a] Conditions: (a) Ac_2O, NaOAc, 100 °C, 2 h; (b) 30% aq NH_3, Na_2CO_3, MeOH, reflux, 8 h.

Scheme 2. Synthesis of Aminoimidazolones, Sulfanylimidazolones, and Aminothiazolones[a]



[a] Conditions: (a) thiohydantoin, NaOAc, AcOH, reflux, 5 h; (b) rhodanine, NaOAc, AcOH, reflux, 5 h; (c) thiohydantoin, $BF_3 \cdot Et_2O$, THF, TEA, rt, 5 days; (d) aq NaOH, MeOH, MeI, rt, 4 h; (e) R'NH_2 or R'R''NH, EtOH, reflux, 24 h or (f) when R = methyl, R'NH_2, EtOH, 110 °C (sealed tube), 18 h; (g) benzyl bromide, NaOH, MeOH, rt, 18 h; (h) (*S*)-(−)-1-phenylethylamine, EtOH, sealed tube, 110 °C, 24 h.

Scheme 3. Synthesis of 5-Aminoazaindole derivatives[a]



[a] Conditions: (a) hexamethylenetetramine, AcOH, H_2O, reflux, 3 h; (b) thiohydantoin, NaOAc, AcOH, reflux, 5 h; (c) aq NaOH, MeOH, MeI, rt, 4 h; (d) benzylamine, EtOH, reflux, 24 h; (e) chromatography; (f) 5% Pd−C/H_2, 40 psi, EtOAc, rt, 24 h; (g) AcOH, TBTU, HOBT, DIEA, DMF, rt, 18 h.

nucleus and whether additional functions on the 7-azaindole ring system would provide an increase of potency (region A, Table 1). As shown in the table, indole cannot replace 7-azaindole without complete loss of activity; therefore, the aza-nitrogen is a critical feature and participates in the binding in the hinge region. Simple substituents on the 7-azaindole ring, for example, 5′-nitro, 5′-amino, and 5′-acetamido, decrease activity.

The double bond, the key junction between the two ring systems, was then considered (region B, Table 2). Its role on

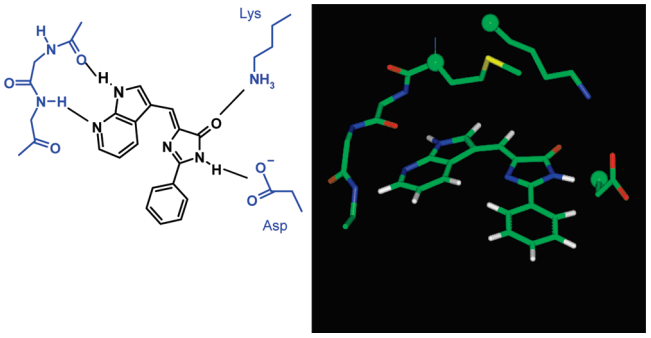


Figure 2. Possible binding mode of azaindole **1** in the homology model of Cdc7 kinase.

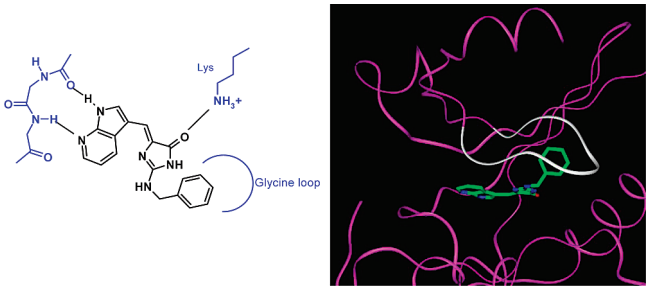


Figure 3. Proposed binding mode of azaindole **10** in the homology model of Cdc7 kinase (the glycine loop is in white).

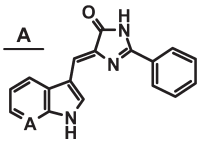
activity is important: absence of substituents (see **10** compared to **34**) and proper stereochemistry (**36** vs **37**) are requisite for activity.

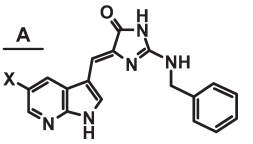
The presence of a substituent Y, disrupting the planarity of the system, seems to prevent efficacious binding, while only the (*Z*) stereochemistry ensures the correct orientation of the carbonyl and the amidic amino group toward lysine and aspartate residues, respectively. Considering the central five-membered ring (region C, Table 3), we found that the influence of atom W, connecting the central heterocycle to the side arm, on activity is small but significant versus Cdc7 kinase but huge versus Cdk9 (see **10** vs **41**).

Nitrogen is moderately preferred to sulfur although sulfur confers remarkable selectivity versus Cdk9 kinase.[27] More difficult to interpret is the role of atom X on the enzyme inhibition and to understand how the loss of contribution of the electrostatic interaction between the amidic NH and aspartate can be more than compensated by sulfur (compound **42** vs **10**, Table 3). One explanation might be the formation of a particularly good lipophilic interaction of the sulfur atom with a leucine present in the Cdc7 kinase model. More importantly, sulfur imparts a substantial improvement to cellular activity even if at expense of selectivity. In fact, compound **42** shows an IC_{50} value of 0.32 μM on the A2780 cell line, 4 times greater than analogues **10** and **41**, but in contrast to them, inhibits 2 out of 38 kinases (Cdk2/A and PKAα) at $IC_{50} < 50$ nM.

After establishing the efficacy of the 7-azaindole nucleus, the need of (*Z*) stereochemistry of the double bond, and the substantially equivalent activity of nitrogen and sulfur on the enzyme in the central part of the molecule, the influence of substituents at position 2 of the imidazolone ring was then evaluated. In Table 4, data relative to derivatives carrying a cyclic moiety R are reported, where R is represented by aromatic rings and cyclic amines. These subsets show

Table 1. SAR: Structural Modifications at Part A (IC_{50}, μM)[a]





compd	A	Cdc7	compd	X	Cdc7
1	N	0.050 ± 0.036	**10**	H	0.020 ± 0.008
2	CH	> 10	**36**	NO_2	0.130 ± 0.098
			39	NH_2	0.238 ± 0.007
			40	NHAc	0.116 ± 0.017

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

comparable activity in the bioassay but different cellular activity, as the compounds with aromatic R groups show on the A2780 cell line IC_{50} values around 1 μM compared to 8 μM of the other subset.

In Table 5, substituted secondary amines are considered. They are somewhat more active than the previous compounds, with IC_{50} values often below 50 nM.

Substitutions at the phenyl ring are detrimental, especially at the para position and less so at the meta (**12** and **11**, **14** and **13**, **16** and **15**). These data are in agreement with the binding mode hypothesis, where an interaction between the phenyl ring and the glycine loop is proposed. Cycloalkanes and alkanes are well accepted as long as they are not too bulky (**24**, **27**, **33**). Heterocyclic rings can be substituted for the phenyl (**18**, **19**, **25**). The flexible phenethyl chain is comparable in activity to benzyl (**20** vs **10**). Notwithstanding the remarkable activity expressed in the bioassay, the cellular activity of imidazolones on the A2780 cell line is only mediocre. Of these molecules, more than half are active on Cdc7 kinase with $IC_{50} < 50$ nM but their cellular activity is seldom below the low micromolar range. These relatively high IC_{50} values in the cell-based assays can be explained by the high affinity that Cdc7 kinase has for ATP (Km of 0.7 μM) and the high levels of intracellular ATP.[28] The high efflux ratios (BA/AB) measured for these compounds in the Caco-2 cells test affirm this result.

In conclusion, the value of this class is impaired by its generally low cellular activity. Only when imidazolone was replaced with the thiazolone ring, cellular activity showed such remarkable improvement as to make **42** a good lead worthy of optimization.

For this reason, a few more thiazolones were prepared and compared with their homologous imidazolones (Table 6).

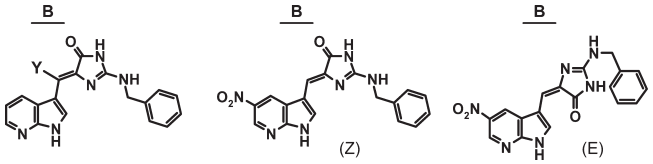
The most remarkable outcome from this comparison is the invariably higher cellular activity of thiazolones regardless of the substantial equi-activity on the enzyme. Of the most representative compounds (**10**, **17**, **42** and **45**), analogues **10**, **17**, **45** show medium/high apparent permeability from PAMPA[29,30] test data and at Caco-2 test only **42** and **45** display low efflux ratios (BA/AB). Overall, compound **45** is unique in having a high PAMPA apparent permeability, low efflux ratio, and high permeability as measured at Caco-2.[31]

This might account for the far superior cellular activity of **45** on the A2780 cell line.

Conclusions

In this paper we present a series of 7-azaindole derivatives, inhibitors of Cdc7 kinase.

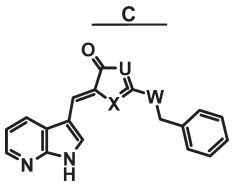
Table 2. SAR: Structural Modifications at Part B (IC_{50}, μM)[a]



compd	Y	Cdc7	compd	stereochemistry of double bond	Cdc7
10	H	0.020 ± 0.008	**36**	*Z*	0.130 ± 0.098
34	CH_3	> 10	**37**	*E*	> 10

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

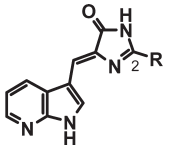
Table 3. SAR: Structural Modifications at Part C (IC_{50}, μM)[a]



compd	X	W	U	Cdc7	Cdk9/T
10	N	NH	NH	0.020 ± 0.008	0.095 ± 0.013
41	N	S	NH	0.049 ± 0.005	6.1 ± 3.9
42	S	NH	N	0.009 ± 0.003	0.015 ± 0.006

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

Table 4. SAR: Variations of Substituent R in Imidazolones (IC_{50}, μM)[a]



Cpd	R	Cdc7	Cpd	R	Cdc7
1		0.050±0.036	**6**		0.025±0.014
3		0.060±0.033	**7**		0.047±0.037
4		0.047±0.018	**8**		0.105±0.080
5		0.030±0.015	**9**		0.066±0.013

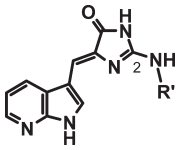
[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$).

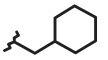
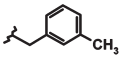
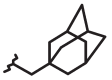
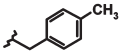
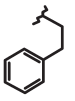
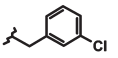
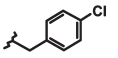
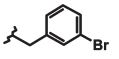
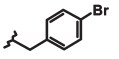
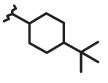
Starting from precursor **1**, the SARs associated with the molecule were explored. Several novel azaindolylidene-imidazolones were prepared that show excellent enzyme inhibition, good selectivity, but inadequate cellular activity. When the imidazolone moiety was replaced with the thiazolone group, a significative increase of cellular activity was observed and a good lead, (*Z*)-2-(benzylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-1,3-thiazol-4(5*H*)-one (**42**), was obtained. Starting from **42**, further work is being produced with the goal to design analogues having optimized overall features for the purpose of cancer drug development.

Experimental Section

1. Chemistry. Unless otherwise noted, 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. Unless otherwise specified, all final compounds were purified to ≥95% purity, as determined by high-performance liquid chromatography (HPLC), using a Waters 2790 HPLC system combined with a 996 Waters PDA detector and Micromass model ZQ single quadrupole mass spectrometer, equipped with an electrospray ion source (ESI). HPLC-UV/MS analysis were carried out at room temperature and a flow rate of 1 mL/min, using an RP C18 Waters XTerra column (4.6 mm × 50 mm; 3.5 μm). Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid):acetonitrile 95:5, and mobile phase B was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid): acetonitrile 5:95; the gradient was from 10 to 90% B in 8 min then hold 90% B for 2 min before re-equilibration. The injection volume was 10 μL. UV Detection was performed between 215 and 400 nm. The mass spectrometer was operated in positive and in negative ion mode, capillary voltage was set up at 2.5 KV; source temperature 120 °C; cone 10 V. Mass spectra were acquired in full scan mode from 100 to 800 *m*/*z*. Masses are given as *m*/*z* ratio. When necessary, compounds have been purified by preparative HPLC on a Waters Symmetry C18 (19 mm × 50 mm, 5 μm) column using a Waters preparative HPLC 600 equipped with a 996 Waters PDA detector and a Micromass model ZMD single quadrupole mass spectrometer, electrospray ionization, positive mode. Mobile phase A was water 0.01% trifluoroacetic acid, and mobile phase B was acetonitrile. Gradient from 10 to 90% B in 8 min, hold 90% B 2 min. Flow rate 20 mL/min. 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. ^{1}H NMR spectra were routinely recorded at a constant temperature of 28 °C on a Varian INOVA 400 spectrometer operating at 400.45 MHz and equipped with a 5 mm indirect detection PFG Probe (^{1}H{^{1}5N−^{31}P}). Where reported, a Varian INOVA 500 spectrometer, operating at 499.7 MHz and equipped with a 5 mm triple resonance indirect detection PFG probe cold probe (^{1}H-{^{1}C, ^{15}N}) was used. Chemical shifts were referenced with respect to the residual solvent signals (DMSO-d_6: 2.50 ppm for ^{1}H). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet), coupling constants (Hz), 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.[32]

Table 5. SAR: Variations of Substituent R′ in Imidazolones (IC_{50}, μM)[a]



Cpd	R'	Cdc7	Cpd	R'	Cdc7	Cpd	R'	Cdc7
10		0.020± 0.008	**18**		0.015± 0.012	**26**		0.064± 0.042
11		0.050± 0.003	**19**		0.018± 0.011	**27**		0.128± 0.091
12		0.162± 0.060	**20**		0.018± 0.004	**28**		0.045± 0.027
13		0.039± 0.006	**21**		0.021± 0.003	**29**		0.013± 0.001
14		0.086± 0.017	**22**		0.033± 0.013	**30**		0.035± 0.026
15		0.055± 0.003	**23**		0.013± 0.006	**31**		0.024± 0.011
16		0.127± 0.015	**24**		0.207± 0.154	**32**		0.037± 0.018
17		0.021± 0.017	**25**		0.021± 0.015	**33**		0.247± 0.161

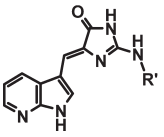
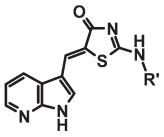
[a] IC_{50} values are reported as the mean ± standard deviation ($n \geq 2$).

Thin-layer chromatography was performed on Merck silica gel 60 plates coated with 250 μM layer with fluorescent indicator. Components were visualized by UV light ($\lambda = 254$ and 366 nm) and iodine vapors. In (*Z*) compounds, the stereochemistry of the exocyclic double bond is predominantly (> 85%) or exclusively (*Z*).

Compound **2** (1,5-dihydro-5-(1*H*-indol-3-ylmethylene)-2-phenyl-4*H*-imidazol-4-one) is commercially available.

(*Z*)-2-Phenyl-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (1). A mixture of 7-azaindole-3-carboxaldehyde (0.380 g, 2.6 mmol), hyppuric acid (0.470 g, 2.6 mmol), and sodium acetate trihydrate (0.360 g, 2.6 mmol) in acetic anhydride (2.5 mL) was heated at 100 °C under stirring for 2 h. After cooling to room temperature, the precipitate was filtered and washed with 95% ethanol. The solid was then dissolved in dichloromethane, the organic solution was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 4-[(1-acetyl-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)methylene]-2-phenyl-1,3-oxazol-5(4*H*)-one as a yellow−orange solid (0.510 g, 45% yield). This intermediate was suspended in 30% aqueous ammonia (40 mL), and solid sodium carbonate (0.220 g, 2.1 mmol) and methanol (40 mL) were added and the mixture was refluxed for 8 h. Half of the solvent was removed by distillation, and the precipitate was filtered and washed with water. The title compound, as the free base, was obtained as a yellow solid (0.290 g, 68%). ^{1}H NMR (DMSO-d_6), δ ppm 7.31 (dd, $J = 7.9$, 4.7 Hz, 1 H) 7.37 (s, 1 H) 7.56−7.64 (m, 3 H) 8.18 (s, 2 H) 8.36 (dd, $J = 4.7$, 1.6 Hz, 1 H) 8.54 (d, $J = 1.9$ Hz, 1 H) 9.04 (d, $J = 7.8$ Hz, 1 H) 11.92 (bs, 1 H) 12.59 (bs, 1 H) 12.79 (bs, 1 H). The compound was suspended in

Table 6. SAR: Imidazolones vs Thiazolones (IC_{50}, μM)[a]

# Cpd	Cdc7	A2780	R'	# Cpd	Cdc7	A2780
10	0.020±0.008	1.2		**42**	0.009±0.003	0.32
29	0.013±0.001	8.8		**43**	0.010±0.004	1.0
18	0.015±0.012	4.0		**44**	0.004±0.003	1.2
17	0.021±0.017	0.38		**45**	0.026±0.005	0.042

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

methanol, excess 4 M hydrochloric acid in dioxane was added, and the mixture was stirred at room temperature for 30 min. The precipitate was filtered and washed with a little methanol and then with diethyl ether to yield the hydrochloride. HRMS $(M + H)^+$ calcd 289.1084, found 289.1084.

By employing the above-described procedure the following compounds were also prepared:

(*Z*)-2-Pyridin-3-yl-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (3). ^{1}H NMR (DMSO-d_6), δ ppm 7.34 (dd, $J = 7.9$, 4.7 Hz, 1 H) 7.48 (s, 1 H) 7.74−7.83 (m, 1 H) 8.38 (dd, $J = 4.7$, 1.6 Hz, 1 H) 8.62 (s, 1 H) 8.66 (d, $J = 8.0$ Hz, 1 H) 8.85 (d, $J = 5.1$ Hz, 1 H) 9.05 (d, $J = 8.2$ Hz, 1 H) 9.39 (d, $J = 1.3$ Hz, 1 H) 12.12 (bs, 1 H) 12.70 (bs, 1 H). HRMS $(M + H)^+$ calcd 290.1036, found 290.1041.

(*Z*)-2-(4-Methylphenyl)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (4). ^{1}H NMR (DMSO-d_6), δ ppm 2.43 (s, 3 H) 7.32 (m, 1H) 7.35 (s, 1 H) 7.42 (d, $J = 7.9$ Hz, 2 H) 8.08 (m, 2 H) 8.37 (m, 1 H) 8.55 (d, $J = 1.4$ Hz, 1 H) 9.03 (d, $J = 8.0$ Hz, 1 H) 11.87 (bs, 1 H) 12.58 (bs, 1 H). HRMS $(M + H)^+$ calcd 303.1241, found 303.1229. Percent of purity 92%.

(*Z*)-2-(3-Methylphenyl)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (5). ^{1}H NMR (DMSO-d_6), δ ppm 2.45 (s, 3 H) 7.30−7.35 (m, 1 H) 7.38 (s, 1 H) 7.43 (m, 1 H) 7.50 (m, 1 H) 7.98 (d, $J = 7.8$ Hz, 1 H) 8.02 (s, 1 H) 8.37 (d, $J = 4.6$ Hz, 1 H) 8.57 (d, $J = 1.7$ Hz, 1 H) 9.03 (d, $J = 7.6$ Hz, 1 H) 11.89 (bs, 1 H) 12.59 (bs, 1 H). HRMS $(M + H)^+$ calcd 303.1241, found 303.1239.

(*Z*)-2-Piperidin-1-yl-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (6). A mixture of 7-azaindole-3-carboxaldehyde (5.98 g, 41 mmol), thiohydantoin (4.75 g, 41 mmol), and sodium acetate (11.30 g, 138 mmol) in glacial acetic acid (60 mL) was refluxed under stirring for 5 h. After cooling in ice bath, the precipitate was filtered and washed with 95% ethanol. After drying, (*Z*)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-2-thioxoimidazolidin-4-one **C** was obtained as a yellow solid (8.90 g, 36.5 mmol, 88%). ^{1}H NMR (DMSO-d_6), δ ppm 6.83 (s, 1 H) 7.21 (dd, $J = 7.8$, 4.6 Hz, 1 H) 8.31 (dd, $J = 6.7$, 1.2 Hz, 1 H) 8.33 (dd, $J = 4.7$, 1.4 Hz, 1 H) 8.57 (d, $J = 2.6$ Hz, 1 H) 11.87 (s, 1 H) 12.21 (s, 1 H) 12.47 (s, 1 H). To a solution of **C** (8.00 g, 32.8 mmol) in 12.6% aqueous NaOH (12 mL) and methanol (80 mL), methyl iodide (2.25 mL, 36 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Most of the solvent was removed by distillation, and the precipitate was filtered and washed first with water (50 mL) and then with diethyl ether (50 mL). The washings were concentrated and extracted with dichloromethane, dried over anhydrous sodium sulfate, and joined to the first solid crop. The whole crop was suspended in methanol, stirred for 30 min, filtered, and dried to yield (*Z*)-2-(methylthio)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one **E** as a yellow solid (8.15 g, 31.6 mmol, 96%). ^{1}H NMR (DMSO-d_6), δ ppm 2.71 (s, 3 H) 7.09 (s, 1 H) 7.21 (dd, $J = 7.9$, 4.6 Hz, 1 H) 8.31 (dd, $J = 4.6$, 1.6 Hz, 1 H) 8.38 (d, $J = 3.0$ Hz, 1 H) 8.84 (d, $J = 7.5$ Hz, 1 H) 11.60 (s, 1 H) 12.36 (bs, 1 H).

To assign the configuration of the exocyclic double bond, we run on **E** the NMR experiment gselJXH by exciting with shaped pulse the ^{13}C signal of the carbonyl function and observing the relative ^{1}H spectrum.[33]

This shows the antiphase doublet of the methylidene protons that exhibit a cis long-range constant (4.5 Hz), enabling us to assign the *Z* configuration.[34]

To a suspension of **E** (0.200 g, 0.77 mmol) in absolute ethanol (5 mL), piperidine (0.96 mL, 9.7 mmol) was added and the mixture was refluxed overnight. After cooling to room temperature, the precipitate was filtered and suspended in methanol (2 mL). To the suspension, 4 M hydrochloric acid in dioxane (0.5 mL) was added and the mixture was stirred at room temperature for 30 min. The yellow precipitate was purified by flash chromatography, eluting with dichloromethane/methanol 10:1. The product was suspended in methanol (2 mL), 4 M hydrochloric acid in dioxane (0.5 mL) was added, and the mixture was stirred at room temperature for 30 min. The precipitate was filtered and washed with methanol and diethyl ether. The title compound was obtained as a yellow solid (0.160 g, 0.54 mmol, 70%). ^{1}H NMR (DMSO-d_6), δ ppm 1.70 (s, 6 H) 3.73 (bs, 4 H) 7.16 (s, 1 H) 7.25 (dd, $J = 7.9$, 4.7 Hz, 1 H) 8.36 (dd, $J = 4.7$, 1.6 Hz, 1 H) 8.38−8.41 (m, 2 H) 12.60 (bs, 1 H). HRMS $(M + H)^+$ calcd 296.1506, found 296.1497.

By employing the above-described procedure the following compounds were also prepared:

(*Z*)-2-Morpholin-4-yl-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-3,5-dihydro-imidazol-4-one Dihydrochloride (7). ^{1}H NMR (DMSO-d_6), δ ppm 3.71−3.81 (m, 8 H) 7.10 (bs, 1 H) 7.25 (dd, $J = 7.6$, 4.7 Hz, 1 H) 8.35 (d, $J = 4.7$ Hz, 1 H) 8.39 (d, $J = 1.3$ Hz, 1 H) 8.46 (d, $J = 7.6$ Hz, 1 H) 12.53 (bs, 1 H). HRMS $(M + H)^+$ calcd 298.1299, found 298.1299. Percent of purity 93%.

(*Z*)-2-(4-Methyl-piperidin-1-yl)-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-3,5-dihydro-imidazol-4-one Dihydrochloride (8). ^{1}H NMR (DMSO-d_6), δ ppm 0.97 (d, $J = 6.3$ Hz, 3 H) 1.23−1.39 (m, 2 H) 1.71−1.77 (m, 1 H) 1.77−1.83 (m, 2 H) 3.23−3.34 (m, 2 H) 4.19 (bs, 2 H) 7.16 (s, 1 H) 7.25 (dd, $J = 7.9$, 4.7 Hz, 1 H) 8.36 (dd, $J = 4.7$, 1.4 Hz, 1 H) 8.38−8.42 (m, 1 H) 8.41 (bs, 1 H) 12.46−12.81 (m, 1 H) 12.61 (bs, 1 H). HRMS $(M + H)^+$ calcd 310.1662, found 310.1654. Percent of purity 91%.

(*Z*)-2-(2-Methyl-morpholin-4-yl)-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-3,5-dihydro-imidazol-4-one Dihydrochloride (9). ^{1}H NMR (DMSO-d_6), δ ppm 1.18 (d, $J = 6.2$ Hz, 3 H) 2.89 − 3.11 (m, 2 H) 3.99 (dd, $J = 11.7$, 3.0 Hz, 3 H) 4.14 (bs, 2 H) 7.13 (bs, 1 H) 7.25 (dd, $J = 7.9$, 4.7 Hz, 1 H) 8.35 (dd, $J = 4.7$, 1.5 Hz, 1 H) 8.41 − 8.49 (m, 2 H) 12.57 (bs, 1 H). HRMS $(M + H)^+$ calcd 312.1455, found 312.1457. Percent of purity 92%.

(*Z*)-2-(Benzylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Hydrochloride (10). To a suspension of 2-(methylthio)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (0.200 g, 0.77 mmol) in absolute ethanol (5 mL) benzylamine (1.1 mL, 9.7 mmol) was added and the mixture was refluxed for 24 h. After cooling to room temperature, the precipitate was filtered and purified by flash chromatography, eluting with dichloromethane/methanol 10:1. The product was suspended in methanol (2 mL), 4 M hydrochloric acid in dioxane (0.5 mL) was added, and the mixture was stirred at room temperature for 30 min. The title compound was obtained as a yellow solid (0.230 g, 0.66 mmol, 86%). ^{1}H NMR (DMSO-d_6), δ ppm 4.73 (bs, 2 H) 7.19 (bs, 1 H) 7.21−7.26 (m, 1 H) 7.32−7.46 (m, 5 H) 8.31−8.44 (m, 3 H) 9.62 (bs, 1 H) 12.62 (bs, 1 H). HRMS $(M + H)^+$ calcd 318.1349, found 318.1350.

By employing the above-described procedure the following compounds were also prepared:

(*Z*)-2-[(3-Methylbenzyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (11). ^{1}H NMR (DMSO-d_6), δ ppm 2.35 (s, 3 H) 4.68 (bs, 2 H) 7.16−7.20 (m, 2 H) 7.21−7.27 (m, 3 H) 7.29−7.35 (m, 1 H) 8.32−8.45 (m, 3 H) 9.62 (bs, 1 H) 12.64 (bs, 1 H). HRMS (M + H)$^+$ calcd 332.1506, found 332.1505.

(*Z*)-2-[(4-Methylbenzyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (12). ^{1}H NMR (DMSO-d_6), δ ppm 2.33 (s, 3 H) 4.67 (bs, 2 H) 7.19 (bs, 1 H) 7.24 (m, 3 H) 7.34 (d, J = 7.5 Hz, 2 H) 8.31−8.46 (m, 4 H) 9.59 (bs, 1 H) 12.63 (bs, 1 H). HRMS (M + H)$^+$ calcd 332.1506, found 332.1500.

(*Z*)-2-[(3-Chlorobenzyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (13). ^{1}H NMR (DMSO-d_6), δ ppm 4.74 (bs, 2 H) 7.18 (bs, 1 H) 7.24 (dd, J = 7.9, 5.0 Hz, 1 H) 7.39−7.48 (m, 4 H) 7.57 (s, 1 H) 8.34−8.45 (m, 3 H) 9.64 (bs, 1 H) 12.63 (bs, 1 H). HRMS (M + H)$^+$ calcd 352.0960, found 352.0970. Percent of purity 92%.

(*Z*)-2-[(4-Chlorobenzyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (14). ^{1}H NMR (DMSO-d_6), δ ppm 4.73 (m, 2 H) 7.18 (bs, 1 H) 7.24 (dd, J = 7.8, 4.0 Hz, 1 H) 7.45−7.54 (m, 4 H) 8.33−8.44 (m, 3 H) 9.62 (bs, 1 H) 12.63 (bs, 1 H). HRMS (M + H)$^+$ calcd 352.0960, found 352.0965.

(*Z*)-2-[(3-Bromobenzyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (15). ^{1}H NMR (DMSO-d_6), δ ppm 4.73 (bs, 2 H) 7.19 (bs, 1 H) 7.25 (dd, J = 7.7, 4.6 Hz, 1 H) 7.36−7.43 (m, 1 H) 7.44−7.49 (m, 1 H) 7.57 (dt, J = 8.2, 1.4 Hz, 1 H) 7.70 (s, 1 H) 8.30−8.45 (m, 3 H) 9.62 (bs, 1 H) 12.63 (bs, 1 H). HRMS (M + H)$^+$ calcd 396.0455, found 396.0466.

(*Z*)-2-[(4-Bromobenzyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (16). ^{1}H NMR (DMSO-d_6), δ ppm 4.70 (bs, 2 H) 7.19 (bs, 1 H) 7.24 (dd, J = 7.7, 4.4 Hz, 1 H) 7.43 (d, J = 8.4 Hz, 2 H) 7.62 (d, J = 8.4 Hz, 2 H) 8.34−8.44 (m, 3 H) 9.63 (bs, 1 H) 12.62 (bs, 1 H).

HRMS (M + H)$^+$ calcd 396.0455, found 396.0464.

(*Z*)-2-((*S*)-1-Phenyl-ethylamino)-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-3,5-dihydro-imidazol-4-one Dihydrochloride (17). ^{1}H NMR (DMSO-d_6), δ ppm 1.62 (d, J = 6.7 Hz, 3 H) 5.08 (bs, 1 H) 7.17 (bs, 1 H) 7.24 (dd, J = 7.7, 4.4 Hz, 1 H) 7.33−7.53 (m, 5 H) 8.35 (m, 3 H) 10.01 (bs, 1 H) 12.62 (bs, 1 H). HRMS (M + H)$^+$ calcd 332.1506, found 332.1507.

Alternatively the compound was obtained as follows:

A mixture of 0.110 g (0.33 mmol) of (*Z*)-2-(benzylthio)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (**41**) and 0.7 mL (5.5 mmol) of (*S*)-(−)-1-phenyl-ethylamine in 1 mL of anhydrous ethanol were stirred at 110 °C overnight in a sealed tube. After evaporation of the solution in order to eliminate the excess amine, the residue was washed with diethyl ether and dried in a vacuum oven. The product was then salified by dissolution in 3 mL of methanol and addition of 0.3 mL of 4 M hydrochloric acid in dioxane. After 1 h evaporation, of the solution gave 0.100 g (80% yield) of the desired product.

(*Z*)-2-[(2-Furylmethyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (18). ^{1}H NMR (DMSO-d_6), δ ppm 4.74 (bs, 2 H) 6.50 (dd, J = 3.1, 1.9 Hz, 1 H) 6.54 (d, J = 3.1 Hz, 1 H) 7.19 (bs, 1 H) 7.25 (dd, J = 7.9, 4.7 Hz, 1 H) 7.72 (dd, J = 1.9, 0.8 Hz, 1 H) 8.35−8.39 (m, 2 H) 8.42 (d, J = 7.9 Hz, 1 H) 9.61 (bs, 1 H) 12.62 (bs, 1 H). HRMS (M + H)$^+$ calcd 308.1142, found 308.1135.

(*Z*)-5-[1-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-2-[(thiophen-2-ylmethyl)-amino]-3,5-dihydro-imidazol-4-one Dihydrochloride (19). ^{1}H NMR (DMSO-d_6), δ ppm 4.91 (bs, 2 H) 7.07 (dd, J = 5.0, 3.5 Hz, 1 H) 7.18 (bs, 1 H) 7.22−7.27 (m, 2 H) 7.56 (dd, J = 5.0, 0.5 Hz, 1 H) 7.99−8.69 (m, 3 H) 9.63 (bs, 1 H) 12.61 (bs, 2 H). HRMS (M + H)$^+$ calcd 324.0914, found 324.0917.

(*Z*)-2-[(2-Phenylethyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (20). ^{1}H NMR (DMSO-d_6), δ ppm 2.90−2.98 (m, 2 H) 3.69 (bs, 2 H) 7.17 (bs, 1 H) 7.22−7.30 (m, 2 H) 7.34−7.37 (m, 4 H) 8.34 (bs, 1 H) 8.37 (dd, J = 4.6, 1.4 Hz, 1 H) 8.40 (d, J = 7.2 Hz, 1 H) 9.19 (bs, 1 H) 11.90 (bs, 1 H) 12.63 (bs, 1 H). HRMS (M + H)$^+$ calcd 332.1506, found 332.1497.

(*Z*)-2-(Cyclohexylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (21). ^{1}H NMR (DMSO-d_6), δ ppm 1.04−2.02 (m, 10 H) 3.50−3.75 (m, 1 H) 7.18 (s, 1 H) 7.25 (dd, J = 7.9, 4.7 Hz, 1 H) 8.34 (s, 1 H) 8.36 (dd, J = 4.7, 1.5 Hz, 1 H) 8.40 (d, J = 7.9 Hz, 1 H) 9.46 (s, 1 H) 11.79 (s, 1 H) 12.62 (s, 1 H). HRMS (M + H)$^+$ calcd 310.1662, found 310.1654.

(*Z*)-2-(Cyclopropylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (22). ^{1}H NMR (DMSO-d_6), δ ppm 0.80−0.86 (m, 2 H) 0.88−0.96 (m, 2 H) 2.87 (bs, 1 H) 7.21 (s, 1 H) 7.26 (dd, J = 7.9, 4.7 Hz, 1 H) 8.34 (d, J = 1.8 Hz, 1 H) 8.36 (dd, J = 4.7, 1.4 Hz, 1 H) 8.40 (dd, J = 7.6, 0.85 Hz, 1 H) 9.61 (bs, 1 H) 11.97 (s, 1 H) 12.63 (bs, 1 H). HRMS (M + H)$^+$ calcd 268.1193, found 268.1187.

(*Z*)-2-[(4-Methylcyclohexyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (23). ^{1}H NMR (DMSO-d_6), δ ppm 0.91 (d, J = 6.3 Hz, 3 H) 0.98−1.12 (m, 2 H) 1.41 (td, J = 12.2, 2.7 Hz, 3 H) 1.71−1.82 (m, 2 H) 1.91−2.03 (m, 2 H) 3.57 (bs, 1 H) 7.17 (s, 1 H) 7.25 (dd, J = 7.9, 4.7 Hz, 1 H) 8.33 (bs, 1 H) 8.34−8.46 (m, 2 H) 9.35 (bs, 1 H) 11.77 (bs, 1 H) 12.62 (bs, 1 H). HRMS (M + H)$^+$ calcd 324.1819, found 324.1809. Percent of purity 94%.

(*Z*)-2-[(4-*tert*-Butylcyclohexyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]-pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (24). ^{1}H NMR (DMSO-d_6), δ ppm 0.86 (s, 9 H) 0.96−1.18 (m, 3 H) 1.30−1.47 (m, 2 H) 1.74−1.87 (m, 2 H) 1.98−2.05 (m, 2 H) 3.45−3.60 (m, 1 H) 7.16 (s, 1 H) 7.23 (dd, J = 7.8, 4.7 Hz, 1 H) 8.30 (bs, 1 H) 8.32−8.43 (m, 2 H) 9.34 (d, J = 8.9 Hz, 1 H) 11.71 (bs, 1 H) 12.60 (bs, 1 H). HRMS (M + H)$^+$ calcd 366.2288, found 366.2293.

(*Z*)-5-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-2-[(tetrahydrofuran-2-ylmethyl)amino]-3,5-dihydro-4*H*-imidazol-4-one Hydrochloride (25). ^{1}H NMR (DMSO-d_6), δ ppm 16.1 (m, 1 H) 1.78−1.96 (m, 3 H) 1.99 (m, 1 H) 3.58 (m, 1 H) 3.68 (m, 1 H) 3.84 (m, 1 H) 4.05 (bs, 1 H) 7.18 (s, 1 H) 7.24 (dd, J = 7.9, 4.7 Hz, 1 H) 8.30−8.41 (m, 3 H) 9.16 (bs, 1 H) 12.65 (bs, 1 H). HRMS (M + H)$^+$ calcd 312.1455, found 312.1450.

(*Z*)-2-[(cyclohexylmethyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one dihydrochloride (26). ^{1}H NMR (DMSO-d_6) δ ppm 0.84−1.08 (m, 2 H) 1.12−1.33 (m, 4 H) 1.55−1.69 (m, 2 H) 1.69−1.81 (m, 4 H) 3.28−3.36 (m, 2 H) 7.17 (s, 1 H) 7.25 (dd, J = 7.8, 4.7 Hz, 1 H) 8.34 (d, J = 2.4 Hz, 1 H) 8.36 (dd, J = 4.7, 1.6 Hz, 1 H) 8.39 (d, J = 7.9 Hz, 1 H) 9.31 (bs, 1 H) 12.64 (bs, 1 H). HRMS (M + H)$^+$ calcd 324.1819, found 324.1805.

(*Z*)-2-(Adamantylmethylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (27). ^{1}H NMR (DMSO-d_6), δ ppm 1.54−1.59 (m, 6 H) 1.59−1.66 (m, 3 H) 1.68−1.75 (m, 3 H) 2.00 (bs, 3 H) 3.17 (d, J = 6.2 Hz, 2 H) 7.19 (s, 1 H) 7.25 (dd, J = 7.9, 4.6 Hz, 1 H) 8.34−8.38 (m, 2 H) 8.41 (d, J = 7.9 Hz, 1 H) 9.40 (bs, 1 H) 11.97 (bs, 1 H) 12.67 (bs, 1 H). HRMS (M + H)$^+$ calcd 376.2132, found 376.2126.

(*Z*)-2-(Ethylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (28). ^{1}H NMR (DMSO-d_6), δ ppm 1.21 (t, 3 H) 3.30−3.50 (m, 2H) 7.15 (s, 1 H) 7.23 (dd, J = 7.9, 4.76 Hz, 1 H) 8.30−8.41 (m, 3 H) 9.17 (bs, 1 H) 11.90 (bs, 1 H) 12.61 (bs, 1 H). HRMS (M + H)$^+$ calcd 256.1193, found 256.1184.

(*Z*)-2-(Isopropylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (29). ^{1}H NMR (DMSO-d_6), δ ppm 1.28 (d, J = 6.4 Hz, 6 H) 3.94 (bs, 1 H) 7.16 (s, 1 H) 7.23 (dd, J = 7.9, 4.7 Hz, 1 H) 8.21−8.49 (m, 3 H) 9.32 (bs, 1 H) 11.78 (bs, 1 H) 12.61 (bs, 1 H). HRMS (M + H)$^+$ calcd 270.1349, found 270.1339.

(*Z*)-2-(Pentylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (30). ^{1}H NMR (DMSO-d_6), δ ppm 0.90 (t, 3 H) 1.27−1.36 (m, 4 H)

1.53−1.68 (m, 2 H) 3.30−3.50 (m, 2 H) 7.16 (s, 1 H) 3.30−3.50 (m, 2H) 7.23 (dd, J = 7.9, 4.7 Hz, 1 H) 8.29−8.42 (m, 3 H) 9.23 (bs, 1 H) 11.88 (bs, 1 H) 12.62 (bs, 1 H). HRMS $(M + H)^+$ calcd 298.1662, found 298.1654.

(*Z*)-2-[(3,3-Dimethylbutyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (31). ^{1}H NMR (DMSO-d_6), δ ppm 0.94 (s, 9 H) 1.54 (bs, 2 H) 3.30−3.50 (m, 2 H) 7.15 (s, 1 H) 7.22 (dd, J = 7.9, 4.7 Hz, 1 H) 8.31−8.35 (m, 2 H) 8.37 (d, J = 8.2 Hz, 1 H) 9.15 (bs, 1 H) 11.92 (bs, 1 H) 12.61 (bs, 1 H).

HRMS $(M + H)^+$ calcd 312.1819, found 312.1828.

(*Z*)-2-[(2-Hydroxyethyl)amino]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one Dihydrochloride (32). ^{1}H NMR (DMSO-d_6), δ ppm 3.62 (bs, 4 H) 7.18 (s, 1 H) 7.24 (dd, J = 7.9, 4.7 Hz, 1 H) 8.34−8.37 (m, 2 H) 8.39 (d, J = 7.9 Hz, 1 H) 9.06 (bs, 1 H) 11.94 (bs, 1 H) 12.64 (bs, 1 H). HRMS $(M + H)^+$ calcd 272.1142, found 272.1151.

(*Z*)-2-(Heptylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (33). ^{1}H NMR (DMSO-d_6), δ ppm 0.82−0.91 (m, 5 H) 1.20−1.39 (m, 6 H) 1.60 (m, 2 H) 3.30−3.50 (m, 2 H) 7.03 (bs, 1 H) 7.20 (dd, J = 7.9, 4.7 Hz, 1 H) 8.21 (bs, 1 H) 8.34 (d, J = 1.4 Hz, 1 H) 8.37−8.43 (m, 1 H) 8.92−9.38 (m, 1 H) 11.51 (s, 1 H) 12.45 (bs, 1 H). HRMS $(M + H)^+$ calcd 326.1976, found 326.1985.

(*Z*)-2-(Benzylamino)-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-ethylidene]-3,5-dihydro-4*H*-imidazol-4-one Hydrochloride (34). To a solution of 3-acetyl, 7-azaindole (0.320 g, 2 mmol), thiohydantoin (0.465 g, 3 mmol), and $BF_3 \cdot Et_2O$ (1.52 mL, 12 mmol) in dry tetrahydrofuran (14 mL), under argon, triethylamine (0.84 mL, 6 mmol) was added dropwise and the reaction mixture stirred for 5 days at room temperature. The mixture was poured in ice and pH made slightly basic by addition of sodium bicarbonate. The solution was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated to give an oil that crystallized from ethyl acetate (0.260 g, 1 mmol, 50% yield). The obtained (5*Z*)-4−5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethylidene]-2-thioxo-imidazolidinone **C1** was dissolved in methanol (5 mL) containing aqueous sodium hydroxide solution (12.6%, 0.4 mL), and methyl iodide (0.4 mL) was added to it under argon. After stirring at room temperature for 3 h, part of the solvent was removed by distillation, water was added and the precipitate was filtered and washed with water. The desired (5*Z*)-3,5-dihydro-2-(methylthio)-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethylidene]-4*H*-imidazol-4-one **E1** (0.220 g, 0.81 mmol, 80% yield) was obtained and used directly in the next step.

^{1}H NMR (DMSO-d_6), δ ppm 2.57 (s, 3 H) 2.84 (s, 3 H) 7.16 (dd, J = 8.2, 4.6 Hz, 1 H) 8.27 (dd, J = 4.6, 1.6 Hz, 1 H) 8.45 (dd, J = 8.05, 0.98 Hz, 1 H) 8.53 (d, J = 3.1 Hz, 1 H) 11.53 (s, 1 H) 12.27 (bs, 1 H). NMR purity 80% as sum of Z/E isomers, LC-MS purity 95%.

The crude product (0.200 g, 0.73 mmol) was suspended in ethanol (5 mL) and benzylamine (2 mL) in a sealed tube and heated to 110 °C overnight. The solvent was evaporated by distillation, diethyl ether (5 mL) was added, and the precipitate was filtered and purified by flash chromatography, eluting with dichloromethane/methanol 12:1. The obtained product was dissolved in methanol, a slight excess of 4 N hydrochloric acid in dioxane was added, and the solution was stirred 30 min. Diethyl ether was added, and the precipitate was filtered, washed with diethyl ether, and dried. The title compound was obtained as a yellow solid (0.160 g, 0.48 mmol, 66%). ^{1}H NMR (DMSO-d_6), δ ppm 2.66 (s, 3 H) 4.52−4.63 (m, 2 H) 7.20 (bs, 1 H) 7.30−7.46 (m, 5 H) 7.97 (s, 1 H) 8.08−8.15 (m, 1 H) 8.30−8.35 (m, 1 H) 9.19 (bs, 1 H) 10.92 (bs, 1 H) 12.43 (bs, 1 H). HRMS $(M + H)^+$ calcd 332.1506, found 332.1518.

(*E*,*Z*)-2-(Benzylamino)-5-[(5-nitro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methylene]-3,5-dihydro-4*H*-imidazol-4-one (35). A mixture of 5-nitro-7-azaindole (2.00 g, 12.2 mmol) and hexamethylenetetramine (2.58 g, 18.4 mmol) in 30% AcOH (18 mL) was warmed at 120 °C for 3 h. The reaction mixture was cooled, water (20 mL) was added, and the precipitate was filtered, washed with water, and dried. 5-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde as a solid (2.00 g, 10.4 mmol, 85%) was obtained. ^{1}H NMR (DMSO-d_6), δ ppm: 8.77 (d, J = 2.93 Hz, 1 H) 9.12 (d, J = 2.56 Hz, 1 H) 9.25 (d, J = 2.56 Hz, 1 H) 10.04 (s, 1 H) 13.41 (s, 1 H). A stirred mixture of aldehyde (0.570 g, 3 mmol), thiohydantoin (0.350 g, 3 mmol), sodium acetate (0.740 g, 9 mmol), and glacial AcOH (15 mL) was heated at 120 °C for 3 h. After cooling, water (20 mL) was added and the precipitate was filtered, washed with water, and dried. The obtained (*E*,*Z*)-5-[(5-nitro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylene]-2-thioxoimidazolidin-4-one (0.600 g, 2.08 mmol, 69%) was treated with 12.6% aqueous NaOH (0.73 mL), methanol (6 mL), and methyl iodide (0.4 mL, 6.4 mmol) under stirring at room temperature for 4 h. After partial concentration, water (15 mL) was added and the precipitate was filtered and dried. Obtained (*E*,*Z*)-2-(methylthio)-5-[(5-nitro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methylene]-3,5-dihydro-4*H*-imidazol-4-one **G** as a solid (0.550 g, 1.8 mmol, 86%). A mixture of **G** (0.175 g, 0.58 mmol) in ethanol (3 mL) and benzylamine (0.88 mL, 8.2 mmol) was heated at 110 °C in a closed tube for 24 h, yielding the title compound (0.190 g, 0.52 mmol, 90%) as a mixture of (*E*) and (*Z*) isomers that were separated by flash chromatography (silica gel, eluant: dichloromethane/methanol 3:1) were obtained:

(*Z*)-2-(Benzylamino)-5-[(5-nitro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methylene]-3,5-dihydro-4*H*-imidazol-4-one (36). ^{1}H NMR (DMSO-d_6), δ ppm 4.69−4.72 (m, 2 H) 6.77 (s, 1 H) 7.25 (t, J = 7.2 Hz, 1 H) 7.34 (m, 3 H) 7.38−7.42 (m, 2 H) 8.25 (d, J = 2.2 Hz, 1 H) 9.10 (d, J = 2.5 Hz, 1 H) 10.21 (bs, 1 H) 12.81 (bs, 1 H). HRMS $(M + H)^+$ calcd 363.1200, found 363.1216.

and:

(*E*)-2-(Benzylamino)-5-[(5-nitro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methylene]-3,5-dihydro-4*H*-imidazol-4-one (37). ^{1}H NMR (DMSO-d_6), δ ppm 4.91 (s, 2 H) 7.17 (bs, 1 H) 7.27−7.33 (m, 3 H) 7.34−7.41 (m, 2 H) 8.27 (bs, 1 H) 8.43 (s, 1 H) 9.16 (s, 1 H) 13.01 (bs, 1 H). HRMS $(M+H)^+$ calcd 363.1200, found 363.1210. Percent of purity 93%.

(*Z*)-5-[(5-Amino-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methylene]-2-(benzylamino)-3,5-dihydro-4*H*-imidazol-4-one (39). A solution of **35** (1.10 g, 3.04 mmol) in ethyl acetate (250 mL) was hydrogenated in the presence of 5% Pd−C (0.500 g) at 40 psi and room temperature for 24 h. After filtration, the crude mixture (*E*,*Z*) **38** was fractionated by flash chromatography, eluting with dichloromethane/methanol 3:1. The title product was obtained as a solid (0.300 g, 0.91 mmol, 30%). ^{1}H NMR (DMSO-d_6), δ ppm 4.99 (s, 2 H) 7.20 (bs, 1 H) 7.31−7.44 (m, 5 H) 8.27 (s, 1 H) 8.32 (bs, 1 H) 8.52 (bs, 1 H). HRMS $(M + H)^+$ calcd 333.1458, found 333.1474.

(*Z*)-*N*-(3-{[2-(Benzylamino)-5-*oxo*-1,5-dihydro-4*H*-imidazol-4-ylidene]methyl}-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)acetamide Hydrochloride (40). Into a solution of 5-amino-7-azaindole (0.600 g, 4.51 mmol) in dry *N*,*N*-dimethylformamide (11 mL) *N*-[(1*H*-1,2,3-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (2.89 g, 9.0 mmol), 1-hydroxybenzotriazole (1.21 g, 9.0 mmol), and glacial AcOH (0.26 mL), diisopropylethylamine (3.1 mL, 17.8 mmol) was slowly dropped under stirring. The reaction mixture was stirred at room temperature for 18 h, concentrated, and the residue was purified by flash chromatography eluting with dichloromethane/methanol 4:1. 1*H*-pyrrolo[2,3-*b*]pyridin-5-yl acetamide was obtained in 95% yield (0.750 g, 4.2 mmol). ^{1}H NMR (DMSO-d_6), δ ppm: 2.07 (s, 3 H) 6.41 (m, 1 H) 7.43 (t, J = 2.93 Hz, 1 H) 8.22 (d, J = 2.07 Hz, 1 H) 8.26 (d, J = 2.32 Hz, 1 H) 9.92 (s, 1 H) 11.51 (s, 1 H). A mixture of the acetamide (0.790 g, 4.5 mmol) and hexamethylenetetramine (0.950 g, 6.75 mmol) in 30% AcOH (21 mL) was warmed at 100 °C for 4 h. After cooling, the mixture was diluted with water (10 mL), the precipitate was filtered, washed with water, and dried. *N*-(3-Formyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-

acetamide (0.700 g, 3.45 mmol, 76%) was obtained . ^{1}H NMR (DMSO-d_6), δ ppm: 2.10 (s, 3 H) 8.43 (d, J = 3.17 Hz, 1 H) 8.50 (d, J=2.44 Hz, 1 H) 8.73 (d, J=2.32 Hz, 1 H) 9.9 (s, 1 H) 10.12 (s, 1 H) 12.60 (s, 1 H). A mixture of *N*-(3-formyl-1*H*-pyrrolo[2,3-*b*]-pyridin-5-yl)acetamide (0.200 g, 1 mmol), thiohydantoin (0.116 g, 1 mmol), sodium acetate (0.246 g, 3 mmol), and glacial AcOH (5 mL) was heated at 125 °C for 3 h. After cooling, water (5 mL) was added, and the precipitate was filtered, washed with water, and dried. To the so obtained *N*-{3-[(5-*oxo*-2-thioxoimidazolidin-4-ylidene)methyl]-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl}acetamide (0.240 g, 0.79 mmol), dissolved in 12.6% aqueous NaOH (0.32 mL) and methanol (4 mL), methyl iodide (0.2 mL, 3.2 mmol) was added and the mixture was stirred at room temperature for 3 h under argon. After partial concentration, water (5 mL) was added and the precipitate was filtered and dried. *N*-(3-{[2-(Methylthio)-5-*oxo*-1,5-dihydro-4*H*-imidazol-4-ylidene]methyl}-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)acetamide **H** was obtained as a solid (0.220 g, 0.7 mmol, 87%). A mixture of **H** (0.200 g, 0.635 mmol), benzylamine (0.5 mL, 4.58 mmol) and EtOH (3 mL) were put in a closed tube and heated at 110 °C for 4 h. After cooling, the precipitate was filtered, washed with ethanol, and dried to yield the desired compound (0.220 g, 0.59 mmol, 92%). The compound was dissolved in methanol, treated with 4 N hydrochloric acid in dioxane, and diluted with ethyl acetate until precipitation of the hydrochloride salt occurred. Filtration of the solid afforded the title compound as a white solid. ^{1}H NMR (DMSO-d_6), δ ppm 2.11 (s, 3 H) 4.72 (bs, 2 H) 6.98 (bs, 1 H) 7.30−7.50 (m, 5 H) 8.30 (bs, 1 H) 8.36 (bs, 1 H) 8.61 (bs, 1 H) 9.54 (bs, 1 H) 10.14 (bs, 1 H) 12.45 (bs, 1 H). HRMS $(M + H)^+$ calcd 375.1564, found 375.1573.

(*Z*)-2-(Benzylthio)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (41). To a solution of (*Z*)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-2-thioxoimidazolidin4-one (0.500 g, 2.05 mmol) in 12.6% aqueous NaOH (1 mL) and methanol (5 mL), benzyl bromide (0.430 g, 2.5 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. Most of the solvent was removed by distillation, and the precipitate was filtered and washed with water and diethyl ether and dried. The crude material was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 15:1). The title compound was obtained as a yellow solid (0.700 g, 2 mmol).

^{1}H NMR (DMSO-d_6), δ ppm 4.63 (s, 2 H) 7.12 (s, 1 H) 7.19 (dd, J=7.9, 4.7 Hz, 1 H) 7.27−7.32 (m, 1 H) 7.37 (t, J=7.3 Hz, 2 H) 7.54 (d, J=7.3 Hz, 2 H) 8.32 (dd, J=4.7, 1.3 Hz, 1 H) 8.45 (d, J= 2.5 Hz, 1 H) 8.80 (dd, J=7.9, 1.3 Hz, 1 H) 11.64 (bs, 1 H) 12.44 (bs, 1 H). HRMS $(M + H)^+$ calcd 335.0961, found 335.0958.

(*Z*)-2-(Benzylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-1,3-thiazol-4(5*H*)-one Hydrochloride (42). A mixture of 7-azaindole-3-carboxaldehyde (5.98 g, 41 mmol), rhodanine (4.96 g, 41 mmol), and sodium acetate (11.30 g, 138 mmol) in glacial acetic acid (60 mL) was refluxed under stirring for 5 h. After cooling in ice bath, the precipitate was filtered and washed with 95% ethanol. After drying, (*Z*)-5-(1*H*-pyrrolo-[2,3-*b*]pyridin-3-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one **D** was obtained as a yellow solid (9.52 g, 36.5 mmol, 88%). ^{1}H NMR (DMSO-d_6), δ ppm 7.28 (dd, J = 7.9, 4.6 Hz, 1 H) 7.93 (s, 1 H) 7.96 (d, J=0.6 Hz, 1 H) 8.36 (d, J=5.9 Hz, 1 H) 8.38 (dd, J = 4.6, 1.6 Hz, 1 H) 8.45 (dd, J = 7.9, 1.5 Hz, 1 H) 12.82 (bs, 1 H) 13.62 (bs, 1 H) 13.63−13.64 (m, 1 H). To a solution of **D** (7.98 g, 30.6 mmol) in 12.6% aqueous NaOH (12 mL) and methanol (80 mL), methyl iodide (2.25 mL, 36.1 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Most of the solvent was removed under reduced pressure, and the precipitate was separated by filtration and washed with water (50 mL) and with diethyl ether (50 mL). The washings were combined, concentrated, and extracted with dichloromethane. The dichloromethane was dried over anhydrous sodium sulfate and combined to the first solid crop. The whole crop was suspended in methanol, stirred 30 min, filtered, and dried to yield (*Z*)-2-(methylthio)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethylene)-1,3-thiazol-4(5*H*)-one **F** as a yellow solid (8.15 g, 29.5 mmol, 96%). To assign the configuration of the exocyclic double bond, the NMR experiment gselJXH was run on compound **F** as previously described.[33] The experiment enabled us to assign the compound the *Z* configuration.[34] ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 3 H) 7.26 (dd, J = 7.9, 4.7 Hz, 1 H) 7.97 (d, J = 1.9 Hz, 1 H) 8.11 (s, 1 H) 8.37 (dd, J = 4.7, 1.5 Hz, 1 H) 8.44 (dd, J = 7.9, 1.5 Hz, 1 H) 12.82 (bs, 1 H).

To a suspension of **F** (0.200 g, 0.77 mmol) in absolute ethanol (5 mL), benzylamine (1.05 mL, 9.7 mmol) was added and the mixture was refluxed overnight. After cooling to room temperature, the precipitate was filtered, suspended in methanol (2 mL), 4 M hydrochloric acid in dioxane (0.5 mL) was added, and the mixture was stirred at room temperature for 30 min. The yellow precipitate was filtered and purified by flash chromatography, eluting with dichloromethane/methanol 12:1. The product was suspended in methanol (2 mL), 4 M hydrochloric acid in dioxane (0.5 mL) was added, and the mixture was stirred at room temperature for 30 min. The precipitate was filtered and washed with methanol and diethyl ether. The title compound was obtained as a yellow solid (0.200 g, 0.59 mmol, 76%). ^{1}H NMR (DMSO-d_6), δ ppm 4.75 (s, 2 H) 7.25 (dd, J = 7.8, 4.8 Hz, 1 H) 7.30−7.43 (m, 5 H) 7.71 (d, J = 2.4 Hz, 1 H) 7.88 (s, 1 H) 8.35−8.40 (m, 2 H) 9.99 (bs, 1 H) 12.48 (bs, 1 H). HRMS $(M + H)^+$ calcd 335.0961, found 335.0954.

By employing the above-described procedure the following compounds were also prepared:

(*Z*)-2-Isopropylamino-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-thiazol-4-one Dihydrochloride (43). ^{1}H NMR (DMSO-d_6), δ ppm 1.26 (d, J = 6.6 Hz, 6 H) 4.13−4.29 (m, 1 H) 7.26 (dd, J = 7.9, 4.7 Hz, 1 H) 7.69 (d, J = 2.2 Hz, 1 H) 7.86 (s, 1 H) 8.23−8.48 (m, 2 H) 9.55 (bs, 1 H) 12.49 (bs, 1 H). HRMS $(M + H)^+$ calcd 287.0961, found 287.0964. Percent of purity 92%.

(*Z*)-2-[(Furan-2-ylmethyl)-amino]-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-thiazol-4-one Dihydrochloride (44). ^{1}H NMR (DMSO-d_6), δ ppm 4.75 (s, 2 H) 6.43−6.45 (m, 1 H) 6.46−6.48 (m, 1 H) 7.26 (dd, J = 7.9, 4.7 Hz, 1 H) 7.68 (dd, J = 1.8, 0.85 Hz, 1 H) 7.71 (d, J = 2.2 Hz, 1 H) 7.88 (s, 1 H) 8.29−8.45 (m, 2 H) 9.97 (bs, 1 H) 12.51 (bs, 1 H). HRMS $(M + H)^+$ calcd 325.0754, found 325.0755.

(*Z*)-2-((*S*)-1-Phenyl-ethylamino)-5-[1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-methylidene]-thiazol-4-one Hydrochloride (45). ^{1}H NMR (DMSO-d_6), δ ppm 1.56 (d, J = 6.9 Hz, 3 H) 5.25−5.37 (m, 1 H) 7.25 (dd, J = 7.9, 4.7 Hz, 1 H) 7.27−7.34 (m, 1 H) 7.38−7.43 (m, 4 H) 7.70 (d, J = 2.3 Hz, 1 H) 7.85 (s, 1 H) 8.37 (s, 2 H) 10.00 (bs, 1 H) 12.49 (bs, 1 H). HRMS $(M + H)^+$ calcd 349.1118, found 349.1119.

2. Registry Numbers (RN). Hyppuric acid (RN, 495-69-2), nicotinoylglycine (RN, 583-08-4), 4-methylhippuric acid (RN, 27115-50-0), 3-methylhippuric acid (RN, 27115-49-7), 7-azaindole-3-carboxaldehyde (RN, 4649-09-6), 3-acetyl-7-azaindole (RN, 83393-46-8), 5-nitro-7-azaindole (RN, 101083-92-5), 5-amino-7-azaindole (RN, 100960-07-4), thiohydantoin (RN, 503-87-7), rhodanine (RN, 141-84-4).

3. Molecular Modeling. See ref 10.

4. In Vitro Kinase Assays. See ref 10.

5. Cell Culture. See ref 10.

6. Inhibition of Cell Proliferation. See ref 10.

7. Cell Permeability. See ref 12.

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