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Bioorganic & Medicinal Chemistry 12 (2004) 3167–3185
Bioorganic & Medicinal Chemistry

Design, synthesis, and biological evaluation of novel 7-azaindolyl-heteroaryl-maleimides as potent and selective glycogen synthase kinase-3β (GSK-3β) inhibitors

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Received 23 February 2004; accepted 6 April 2004
Available online 12 May 2004

Abstract—Two approaches were developed to synthesize the novel 7-azaindolyl-heteroarylmaleimides. The first approach was based upon the palladium-catalyzed Suzuki cross-coupling or Stille cross-coupling of 2-chloro-maleimide **5** with various arylboronic acids or arylstannanes. The second approach was based upon the condensation of ethyl 7-azaindolyl-3-glyoxylate **12** with various acetamides. The hydroxypropyl-substituted 7-azaindolylmaleimide template was first used to screen different heteroaryls attached to the maleimide. Replacement of hydroxypropyl with different chain lengths and different functional groups were studied next. Many compounds synthesized were demonstrated to have high potency at GSK-3β, good GS activity in HEK293 cells and good to excellent metabolic stability in human liver microsomes. Three representative compounds (**21**, **33**, and **34**) were demonstrated to have good selectivity against a panel of 80 kinase assays. Among them, compound **33** exhibited very weak inhibitions at the other 79 kinase assays, and behaved as a highly selective GSK-3β inhibitor.

1. Introduction

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase that was first identified over 20 years ago because of its ability to phosphorylate and inhibit glycogen synthase (GS),[1] the rate-limiting enzyme of glycogen biosynthesis.[2] Mammalian GSK-3 exists as two isoforms, GSK-3α and GSK-3β, sharing 98% homology in their catalytic domain.[3] Both isoforms are ubiquitously expressed in cells and tissues, and have similar biochemical properties.[3] Today, it is known that GSK-3 is involved in diverse cellular processes and might have multiple substrates.[4,5] For example, GSK-3 phosphorylates and inhibits the functioning of insulin receptor substrate-1 (IRS-1) and GS, the two key targets in the insulin signaling pathway.[6] Suppression of these targets may limit most insulin-mediated biological responses. In addition, elevated GSK-3 activity was found in diabetic tissues, reinforcing GSK-3 as a promising therapeutic target for insulin resistance and Type 2 diabetes. Another important substrate of GSK-3 is Tau, a protein that is critical in microtubule function in certain neurons. Tau hyperphosphorylation has been postulated to promote microtubule disassembly, an early event in the progression of Alzheimer's disease.[7] Inhibition of GSK-3 has also been shown to attenuate apoptotic signals.[8] Therefore, GSK-3 inhibitors may be useful for the treatment of Alzheimer's disease and protection against cell death.[9] Lithium ions and valproic acid have been used as mood stabilizers for the chronic treatment of patients with bipolar disorder. Recently, these compounds have been shown to be GSK-3 inhibitors.[10] Finally, studies on fibroblasts from the GSK-3β knockout mice indicate that inhibition of GSK-3 may be

Keywords: Highly selective inhibitor; Kinase; Azaindolemaleimide; Cross-coupling.
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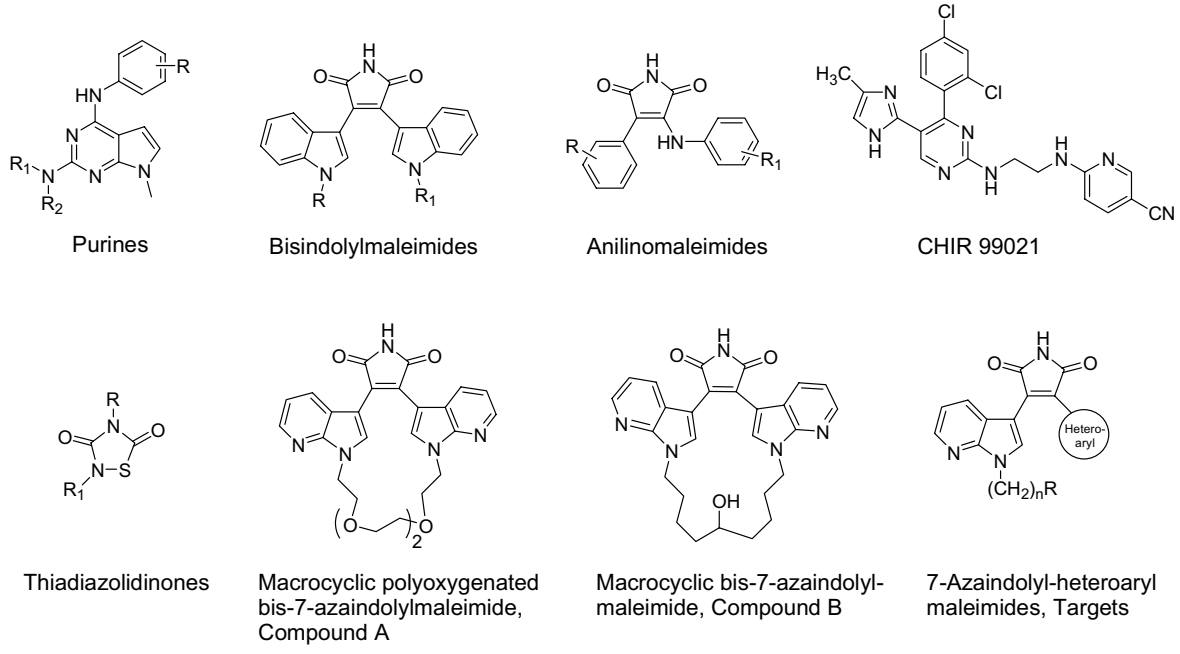
doi:10.1016/j.bmc.2004.04.010



Scheme 1.

useful in treating inflammatory disorders or diseases through the negative regulation of NFκB activity.[11]

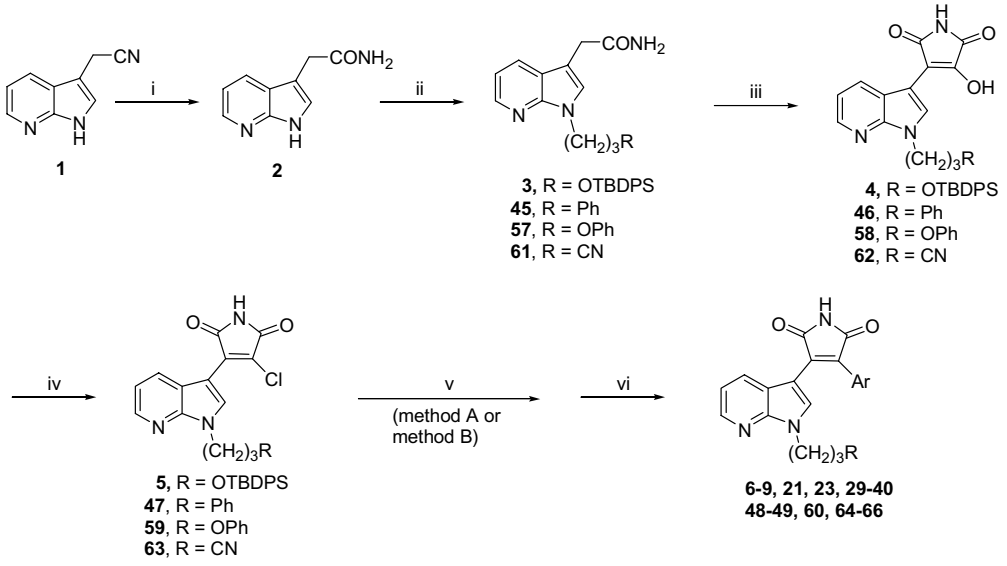
Since previous report showed that purines[12] (Scheme 1) are capable of exhibiting GSK-3 inhibitory activities, many chemical series[13–15] (pyrazines, pyrimidines, heterocyclic-pyrimidones, amine pyrazoles, bisindolylmaleimides, hymenialdisine, paullones, indirubines, anilinomaleimides, [1,2,3]triazole-furazan, and CHIR99021) have been developed as ATP competitive GSK-3 inhibitors while thiadiazolidinones[16] were reported to be the first ATP noncompetitive GSK-3 inhibitors. However, with the exception of [1,2,3]triazole-furazan,[13c] CHIR99021,[14] and anilinomaleimides,[15] which were reported as selective GSK-3 inhibitors versus 20–40 protein kinases, the majority of ATP competitive GSK-3 inhibitors all showed equivalent activities at other protein kinases. In general, it is always desirable to have a therapeutic agent to specifically inhibit the enzyme target to minimize the potential side effects.

In an attempt to identify potent and selective protein kinase C gamma (PKCγ) inhibitors for the treatment of chronic pain, we unexpectedly discovered that macrocyclic polyoxygenated bis-7-azaindolylmaleimide (compound A, $K_i = 0.017\,\mu M$, Scheme 1)[17a] and macrocyclic bis-7-azaindolylmaleimide (compound B, $K_i = 0.011\,\mu M$)[17b] are potent and highly selective GSK-3β inhibitors. However, these compounds were found to be metabolically liable (decreased metabolic stability in human liver microsomes (HLM)), partially due to the metabolism of the bottom cyclic linkers.[18] This article describes our continued efforts toward the identification of several novel 7-azaindolyl-heteroarylmaleimides as potent and selective GSK-3β inhibitors with improved metabolic stability in HLM.[19]

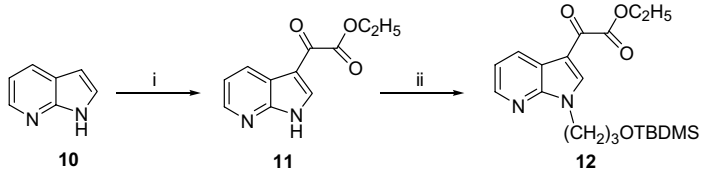
2. Chemistry

Two approaches were used to synthesize these novel heteroaryl-7-azaindolylmaleimides. The first approach was based upon the palladium-catalyzed Suzuki cross-coupling[20] or Stille cross-coupling[21] of 2-chloromaleimide **5** with various arylboronic acids (method A) or arylstannanes (method B) (Scheme 2). The chloride **5** was prepared from a readily available 7-azaindole-3-acetonitrile **1**[22] in four steps. Oxidation of **1** gave acetamide **2**, and *N*-1 alkylation of **2** with the bromide gave the three-carbon side chain attached acetamide **3**. Using a procedure for the synthesis of aryl substituted hydroxymaleimide derivatives,[23] acetamide **3** was reacted with diethyl oxalate in the presence of potassium *tert*-butoxide to give 2-hydroxy-maleimide **4** in 80% yield. Reaction of **4** with oxalyl chloride gave the key common intermediate **5**. It is known in the literature that the electron-rich/steric bulky P(*t*-Bu)$_3$ is one of the most desirable ligands for oxidative addition of palladium(0) into the C–Cl bond.[20,21] Indeed, treatment of the commercially available Pd(P(*t*-Bu)$_3$)$_2$ and the chloride **5** with either arylboronic acids or arylstannanes gave moderate to good yields of the desired coupling products **6**–**9**, **21**, **23**, **29**–**40** after deprotection with *n*-Bu$_4$NF in THF (Scheme 2).

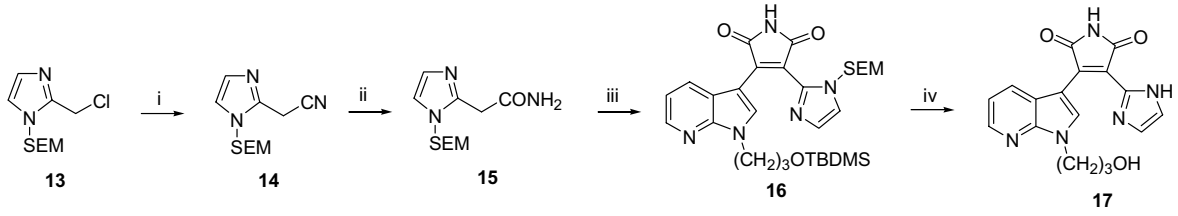
The second approach was based upon the condensation of ethyl 7-azaindolyl-3-glyoxylate **12** with various acetamides.[24] The common intermediate **12** was prepared in two steps (Scheme 3). Reaction of diethyl oxalate with the magnesium salt of **10** gave **11**. Alkylation of **11** with the bromide gave glyoxylate **12**. The acetamide **15** was prepared from the known chloride **13**[25] in two steps (Scheme 4). Displacement of the chloride with KCN gave **14**, followed by oxidation gave



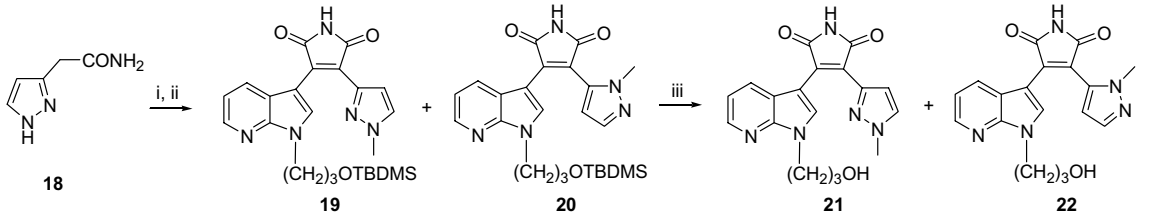
Scheme 2. Reagents and conditions: (i) H_2O_2, K_2CO_3, DMSO; (ii) $Br(CH_2)_3R$, Cs_2CO_3, DMF; (iii) $(CO_2Et)_2$, KO*t*-Bu, THF; (iv) $(COCl)_2$, DMF/CH_2Cl_2; (v) method A: $Pd_2(dba)_3$, $Pd(P(t\text{-}Bu)_3)_2$, $ArB(OH)_2$; method B: $Pd(P(t\text{-}Bu)_3)_2$, $ArSnBu_3$; (vi) TBAF, THF (for **5**, R = OTBDPS series only).



Scheme 3. Reagents and conditions: (i) EtMgBr, $(C_2H_5OCO)_2$, THF; (ii) $Br(CH_2)_3OTBDMS$, Cs_2CO_3, DMF.



Scheme 4. Reagents and conditions: (i) KCN, EtOH; (ii) H_2O_2, K_2CO_3, DMSO; (iii) **12**, KO*t*-Bu, THF; (iv) TFA, CH_2Cl_2.



Scheme 5. Reagents and conditions: (i) CH_3I, Cs_2CO_3, DMF; (ii) **12**, KO*t*-Bu, THF; (iii) TBAF, THF.

15. Condensation of **12** with **15** in the presence of KO*t*-Bu gave **16**, removal of the silyl-protecting groups with TFA gave the product **17** (Scheme 4).

Methylation of pyrazole-acetamide **18**[26] gave a 2:1 mixture of 2-(1-methyl-1*H*-pyrazole-3-yl)-acetamide and 2-(2-methyl-2*H*-pyrazol-3-yl)-acetamide. Condensation of **12** with these mixtures in the presence of base gave **19** and **20** (Scheme 5). Removal of the silyl-protecting group from **19** (or **20**) with TBAF gave product **21** (or **22**). The structure differentiation of **21** and **22** was confirmed by an independent synthesis of **21** via

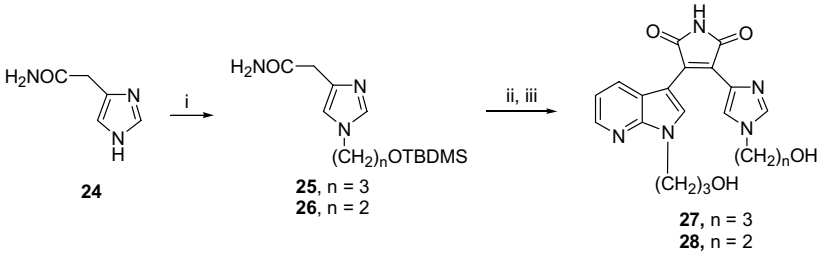
palladium-catalyzed Stille coupling reaction of **5** with 2-1-methyl-3-tributylstannanyl-1*H*-pyrazole[27] (Scheme 2).

Alkylation of acetamide **24**[28] with the bromides gave **25** (or **26**) (Scheme 6). Condensation of **12** with **25** (or **26**), followed by TBAF treatment gave product **27** (or **28**). During the palladium-catalyzed Stille reaction of **5** with organo-tin **43**, we also isolated 21% yield of the *n*-butyl coupling product **44** (Scheme 7) in addition to the expected product **34** (36% yield). The butyl- (vs phenyl-) transferred from phenyltributyltin was also observed previously by Farina et al.[29]

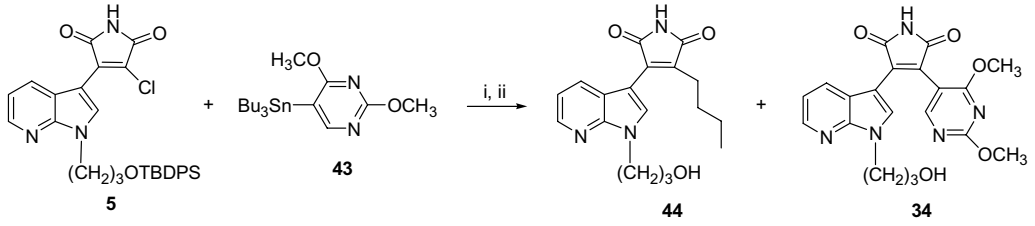
Again in Scheme 2, alkylation of acetamide **2** with various bromides gave **45**, **57**, and **61**, condensation with diethyl oxalate gave **46**, **58**, and **62**, followed by chlorination gave the chlorides **47**, **59**, and **63**. Palladium-catalyzed cross-coupling reactions of the chlorides gave desired products **48**–**49**, **60**, and **64**–**66**. The *N*-methyl analogue of the key intermediate **5**, that is chloride **50**, could also be prepared in a direct manner[30] (Scheme 8). Condensation of the Grignard reagent of **10** with 2,3-dichloro-*N*-methylmaleimide gave **50** in 21% yield. Alkylation, followed by cross-coupling reaction with organo-tin **43** in microwave gave **53** (or **54**). Hydrolysis and ammonolysis[31] gave the desired product **55** (or **56**).

3. Results and discussion

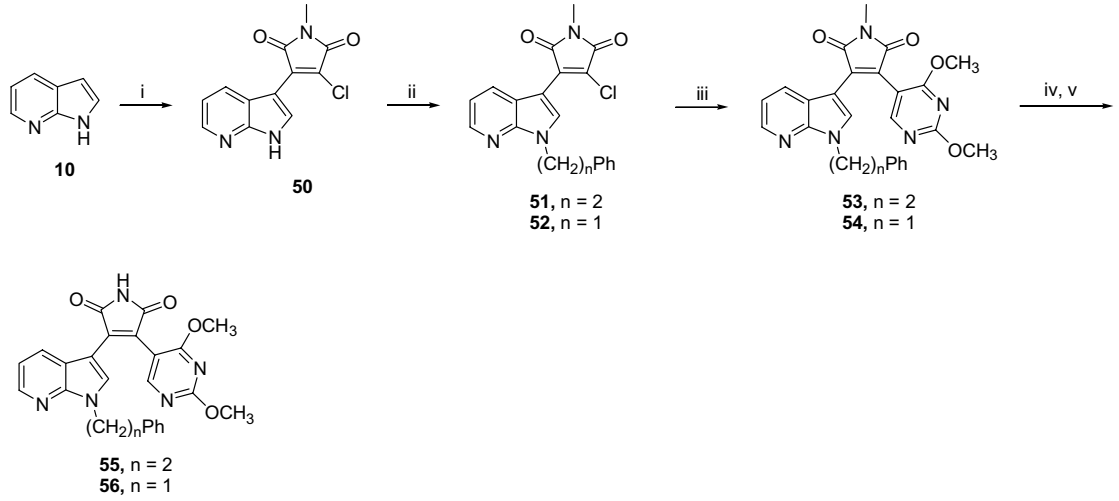
It has been demonstrated that the acyclic bis-indolylmaleimides (GF 109,203 where R = $Me_2N(CH_2)_3$, R_1 = H; Ro 31-8220 where R = $NH_2CS(=NH)(CH_2)_3$, $R_1 = CH_3$, Scheme 1), widely



Scheme 6. Reagents and conditions: (i) $Br(CH_2)_nOTBDMS$, Cs_2CO_3, DMF, 80 °C; (ii) **12**, KO*t*-Bu, THF; (iii) TBAF, THF.



Scheme 7. Reagents and conditions: (i) $Pd(P(t\text{-}Bu)_3)_2$, THF; (ii) TBAF, THF.



Scheme 8. Reagents and conditions: (i) EtMgBr, 2,3-dichloro-*N*-methylmaleimide, toluene; (ii) $Ph(CH_2)_nBr$, NaH, DMF; (iii) **43**, $Pd_2(dba)_3$, $P(t\text{-}Bu)_3$, THF/DMF, microwave; (iv) KOH, EtOH, 10% citric acid; (v) HMDS, MeOH/DMF, 80 °C.

used as protein kinase C (PKC) inhibitors are also potent GSK-3 inhibitors.[32] We thus decided to focus our initial chemistry efforts on the preparation of three-carbon chain molecules. Since the hydroxyl analog (compound B, $K_i = 0.011\,\mu M$, Scheme 1) was the most potent GSK-3β inhibitor in our previous studies,[17b] we felt the combination of a hydroxypropyl side chain and 7-azaindolylmaleimide may provide a good template for searching for novel molecules with high potency and selectivity at GSK-3β.

Four pyrrole or furan attached 7-azaindolylmaleimides were first synthesized (**6**–**9**, Table 1). We were pleased to see that all four acyclic maleimides showed comparable high potency ($K_i = 0.006$–$0.089\,\mu M$) to the cyclic bis-7-azaindolylmaleimide (compound B, $K_i = 0.011\,\mu M$) although the furan **9** displayed slightly lower potency ($K_i = 0.089\,\mu M$). We then explored the influence of bis-nitrogen containing five-member-heteroaryl maleimides (**17**, **21**–**23**) on the GSK-3β inhibitory potency. It was very surprised to find out that while all three pyrazole analogs (**21**–**23**) exhibited good to moderate potency ($K_i = 0.048$–$0.285\,\mu M$), imidazole **17** was poorly active (29.9% inhibition at 1 μM). Among the three pyrazole analogs (**21**–**23**), pyrazole **22** with the *N*-CH_3 substitution at the 2-position relative to the maleimide displayed the lowest potency ($K_i = 0.285\,\mu M$).

We next examined the impact of introduction of the second hydroxyalkyl side chain to the molecule. Both compound **27** and compound **28** with additional hydroxypropyl or hydroxyethyl side chains gave much lower potency ($K_i = 5.54\,\mu M$ for **27** and $K_i = 1.9\,\mu M$ for **28**) unfortunately. It was decided to re-visit the mono-hydroxypropyl-substituted series. Both bismethyl-substituted isoxazole **29** and thiazole **30** gave poor activity (28.5% inhibition at 1 μM for **29** and 8.5% inhibition at 1 μM for **30**). Up to this stage, it seems consistent that the steric hindrance at the 2-position of the heteroaryls (such as **22** and **29**) or the installation of heteroatoms at both of the 2-position of the five-member rings (such as **17** and **30**) are unfavorable to the kinase inhibition at GSK-3β.

Replacement of the five-member heteroaryls with six-member heteroaryls gave compounds **31**–**34** with high potency ($K_i = 0.006$–$0.025\,\mu M$) except compound **32**. It is interesting to note that while the installation of nitrogen atoms at both of the *ortho*-position of the six-member ring gave, consistently, poor activity (21.5% inhibition at 1 μM for **32**); the increased steric hindrance of the OCH_3 substituent at the 2-position of the pyrimidine gave even better potency ($K_i = 0.006\,\mu M$ for **34** vs $K_i = 0.020\,\mu M$ for **31**). There is no obvious rationale for these observations. Meanwhile, we also examined if there is any correlation between the basicity of the heteroaryls (pK_a of the protonated heteroaryls) and the GSK-3β inhibitory potency. Since some of the most basic heteroaryls such as pyrrole **6** ($K_i = 0.006\,\mu M$), imidazole **17** (29.9% inhibition @ 1 μM) imidazole **27** ($K_i = 5.54\,\mu M$) displayed a wide range of potency, some of the less basic heteroaryls such as pyrimidine **31** ($K_i = 0.020\,\mu M$), pyrimidine **32** (21.5% inhibition @ 1 μM), pyrazole **23** ($K_i = 0.098\,\mu M$), and thiazole **30** (8.5% inhibition @ 1 μM) also displayed a wide range of potency, it appears that the basicity of the heteroaryls did not have any impact on the GSK-3β inhibitory potency. Attachment of a heterocycle instead of the heteroaryl to the maleimide resulted in compound **35** with lower potency ($K_i = 0.084\,\mu M$) as compared to compound **33** ($K_i = 0.025\,\mu M$).

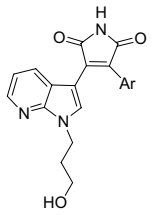
We continued to examine the impact of fused-biaryl rings (**36**–**39**) on the GSK-3β inhibitory potency. Similar to the observation of methoxy-substituted pyrimidine **34**, the extra ring fused at either 2,3-position (**36**, $K_i = 0.057\,\mu M$) or 3,4-position ($K_i = 0.029\,\mu M$ for **37**; $K_i = 0.081\,\mu M$ for **38**, and $K_i = 0.098\,\mu M$ for **39**) did not seem to be detrimental to the potency. However, the potency was reduced significantly if the fused-triaryl ring was installed (**40**, 55% inhibition at 1 μM). While the replacement of the heteroaryl with small hydroxyl group or nitrile group totally abolished the kinase inhibition (4% inhibition at 1 μM for **41** and 1% inhibition at 1 μM for **42**, Table 2), the *n*-butyl group replacement retained moderate potency (**44**, $K_i = 0.129\,\mu M$).

After exploring the structure–activity relationship at the heteroaryl site, we turned our attention to optimize the hydroxypropyl side chain portion. Replacing the hydroxyl group of compound **34** ($K_i = 0.006\,\mu M$) and **31** ($K_i = 0.020\,\mu M$) with phenyl group gave **48** ($K_i = 0.006\,\mu M$, Table 3) and **49** ($K_i = 0.178\,\mu M$). It seems the more lipophilic phenyl group did not offer improvement in potency. Shortening the chain length to two-carbon or one-carbon linker afforded **55** ($K_i = 0.063\,\mu M$) and **56** (61.4% inhibition at 1 μM). As compared to the first phenyl analog **48** ($K_i = 0.006\,\mu M$), the three-carbon chain is still more desirable from the potency point of view. Insertion of one oxygen atom into the side chain of **48**, which potentially might serve as the hydrogen-bond acceptor, gave **60** ($K_i = 0.026\,\mu M$). No improvement was observed when compared to **48**. Replacing the hydroxyl group of **34** ($K_i = 0.006\,\mu M$), **33** ($K_i = 0.025\,\mu M$), and **21** ($K_i = 0.048\,\mu M$) with a nitrile group gave the corresponding **64** ($K_i = 0.018\,\mu M$), **65** ($K_i = 0.045\,\mu M$), and **66** ($K_i = 0.051\,\mu M$). Once more, the hydroxyl group proved to be highly favorable for GSK-3β inhibitory potency in the 7-azaindolylmaleimide series, although for a reason not clearly understood yet.

3.1. Cellular activity

Among the multiple cellular processes in which GSK-3 has been implicated, the ability to phosphorylate and inhibit GS was the first regulatory process discovered and is perhaps the most thoroughly studied.[1] Therefore, the cell-based assay examining GS activation represents a direct functional assay to measure the cellular activity of GSK-3 inhibitors. As described above, LiCl is a known inhibitor of GSK-3β. LiCl increases GS activity in isolated rat adipocytes and hepatocytes,[33] and produces intracellular effects similar to that achieved by GSK-3 inhibition.[34,35] All potent compounds

Table 1. Inhibition constants at GSK-3β[a]



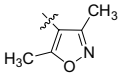
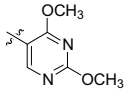
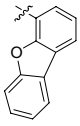
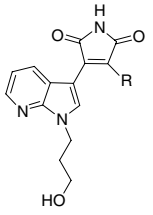
Compd	Ar	GSK-3β	
		$K_i \pm$ SEM[b] (μM)	% Inhibition @ 1 μM (±SEM)
6		0.006 ± 0.001	
7		0.019 ± 0.001	
8		0.050 ± 0.014	
9		0.089 ± 0.012	
17			29.9 ± 4.7
21		0.048 ± 0.009	
22		0.285 ± 0.032	
23		0.098 ± 0.006	
27		5.54 ± 1.09	
28		1.9 ± 0.27	
29			28.5 ± 2.5
30			8.5 ± 3.2
31		0.020 ± 0.001	
32			21.5 ± 1.1
33		0.025 ± 0.001	
34		0.006 ± 0.001	
35		0.084 ± 0.007	

Table 1 (*continued*)

Compd	Ar	GSK-3β	
		$K_i \pm$ SEM[b] (μM)	% Inhibition @ 1 μM (±SEM)
36		0.057 ± 0.003	
37		0.029 ± 0.005	
38		0.081 ± 0.013	
39		0.098 ± 0.013	
40			55.5 ± 5.3

[a] Assay details were described in the Experimental section.
[b] SEM: standard error mean.

Table 2. Inhibition constants at GSK-3β[a]



Compd	R	GSK-3β	
		$K_i \pm$ SEM[b] (μM)	% Inhibition @ 1 μM (±SEM)
41	OH		4.0 ± 2.8
42	CN		1.0 ± 0.7
44	n-C_4H_9	0.129 ± 0.028	

[a] Assay details were described in the Experimental section.
[b] SEM: standard error mean.

($K_i < 0.050$ μM) and LiCl were tested for the ability to increase GS activity in human embryonic kidney (HEK293) cells. In general, all of the compounds exhibited much greater potency ($EC_{50} = 0.032$–1.7 μM, Table 4) than LiCl ($EC_{50} > 3000$ μM) in the HEK293 cells. The 6–12-fold difference in potencies between the EC_{50} of the GS cell assay and the K_i of the GSK-3β kinase assay for most of the compounds may attribute to the differences in the species tested, that is, human cells versus recombinant rabbit enzyme. The good GS activity demonstrated that these maleimides should have good cell permeabilities.

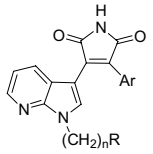
3.2. Metabolic stability in human liver microsomes

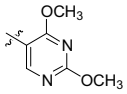
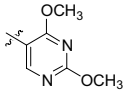
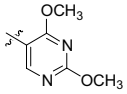
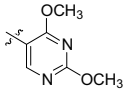
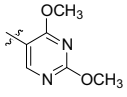
We were pleased to note that most of the compounds tested exhibited acceptable metabolic stability (**6**, $T_{1/2} = 41$ min; **34**, $T_{1/2} = 28$ min; **37**, $T_{1/2} = 35$ min, and **64**, $T_{1/2} = 44$ min, Table 4) to high metabolic stability (**21**, $T_{1/2} = 83$ min; **31**, **33**, **65**, $T_{1/2} > 100$ min, and **66**, $T_{1/2} = 97$ min) in HLM. It is interesting to observe that while *N*-methyl pyrazole **21** showed high metabolic stability ($T_{1/2} = 83$ min), the corresponding *N*-methyl pyrrole **7** showed much lower metabolic stability ($T_{1/2} = 17$ min). On the other hand, in the series of dimethoxypyrimidine, the hydroxypropyl **34** ($T_{1/2} = 28$ min) and cyanopropyl **64** ($T_{1/2} = 44$ min) are metabolically more stable than phenylpropyl **48** ($T_{1/2} < 2$ min) or phenoxypropyl **60** ($T_{1/2} = 2$ min). Therefore, although it is difficult to predict the metabolic stability of compounds in HLM in general, our designed molecular template, the combination of hydroxypropyl side chain and 7-azaindolylmaleimide, seems to be metabolically stable in HLM.

3.3. Kinase selectivity

Since many reported specific inhibitors of protein kinases were found to be nonspecific when reexamined against a large panel of protein kinases by Cohen and co-workers,[36] we decided to evaluate the selectivity of our compounds against a broad panel of 80 protein kinase assays at UBI (Upstate Biotech Inc.). Three potent compounds (**21**, **33**, and **34**) that covered a broad spectrum in GSK-3β inhibitory potency, GS cell-based activity and metabolic stability in HLM were selected for these kinase selectivity studies. In the presence of 100 μM ATP, compounds **21**, **33**, and **34** inhibited GSK-3β kinase activity by 92%, 88%, and 96% at a concentration of 10 μM, respectively (Table 5). Interestingly, compound **21** only showed moderate inhibitions in the CDK, PKB, and RsK assays and exhibited very weak inhibitory activities at the other 74 kinases. Compound **34** also only showed moderate inhibitions at CDK

Table 3. Inhibition constants at GSK-3β[a]



Compd	*n*	R	Ar	GSK-3β	
				$K_i \pm$ SEM[b] (μM)	% Inhibition @ 1 μM
48	3	Ph		0.006 ± 0.001	
49	3	Ph		0.178 ± 0.004	
55	2	Ph		0.063 ± 0.009	
56	1	Ph			61.4 ± 3.3
60	3	OPh		0.026 ± 0.003	
64	3	CN		0.018 ± 0.001	
65	3	CN		0.045 ± 0.004	
66	3	CN		0.051 ± 0.009	

[a] Assay details were described in the Experimental section.
[b] SEM: standard error mean.

Table 4. Glycogen synthase activity in HEK293 cells and metabolic stability in human liver microsomes[a]

Compd	$EC_{50} \pm$ SEM (μM)	$T_{1/2}$ (min)
6	0.043 ± 0.005	41
7	0.165 ± 0.025	17
8	0.290 ± 0.021	10
21	1.700 ± 0.284	83
31	0.168 ± 0.028	>100
33	0.032 ± 0.013	>100
34	0.075 ± 0.011	28
37	0.035 ± 0.011	35
48	0.053 ± 0.008	<2
60	0.181 ± 0.031	2
64	0.150 ± 0.042	44
65	0.391 ± 0.031	>100
66	0.350 ± 0.041	97
LiCl	>3000	—

[a] Assay details were described in the Experimental section.

assays and exhibited very weak inhibitions at the other 75 kinases. It was reported recently that some potent CDK inhibitors could also inhibit GSK-3β,[37] and bisindolylmaleimides (Scheme 1) displayed similar potency at PKC/GSK-3β.[32a,38] Therefore, it was not unusual to see that both **21** and **34** displayed moderate inhibitions at CDK isoenzymes. However, it was surprised to observe very weak inhibitions at the PKC isoenzymes for both **21** and **34** considering the structure similarity between them and bisindolylmaleimides. Finally and remarkably, compound **33** exhibited very low activity against all of the other 79 kinases and thus representing a 'specific inhibitor' of GSK-3β.

4. Conclusion

Two approaches were developed to synthesize the novel 7-azaindolyl-heteroarylmaleimides. The first approach was based upon the palladium-catalyzed Suzuki cross-coupling or Stille cross-coupling of 2-chloro-maleimide **5** with various arylboronic acids or arylstannanes. The second approach was based upon the condensation of ethyl 7-azaindolyl-3-glyoxylate **12** with various acetamides. The hydroxypropyl-substituted 7-azaindolylmaleimide template was first used to screen different heteroaryls attached to the maleimide.

Table 5. Activities at 80 protein kinases[a]

Protein kinase	Activity (% of control)		
	21	**33**	**34**
GSK3β (h)	*8*	*12*	*4*
Abl (m)	90	95	85
AMPK (r)	66	67	82
Arg (m)	99	100	101
Aurora-A (h)	97	83	70
Axl (h)	76	86	79
Blk (m)	97	89	84
Bmx (h)	87	65	55
CAMKII (r)	89	96	103
CAMKIV (h)	64	68	87
CDK1/cyclinB (h)	*39*	61	*27*
CDK2/cyclinA (h)	56	70	*11*
CDK3/cyclinE (h)	*46*	64	*17*
CDK5/p35 (h)	60	68	*37*
CDK6/cyclinD3	73	78	55
CDK7/cyclinH	81	82	82
CHK1 (h)	67	88	75
CHK2 (h)	82	82	79
CK1 (y)	84	92	63
CK2 (h)	89	71	57
c-RAF (h)	97	92	87
CSK	86	75	89
cSRC (h)	99	104	90
Fes (h)	89	87	82
FGFR3 (h)	76	80	58
Fyn (h)	82	100	106
IGF-1R	98	93	80
IKKα	88	93	101
IKKβ	117	82	115
IR	99	91	79
JNK1α1 (h)	103	94	88
JNK2α2 (h)	122	121	121
JNK3 (r)	105	79	63
Lck (h)	65	68	55
Lyn (h)	80	89	79
Lyn (m)	88	90	62
MAPK1 (h)	107	94	88
MAPK2 (h)	98	96	106
MAPK2 (m)	112	100	97
MAPKAP-K2 (h)	93	100	95
MEK1 (h)	92	103	100
MKK4 (m)	93	96	90
MKK6 (h)	83	89	106
MKK7β (h)	86	80	87
MSK1 (h)	68	70	67
p70S6K (h)	104	113	108
PAK2 (h)	87	94	86
PDGFRα	102	106	107
PDGFRβ	73	89	84
PDK1 (h)	74	94	83
PKA (b)	93	96	96
PKA (h)	95	95	101
PKBα (h)	88	95	94
PKBβ (h)	*45*	63	136
PKBγ (h)	89	95	89
PKCα (h)	92	95	92
PKCβ II (h)	105	101	97
PKCγ (h)	57	83	64
PKCδ (h)	105	129	102
PKCε (h)	91	102	118
PKCη (h)	120	119	108
PKCμ (h)	52	69	77
PKCθ (h)	93	90	97
PKD2 (h)	51	61	74
PRAK (h)	75	77	90
PRK2 (h)	80	100	91
ROCK-II (h)	98	111	104
ROCK-II (r)	97	101	106
Rsk1 (r)	64	86	84
Rsk2 (h)	*49*	72	78
Rsk3 (h)	*28*	58	69
SAPK2a (h)	92	69	98
SAPK2b (h)	93	93	91
SAPK3 (h)	99	102	95
SAPK4 (h)	95	98	99
SGK (h)	68	91	77
Syk (h)	106	79	83
TrkB (h)	91	93	85
Yes (h)	89	96	74
ZAP-70 (h)	96	80	89

[a] Protein kinase were assayed with 10 μM of **21**, **33**, and **34** in the presence of 100 μM ATP. Activities were given as the mean percentage of that in control incubations (averages of duplicate determinations). Assay details were described in the Experimental section.

Replacement of hydroxypropyl with different chain lengths and different functional groups were studied next. Many compounds synthesized were demonstrated to have high potency at GSK-3β and good GS activity in HEK293 cells. More importantly, most of these potent GSK-3β inhibitors possess good to excellent metabolic stability in human liver microsomes. Three representative compounds (**21**, **33**, and **34**) were demonstrated to have good selectivity against a panel of 80 kinase assays. Among them, compound **33** exhibited very weak inhibitions at the other 79 kinase assays, and behaved as a GSK-3β 'specific inhibitor'. The high inhibitory potency, selectivity, cellular activities, and metabolic stability in HLM suggested that these 7-aza-indolyl-heteroarylmaleimides may render them as valuable pharmacological tools in elucidating the complex roles of GSK-3β in cell signaling pathways and the potential usage for the treatment of elevated level of GSK-3β involved diseases.

5. Experimental

5.1. Chemistry

5.1.1. General information. ^{1}H NMR spectra were measured on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Elemental analyses were obtained by Quantitative Technologies Inc. (Whitehouse, New Jersey), and the results were within 0.4% of the calculated values unless otherwise mentioned. Melting points were determined in open capillary tubes with a Thomas–Hoover apparatus and were uncorrected. Electrospray mass spectra (MS-ES) were recorded on a Hewlett Packard 59987A spectrometer. High resolution mass spectra (HRMS) were obtained on a Micromass Autospec. E. spectrometer. The term 'DMAP' refers to dimethylaminopyridine, 'TFA' refers to trifluoroacetic acid, 'NMP' refers to 1-methyl-2-pyrrolidinone, 'DPPF' refers to

1,1′-bis(diphenylphosphino)ferrocene, '$Pd_2(dba)_3$' refers to tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct, 'DPPA' refers to diphenylphosphoryl azide, 'TBAF' refers to tetrabutylammonium fluoride.

5.1.2. 2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-acetamide (2). Potassium carbonate (3.4 g, 24.7 mmol) was added to a solution of compound **1** (7.75 g, 49.4 mmol) in DMSO (15 mL) at 0 °C, followed by dropwise addition of hydrogen peroxide (8.4 mL, 74 mmol; 30% solution in H_2O). The resulting solution was stirred for 10 min, CH_2Cl_2 was added and the reaction mixture was then filtered and concentrated. CH_2Cl_2 (100 mL) was added followed by Et_2O (20 mL) and the mixture cooled. The resulting precipitate was filtered off to give 7.212 g (84%) of compound **2** as a yellow solid: ^{1}H NMR (300 MHz, DMSO) δ 11.44 (br s, 1H), 8.19 (d, $J = 4.7$, 1.5 Hz, 1H), 7.95 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.39 (br s, 1H), 7.29 (s, 1H), 7.06 (dd, $J = 7.9$, 4.9 Hz, 1H), 6.86 (br s, 1H), 3.50 (s, 2H); MS (ES) m/z 176 ($M+H^+$).

5.1.3. 2-{1-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-acetamide (3). Cesium carbonate (0.45 g, 1.37 mmol) and (3-bromo-propoxy)-*tert*-butyl-diphenyl-silane (0.19 g, 0.5 mmol) were added to a solution of compound **2** (0.08 g, 0.46 mmol) in DMF (2 mL) and the resulting mixture was stirred at 70 °C. After 6 h, the reaction mixture was filtered through Celite, diluted with EtOAc (10 mL), and washed with water (5 × 10 mL). The organic layer was then dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (SiO_2) to give 0.132 g (60%) of compound **3** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, $J = 4.6$, 1.3 Hz, 1H), 7.85 (dd, $J = 4.6$, 1.3 Hz, 1H), 7.64 (m, 4H), 7.38 (m, 6H), 7.05 (m, 2H), 4.42 (t, $J = 6.6$ Hz, 2H), 3.64 (t, $J = 5.9$ Hz, 2H), 3.62 (s, 2H), 2.09 (m, 2H), 1.08 (s, 9H); MS (ES) m/z 472 ($M+H^+$).

5.1.4. 3-{1-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-4-hydroxy-pyrrole-2,5-dione (4). Potassium *tert*-butoxide (0.69 mL, 0.69 mmol; 1 M solution in THF) was added dropwise to a solution of compound **3** (0.13 g, 0.35 mmol) and diethyl oxalate (0.101 g, 0.69 mmol) in TMF (2 mL) at 0 °C under nitrogen. After 20 min the reaction mixture was concentrated and a crude product was purified by column chromatography (SiO_2) to give 0.117 g (80%) of compound **4** as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.69 (dd, $J = 7.9$, 1.3 Hz, 1H), 8.33 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.20 (s, 1H), 7.69 (m, 4H), 7.41 (m, 6H), 7.14 (dd, $J = 7.9$, 4.5 Hz, 1H), 4.6 (t, $J = 6.8$ Hz, 2H), 3.73 (t, $J = 6.0$ Hz, 2H), 2.2 (m, 2H), 1.07 (s, 9H); MS (ES) m/z 526 ($M+H^+$).

5.1.5. 3-{1-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-4-chloro-pyrrole-2,5-dione (5). Oxalyl chloride (0.015 mL, 0.18 mmol) was added in one portion to a solution of compound **4** (0.03 g, 0.06 mmol) in 1:1 CH_2Cl_2/DMF (2 mL) at 23 °C under nitrogen. After 1 h the reaction mixture was concentrated and a crude product was purified by column chromatography (SiO_2) to give 0.023 g (73%) of compound **5** as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.69 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.4 (dd, $J = 4.6$, 1.5 Hz, 1H), 8.36 (s, 1H), 7.67 (m, 4H), 7.41 (m, 6H), 7.25 (dd, $J = 8.1$, 4.6 Hz, 1H), 4.67 (t, $J = 6.8$ Hz, 2H), 3.74 (t, $J = 6.0$ Hz, 2H), 2.24 (m, 2H), 1.04 (s, 9H); MS (ES) m/z 544 ($M+H^+$).

5.1.6. General procedure for the synthesis of 6, 8, 29, 31, 36–38, and 40 (method A). 4-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-[3,3′-bi-1*H*-pyrrole]-2,5-dione (6). 1-(Triisopropyl)silyl-pyrrole-3-boronic acid (0.053 mL, 0.2 mmol) was added to a solution of compound **5** (0.054 g, 0.1 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol), $Pd(^tBu_3P)_2$ (5 mg, 0.01 mmol), and potassium fluoride (20 mg, 0.34 mmol) in THF (1 mL) at 23 °C under nitrogen. The mixture was stirred at 23 °C for 18 h, then diluted with EtOAc (10 mL), filtered through Celite, and concentrated. The product was purified by column chromatography (SiO_2) to give 0.044 g (60%) of silyl-protected product as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, $J = 4.9$ Hz, 1H), 7.74 (s, 1H), 7.66 (m, 4H), 7.36 (m, 7H), 7.17 (m, 1H), 6. 89 (dd, $J = 8.3$, 4.9 Hz, 1H), 6.62 (m, 1H), 6.37 (m, 1H), 4.53 (t, $J = 6.8$ Hz, 2H), 3.7 (t, $J = 6.0$ Hz, 2H), 2.2 (m, 2H), 1.37 (sep, $J = 7.4$ Hz, 3H),1.09 (s, 9H), 1.05 (s, 9H), 1.02 (s, 9H); MS (ES) m/z 731 ($M+H^+$).

TBAF (0.12 mL, 1 M solution in THF, 0.12 mmol) as added dropwise to a solution of this silyl-ether in THF (1 mL) under nitrogen. After 18 h, the mixture was concentrated and purified by column chromatography (SiO_2) to give 0.017 g (84%) of compound **6** as an orange solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 10.47 (s, 1H), 9.57 (s, 1H), 8.3 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.9 (s, 1H), 7.56 (m, 1H), 7.49 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.01 (dd, $J = 7.9$, 4.7 Hz, 1H), 6.75 (m, 1H), 6.22 (m, 1H), 4.55 (t, $J = 6.6$ Hz, 2H), 4.02 (t, $J = 5.7$ Hz, 1H), 3.56 (q, $J = 5.8$ Hz, 2H), 2.11 (m, 2H); MS (ES) m/z 337 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 337.1301, found 337.1292.

5.1.7. General procedure for the synthesis of 7, 9, 21, 23, 30, 32–35, and 39 (method B). 4-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1′-methyl-1′*H*-[3,3′]bipyrrolyl-2,5-dione (7). To a solution of compound **5** (54 mg, 0.1 mmol) and $Pd(^tBu_3P)_2$ (5 mg, 0.01 mmol) in THF (2 mL) was added 1-methyl-3-tributylstannanyl-1*H*-pyrrole (51 mg, 0.13 mmol), at 23 °C under nitrogen. The reaction mixture was refluxed for 18 h. Upon cooling, the mixture was diluted with EtOAc (10 mL) and washed with H_2O, KF, brine, and dried. After concentration, the crude product was purified by column chromatography (SiO_2) to give 35 mg (60%) of silyl-protected product as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.74 (s, 1H), 7.64 (m, 4H), 7.35 (m, 9H), 6.97 (dd, $J = 7.9$, 4.7 Hz, 1H), 6.43 (m, 1H), 6.12 (m, 1H), 4.53 (m, 2H),

4.01 (m, 1H), 3.72 (m, 2H), 3.66 (s, 3H), 2.18 (m, 2H), 1.09 (s, 9H); MS (ES) m/z 589 ($M+H^+$).

To a solution of this silyl-ether (35 mg, 0.06 mmol) in THF (2 mL) was added TBAF (1 M solution in THF, 1.5 equiv) dropwise under nitrogen. After 18 h, the mixture was concentrated and purified by column chromatography (SiO_2) to give 15 mg (71%) of compound **7** as an orange solid: ^1H NMR (300 MHz, acetone-d_6) δ 9.54 (s, 1H), 8.30 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.89 (s, 1H), 7.50 (dd, $J = 8.1$, 1.7 Hz, 1H), 7.44 (m, 1H), 7.02 (dd, $J = 7.9$, 4.7 Hz, 1H), 6.60 (m, 1H), 6.11 (dd, $J = 2.8$, 1.7 Hz, 1H), 4.54 (m, 2H), 4.01 (m, 1H), 3.70 (s, 3H), 3.55 (m, 2H), 2.11 (m, 2H); MS (ES) m/z 351 ($M+H^+$). Anal. Calcd for $C_{19}H_{18}N_4O_3 \cdot 0.1H_2O$: C, 64.80; H, 5.21; N, 15.91. Found: C, 64.77; H, 5.08; N, 15.82.

5.1.8. 3-Furan-3-yl-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (8). Method A: using 3-furanboronic acid (2 equiv) and following the same procedure as in the preparation of **6** gave **8** (59%) as an orange solid: ^1H NMR (300 MHz, acetone-d_6) δ 8.34 (d, $J = 4.5$, 1.5 Hz, 1H), 8.16 (m, 1H), 8.01 (s, 1H), 7.53 (m, 2H), 7.11 (dd, $J = 8.1$, 4.7 Hz, 1H), 6.47 (dd, $J = 2.1$, 0.8 Hz, 1H), 4.56 (m, 2H), 3.59 (m, 2H), 2.13 (m, 2H); MS (ES) m/z 338 ($M+H^+$).

5.1.9. 3-Furan-2-yl-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (9). Method B: using 2-(tributylstannyl)furan (1.5 equiv) and following the same procedure as in the preparation of **7** gave **9** (64%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, $J = 4.7$, 1.3 Hz, 1H), 7.96 (s, 1H), 7.57 (s, 1H), 7.51 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.39 (d, $J = 1.1$ Hz, 1H), 7.31 (d, $J = 3.6$ Hz, 1H), 7.03 (dd, $J = 8.1$, 4.7 Hz, 1H), 6.58 (dd, $J = 3.6$, 1.7 Hz, 1H), 4.54 (m, 2H), 3.50 (m, 2H), 2.07 (m, 2H); MS (ES) m/z 338 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 338.1141, found 338.1153.

5.1.10. Oxo-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid ethyl ester (11). To a THF solution (20 mL) of 7-azaindole **10** (2.30 g, 19.5 mmol) was added EtMgBr (21.5 mmol, 1 M solution in THF), and the mixture was heated to gentle reflux for 1 h, and cooled to 20 °C. Diethyl oxolate (8.0 mL, 58.5 mmol) was dissolved in THF (50 mL) and cooled to −40 °C, and the freshly prepared Grignard reagent was introduced slowly via a cannula. After the addition was complete, the mixture was heated to 70 °C for 1.5 h, and cooled to 20 °C. It was quenched with 5 mL of saturated $NaHCO_3$, and diluted with water. The aqueous layer was extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel, eluting gradually with hexane/EtOAc to give 1 g (23%) of compound **11** as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 11.8 (s, 1H), 8.75 (dd, $J = 7.9$, 1.5 Hz, 1H), 8.70 (s, 1H), 8.45 (dd, $J = 4.8$, 1.5 Hz, 1H), 7.35 (dd, $J = 7.9$, 4.8 Hz, 1H), 4.44 (q, $J = 7.1$ Hz, 2H), 1.46 (t, $J = 7.1$ Hz, 3H); MS (ES) m/z 219 ($M+H^+$).

5.1.11. {1-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-oxo-acetic acid ethyl ester (12). To a mixture of compound **11** (318 mg, 1.46 mmol) and Cs_2CO_3 (2.38 g, 7.30 mmol) in DMF (5 mL) was added a DMF (2 mL) solution of (3-bromopropoxy)-*tert*-butyldimethylsilane (1.85 g, 7.30 mmol) at 80 °C. After it was stirred at 80 °C for 10 min, the mixture was cooled, diluted with EtOAc, and filtered through Celite. The filtrate was washed with water (4 × 25 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel, eluting gradually with hexane/EtOAc to give 457 mg (80%) of compound **12** as a white crystalline solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, $J = 6.3$, 1.5 Hz, 1H), 8.46 (s, 1H), 8.35 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.22 (m, 1H), 4.43 (t, $J = 6.8$ Hz, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.57 (t, $J = 5.7$ Hz, 2H), 2.05 (m, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 0.87 (s, 9H), 0.00 (s, 6H); MS (ES) m/z 391 ($M+H^+$).

5.1.12. [1-(2-Trimethylsilanylethoxymethyl)-1*H*-imidazol-2-yl]acetonitrile (14). To a water solution (20 mL) of KCN (5.46 g, 83.9 mmol) at 0 °C was added compound **13** (2.3 g, 9.32 mmol) in EtOH (40 mL) dropwise. Once addition was completed, the mixture was stirred at 23 °C for 4 h. The solution was filtered and the precipitate was washed with 95% EtOH (100 mL). The filtrate was then concentrated to small volume and water added (20 mL). After extraction of the aqueous layer with $CHCl_3$ (4 × 50 mL), the combined organic layers were concentrated to give a dark oil, which was purified by column chromatography (SiO_2) to give 0.813 g (40%) of compound **14** as a pale oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 2H), 5.26 (s, 2H), 3.89 (s, 2H), 3.45 (br t, $J = 8.4$ Hz, 2H), 0.87 (br t, $J = 8.4$ Hz, 2H), −0.06 (s, 9H); MS (ES) m/z 260 ($M+Na^+$).

5.1.13. 2-[1-(2-Trimethylsilanylethoxymethyl)-1*H*-imidazol-2-yl]acetamide (15). To a DMSO solution (3 mL) of compound **14** (0.813 g, 3.4 mmol) at 0 °C was added K_2CO_3 (0.2 g, 1.7 mmol) in one portion followed by H_2O_2 (0.5 mL, 5.1 mmol) dropwise. After 5 min, MeOH (5 mL) was added and the mixture was filtered, concentrated, and the DMSO was removed by a nitrogen stream. The product compound **15** (0.648 g, 74%) was then obtained by recrystallization from Et_2O as pale crystals: ^1H NMR (300 MHz, CD_3OD) δ 7.18 (s, 1H), 6.90 (s, 1H), 5.37 (s, 2H), 3.77 (s, 2H), 3.53 (br t, $J = 7.9$ Hz, 2H), 0.89 (br t, $J = 8.2$ Hz, 2H), −0.02 (s, 9H); MS (ES) m/z 256 ($M+H^+$).

5.1.14. 3-[1-[3-(*tert*-Butyl-dimethylsilanyloxy)propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-[1-(2-trimethylsilanylethoxymethyl)-1*H*-imidazol-2-yl]pyrrole-2,5-dione (16). To a THF solution (0.4 mL) of compound **15** (0.126 g, 0.493 mmol) and compound **12** (0.214 g, 0.548 mmol) at 0 °C was added potassium *tert*-butoxide (1.1 mL, 1 M solution in THF, 1.1 mmol) dropwise under nitrogen. After 15 min the mixture was allowed to warm to 23 °C and stirred for 30 min. The crude product was then partially concentrated and purified by column

chromatography (SiO_2) to give 0.06 g (21%) of compound **16** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.31 (m, 2H), 7.32 (m, 1H), 6.91 (dd, $J = 8$, 4.8 Hz, 1H), 6.57 (d, $J = 7.7$ Hz, 1H), 5.21 (s, 2H), 4.50 (t, $J = 6.8$ Hz, 2H), 3.7 (t, $J = 5.7$ Hz, 2H), 3.44 (br t, $J = 8.2$ Hz, 2H), 2.15 (m, $J = 6.2$ Hz, 2H), 0.97 (s, 9H), 0.79 (br t, $J = 8.2$ Hz, 2H), 0.12 (s, 6H), −0.08 (s, 9H); MS (ES) m/z 583 (M+H$^+$).

5.1.15. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-(1*H*-imidazol-2-yl)-1*H*-pyrrole-2,5-dione (17). To a CH_2Cl_2 solution (2 mL) of compound **16** (0.048 g, 0.082 mmol) at 20 °C was added TFA (1 mL). After 20 h toluene (5 mL) was added and the mixture was concentrated. The crude product was purified by column chromatography (SiO_2) to give 0.008 g (29%) of compound **17** as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.24 (dd, $J = 4.8$, 1.5 Hz, 1H), 7.28 (m, 2H), 7.12 (dd, $J = 8$, 1.5 Hz, 1H), 6.98 (dd, $J = 7.9$, 4.6 Hz, 1H), 4.48 (t, $J = 6.8$ Hz, 2H), 3.61 (t, $J = 6.2$ Hz, 2H), 2.10 (m, $J = 6.4$ Hz, 2H); MS (ES) m/z 338 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 338.1253, found 338.1261.

5.1.16. 3-{1-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-pyrrole-2,5-dione 19 and 3-{1-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-4-(2-methyl-2*H*-pyrazol-3-yl)-pyrrole-2,5-dione (20). Cesium carbonate (3.5 g, 10.8 mmol) and iodomethane (0.51 g, 3.6 mmol) were added to a solution of **18** (0.45 g, 3.6 mmol) in DMF (5 mL) at 23 °C under nitrogen. The mixture was warmed to 70 °C and stirred for 3 h. After cooling, the mixture was diluted with EtOAc (20 mL), filtered through Celite, and washed with water (4 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a crude product (0.46 g) as a white solid. After chromatography, the isolated product was shown to be a 2:1 mixture of 2-(1-methyl-1*H*-pyrazol-3-yl)-acetamide and 2-(2-methyl-2*H*-pyrazol-3-yl)-acetamide.

Potassium *tert*-butoxide (6.6 mL, 6.6 mmol; 1 M solution in THF) was added dropwise to a solution of the above mixture of products and compound **12** (1.36 g, 3.47 mmol) in THF (20 mL) at 0 °C under nitrogen. After warming to 23 °C, the reaction mixture was stirred for 2 h and then concentrated. The crude reaction mixture was purified by column chromatography (SiO_2) to give a yellow solid, which was then recrystallized (EtOAc/hexanes) to give 0.36 g (21%) of compound **19** and 0.1 g (6%) of compound **20**. For compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.30 (dd, $J = 4.8$, 1.7 Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.37 (s, 1H), 7. 09 (dd, $J = 7.9$, 1.5 Hz, 1H), 6.93 (dd, $J = 7.9$, 4.6 Hz, 1H), 6.73 (d, $J = 2.2$ Hz, 1H), 4.47 (t, $J = 7.0$ Hz, 2H), 3.84 (s, 3H), 3.71 (t, $J = 5.9$ Hz, 2H), 2.15 (m, 2H), 0.92 (s, 9H), 0.07 (s, 6H); MS (ES) m/z 466 (M+H$^+$). For compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.30 (s, 1H), 8.25 (dd, $J = 4.7$, 1.4 Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 6.83 (dd, $J = 8.1$, 4.6 Hz, 1H), 6.47 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.45 (d, $J = 1.8$ Hz, 1H), 4.43 (m, 2H), 3.61 (m, 2H), 3.47 (s, 3H), 2.07 (m, 2H), 0.87 (s, 9H), 0.00 (s, 6H); MS (ES) m/z 466 (M+H$^+$).

5.1.17. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2,5-dione (21). TBAF (1.3 mL, 1 M solution in THF, 1.3 mmol) was added to a solution of compound **19** (0.35 g, 0.75 mmol) in THF (15 mL) at 23 °C dropwise under nitrogen. After 18 h, the mixture was concentrated and the product was purified by column chromatography (SiO_2) followed by recrystallization to give 0.22 g (82%) of compound **21** as a yellow solid: ^{1}H NMR (300 MHzMHz, DMSO-d_6) δ 11.05 (s, 1H). 8.45 (s, 1H), 8.27 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.78 (d, $J = 2.3$ Hz, 1H), 7.27 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.05 (dd, $J = 8.1$, 4.7 Hz, 1H), 6.67 (d, $J = 2.3$ Hz, 1H), 4.4 (t, $J = 7$ Hz, 2H), 3.79 (s, 3H), 3.46 (t, $J = 6$ Hz, 2H), 1.99 (m, 2H); MS (ES) m/z 352 (M+H$^+$). Anal. Calcd for $C_{18}H_{17}N_5O_3 \cdot 0.1H_2O$: C, 61.22; H, 4.91; N, 19.83. Found: C, 61.03; H, 4.75; N, 19.78.

Compound **21** was also prepared by an alternative route. Method B: using 2-1-methyl-3-tributylstannanyl-1*H*-pyrazole (1.5 equiv) and following the same procedure as in the preparation of **7** gave **21** (75%) as a yellow solid.

5.1.18. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-(2-methyl-2*H*-pyrazol-3-yl)-pyrrole-2,5-dione (22). TBAF (1.3 mL, 1 M solution in THF, 1.3 mmol) was added to a solution of **20** (92 mg, 0.20 mmol) in THF (15 mL) at 23 °C dropwise under nitrogen. After 18 h, the mixture was concentrated and the crude product was then recrystallized (CH_2Cl_2/hexane) to give 64 mg (91%) of compound **22** as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (m, 2H), 7.62 (d, $J = 1.9$ Hz, 1H), 6.94 (dd, $J = 8.5$, 5.1 Hz, 1H), 6.59 (dd, $J = 8.1$, 1.3 Hz, 1H), 6.51 (d, $J = 1.7$ Hz, 1H), 4.53 (m, 2H), 4.13 (m, 1H), 3.54 (s, 3H), 3.43 (m, 2H), 2.07 (m, 2H); MS (ES) m/z 352 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 352.1410, found 352.1406.

5.1.19. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-(1-methyl-1*H*-pyrazol-4-yl)-pyrrole-2,5-dione (23). Method B: using 1-methyl-4-tributylstannanyl-1*H*-pyrazole (1.5 equiv) and following the same procedure as in the preparation of **7** gave **23** (31%): ^{1}H NMR (300 MHz, acetone-d_6) δ 8.38 (s, 1H), 8.29 (m, 1H), 8.07 (s, 1H), 7.51 (s, 1H), 6.9 (dd, $J = 8.1$, 4.7 Hz, 1H), 6.67 (d, $J = 2.3$ Hz, 1H), 6.42 (s, 1H), 4.56 (m, 2H), 3.51 (m, 5H), 2.05 (m, 2H); MS (ES) m/z 352 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 352.1410, found 352.1424.

5.1.20. 2-{1-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-1*H*-imidazol-4-yl}-acetamide (25). To a mixture of compound **24** (115 mg, 0.92 mmol) and Cs_2CO_3 (450 mg, 1.38 mmol) in DMF (2.0 mL), (3-bromopropoxy)-*tert*-

butyldimethylsilane (350 mg, 1.38 mmol) was added. The resulting mixture was heated to 80 °C for 5.5 h, and it was then cooled to 20 °C. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to give 100 mg (36%) of compound **25** as a sticky yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.70 (s, 1H), 3.98 (t, $J = 6.9$ Hz, 2H), 3.52 (t, $J = 5.6$ Hz, 2H), 3.46 (s, 2H), 1.87 (m, 2H), 0.86 (s, 9H), 0.00 (s, 6H); MS (ES) m/z 298 ($M+H^+$).

5.1.21. 2-{1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-1*H*-imidazol-4-yl}-acetamide (26). DMF (1.0 mL) solution of (2-bromoethoxy)-*tert*-butyldimethylsilane (301 mg, 1.26 mmol) was added to a mixture of compound **24** (105 mg, 0.84 mmol) and Cs_2CO_3 (411 mg, 1.26 mmol) in DMF (2.0 mL). The mixture was heated to reflux for 5 h, and it was then cooled to 20 °C. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to give 149 mg (63%) of compound **26** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.86 (s, 1H), 4.03 (t, $J = 4.7$ Hz, 2H), 3.86 (t, $J = 4.8$ Hz, 2H), 3.54 (s, 2H), 0.89 (s, 9H), 0.00 (s, 6H); MS (ES) m/z 284 ($M+H^+$).

5.1.22. 3-[1-(3-Hydroxypropyl)-1*H*-imidazol-4-yl]-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (27). KO*t*-Bu (0.24 mL, 0.24 mmol, 1 M solution in THF) at 0 °C was added to a THF (0.25 mL) solution of oxolate compound **12** (48 mg, 0.12 mmol) and imidazole **25** (33 mg, 0.11 mmol). After the mixture was stirred at 0 °C for 15 min, it was warmed to 20 °C for 1 h. After the solvent was removed under reduced pressure, the residue was chromatographed on silica gel, eluting with Hex/EtOAc to give 32 mg of silylated product as an orange red oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, $J = 4.7$, 1.3 Hz, 1H), 8.25 (s, 1H), 7.74 (s, 1H), 7.54 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.44 (s, 1H), 6.96 (dd, $J = 8.0$, 4.7 Hz, 1H), 4.47 (t, $J = 7.0$ Hz, 2H), 4.12 (t, $J = 6.8$ Hz, 2H), 3.72 (t, $J = 5.8$ Hz, 2H), 3.60 (t, $J = 5.6$ Hz, 2H), 2.14 (m, 2H), 1.98 (m, 2H), 0.92 (s, 9H), 0.91 (s, 9H), 0.07 (s, 6H), 0.00 (s, 6H); MS (ES) m/z 624 ($M+H^+$).

TBAF (0.4 mL, 0.40 mmol, 1 M solution in THF) at 20 °C was added to a THF (1.0 mL) solution of the above silylated product. After the mixture was stirred for 30 min, the solvent was removed under reduced pressure. The residue was crystallized from MeOH/EtOAc to give 21 mg (48%) of compound **27** as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1H), 8.33 (s, 1H), 8.25 (d, $J = 4.4$ Hz, 1H), 7.84 (s, 1H), 7.69 (s, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.02 (m, 1H), 4.65 (s, 1H), 4.64 (s, 1H), 4.39 (t, $J = 6.7$ Hz, 2H), 4.10 (t, $J = 6.6$ Hz, 2H), 3.47 (d, $J = 5.8$ Hz, 2H), 3.38 (d, $J = 5.5$ Hz, 2H), 1.98 (t, $J = 6.2$ Hz, 2H), 1.87 (t, $J = 6.1$ Hz, 2H); MS (ES) m/z 396 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 396.1672, found 396.1668.

5.1.23. 3-[1-(2-Hydroxyethyl)-1*H*-imidazol-4-yl]-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (28). KO*t*-Bu (1.2 mL, 1.20 mmol, 1 M in THF) at 0 °C was added to a THF (1.1 mL) solution of oxolate **12** (234 mg, 0.60 mmol) and imidazole **26** (153 mg, 0.54 mmol). The mixture was stirred at 0 °C for 10 min, and then warmed to 20 °C for 1.5 h. It was concentrated and the resulting residue was chromatographed on silica gel, eluting with EtOAc/hexane to give 161 mg of silylated product as a red chip: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.29 (s, 1H), 8.24 (d, $J = 4.5$ Hz, 1H), 7.91 (s, 1H), 7.61 (s, 1H), 7.59 (d, $J = 8.1$ Hz, 1H), 7.00 (m, 1H), 4.39 (t, $J = 7.1$ Hz, 2H), 4.13 (t, $J = 4.3$ Hz, 2H), 3.83 (t, $J = 4.5$ Hz, 2H), 3.64 (t, $J = 5.8$ Hz, 2H), 2.03 (t, $J = 6.4$ Hz, 2H), 0.87 (s, 9H), 0.81 (s, 9H), 0.01 (s, 6H), −0.01 (s, 6H); MS (ES) m/z 610 ($M+H^+$).

TBAF (0.56 mL, 0.56 mmol, 1 M in THF) at 20 °C was added to a THF (2.0 mL) solution of the above silylated product. The mixture was stirred at 20 °C for 2 h, and then concentrated under reduced pressure. The residue was purified by column chromatography eluting with MeOH/CH_2Cl_2 to give 90 mg (44%) of compound **28** as an orange red solid after recrystallized from MeOH/EtOAc: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.35 (s, 1H), 8.26 (d, $J = 4.3$ Hz, 1H), 7.90 (s, 1H), 7.68 (s, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.04 (dd, $J = 7.9$, 4.6 Hz, 1H), 5.00 (t, $J = 5.1$ Hz, 1H), 4.66 (d, $J = 4.6$ Hz, 1H), 4.40 (t, $J = 6.9$ Hz, 2H), 4.08 (t, $J = 5.1$ Hz, 2H), 3.68 (q, $J = 4.6$ Hz, 2H), 3.48 (d, $J = 4.9$ Hz, 2H), 1.99 (m, 2H); MS (ES) m/z 382 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 382.1516, found 382.1517.

5.1.24. 3-(3,5-Dimethyl-isoxazol-4-yl)-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (29). Method A: using 3,5-dimethylisoxazole-4-boronic acid (2 equiv) and following the same procedure as in the preparation of **6** gave **29** (10%): ^{1}H NMR (300 MHz, acetone-d_6) δ 8.33 (dd, $J = 4.6$, 1.5 Hz, 1H), 8.24 (s, 1H), 7.24 (dd, $J = 8.1$, 1.7 Hz, 1H), 7.03 (dd, $J = 8.1$, 4.8 Hz, 1H), 4.56 (m, 2H), 3.53 (m, 2H), 2.11 (m, 2H), 2.08 (s, 3H), 2.02 (s, 3H); MS (ES) m/z 367 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 367.1406, found 367.1398.

5.1.25. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-thiazol-2-yl-pyrrole-2,5-dione (30). Method B: using 2-tributylstannylthiazole (1.5 equiv) and following the same procedure as in the preparation of **7** gave **30** (9%): ^{1}H NMR (300 MHz, acetone-d_6) δ 8.89 (s, 1H), 8.33 (d, $J = 2.1$ Hz, 1H), 7.94 (m, 2H), 7.71 (d, $J = 2.3$ Hz, 1H), 7.1 (dd, $J = 8.1$, 4.7 Hz, 1H), 4.58 (m, 2H), 3.99 (m, 1H), 3.61 (m, 2H), 2.14 (m, 2H); MS (ES) m/z 355 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 355.0865, found 355.0865.

5.1.26. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-pyrimidin-5-yl-pyrrole-2,5-dione (31). Method A: using pyrimidine-5-boronic acid (2 equiv) and following

the same procedure as in the preparation of **6** gave **31** (29%) as an orange solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 9.11 (s, 1H), 8.86 (s, 2H), 8.29 (m, 2H), 6.95 (m, 2H), 4.58 (m, 2H), 3.55 (m, 2H), 2.11 (m, 2H); MS (ES) m/z 348 (M−H$^+$); FAB-HRMS (M+H$^+$). Calcd 350.1253, found 350.1265.

5.1.27. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-pyrimidin-2-yl-pyrrole-2,5-dione (32). Method B: using 2-tributylstannylpyrimidine (1.5 equiv) and following the same procedure as in the preparation of **7** gave **32** (70%): ^{1}H NMR (300 MHz, CD_3OD) δ 8.85 (d, $J = 4.9$ Hz, 2H), 8.32 (s, 1H), 8.21 (d, $J = 4.0$ Hz, 1H), 7.49 (m, 1H), 6.87 (dd, $J = 8.1$, 4.8 Hz, 1H), 6.68 (d, $J = 7.9$ Hz, 1H), 4.47 (m, 2H), 3.56 (m, 2H), 2.08 (m, 2H); MS (ES) m/z 350 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 350.1253, found 350.1262.

5.1.28. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-pyrazin-2-yl-pyrrole-2,5-dione (33). Method B: using 2-tributylstannylpyrazine (1.5 equiv) and following the same procedure as in the preparation of **7** gave **33** (46%): ^{1}H NMR (300 MHz, acetone-d_6) δ 9.01 (s, 1H), 8.58 (m, 1H), 8.42 (s, 1H), 8.27 (dd, $J = 4.4$, 1.8 Hz, 1H), 6.94 (m, 2H), 4.54 (m, 2H), 3.57 (m, 2H), 2.11 (m, 2H); MS (ES) m/z 350 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 350.1253, found 350.1258.

5.1.29. 3-(2,4-Dimethoxy-pyrimidin-5-yl)-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (34). Method B: using 2,4-dimethoxy-5-tributylstannanyl-pyrimidine **43** (1.5 equiv) and following the same procedure as in the preparation of **7** gave **34** (36%): ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (s, 1H), 8.26 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.13 (s, 1H), 7.20 (dd, $J = 7.9$, 1.3 Hz, 1H), 6.96 (dd, $J = 8.1$, 4.7 Hz, 1H), 4.49 (m, 2H), 4.01 (s, 3H), 3.56 (m, 2H), 3.42 (s, 3H), 2.10 (m, 2H); MS (ES) m/z 410 (M+H$^+$).

5.1.30. 3-(5,6-Dihydro-[1,4]dioxin-2-yl)-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (35). Method B: using tributyl-(5,6-dihydro-[1,4]dioxin-2-yl)-stannane (1.5 equiv) and following the same procedure as in the preparation of **7** gave **35** (49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, $J = 4.7$, 1.3 Hz, 1H), 7.93 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.76 (s, 1H), 7.39 (s, 1H), 7.16 (dd, $J = 7.9$, 4.9 Hz, 1H), 4.49 (m, 2H), 4.14 (m, 2H), 3.89 (m, 2H), 3.46 (m, 2H), 2.05 (m, 2H); MS (ES) m/z 356 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 356.1247, found 356.1246.

5.1.31. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-quinolin-8-yl-pyrrole-2,5-dione (36). Method A: using 8-quinolineboronic acid (2 equiv) and following the same procedure as in the preparation of **6** gave **36** (50%) as an orange solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.69 (dd, $J = 4.0$, 1.7 Hz, 1H), 8.37 (dd, $J = 8.5$, 1.7 Hz, 1H), 8.13 (s, 1H), 8.08 (m, 2H), 7.78 (dd, $J = 7.0$, 1.5 Hz, 1H), 7.65 (dd, $J = 8.1$, 7.4 Hz, 1H), 7.45 (dd, $J = 8.5$, 4.1 Hz, 1H), 6.52 (m, 2H), 4.44 (m, 2H), 3.46 (m, 2H), 1.99 (m, 2H); MS (ES) m/z 399 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 399.1457, found 399.1456.

5.1.32. 3-(2-Benzofuranyl)-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (37). Method A: using benzofuran-2-boronic acid (2 equiv) and following the same procedure as in the preparation of **6** gave **37** (57%) as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.32 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.27 (s, 1H), 7.77 (m, 1H), 7.65 (s, 1H), 7.57 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.29 (m, 3H), 7.02 (dd, $J = 7.9$, 4.5 Hz, 1H), 4.47 (t, $J = 6.9$ Hz, 2H), 3.5 (t, $J = 6.0$ Hz, 2H), 2.05 (m, 2H); MS (ES) m/z 388 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 388.1297, found 388.1311.

5.1.33. 3-Benzo[*b*]thiophen-2-yl-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (38). Method A: using benzothiophene-2-boronic acid (2 equiv) and following the same procedure as in the preparation of **6** gave **38** (40%): ^{1}H NMR (300 MHz, acetone-d_6) δ 8.52 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.39 (m, 2H), 8.32 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.18 (s, 1H), 7.83 (m, 1H), 7.39 (m, 2H), 7.27 (dd, $J = 8.1$, 4.7 Hz, 1H), 6.97 (dd, $J = 8.1$, 4.7 Hz, 1H), 4.59 (m, 2H), 3.58 (m, 2H), 2.14 (m, 2H); MS (ES) m/z 404 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 404.1069, found 404.1056.

5.1.34. 3-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-(4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyridin-2-yl)-pyrrole-2,5-dione (39). Method B: using 2-tributylstannanyl-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyridine (1.5 equiv) and following the same procedure as in the preparation of **7** gave **39** (71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.27 (dd, $J = 4.7$, 1.3 Hz, 1H), 7.53 (s, 1H), 7.19 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.98 (dd, $J = 8.1$, 4.7 Hz, 1H), 6.51 (s, 1H), 4.50 (m, 2H), 4.00 (m, 2H), 3.48 (m, 2H), 2.85 (m, 2H), 2.06 (m, 4H), 1.89 (m, 2H); MS (ES) m/z 392 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 392.1723, found 392.1710.

5.1.35. 3-(4-Dibenzofuranyl)-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (40). Method A: using 4-dibenzofuranboronic acid (2 equiv) and following the same procedure as in the preparation of **6** gave **40** (34%) as a yellow solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.28 (s, 1H), 8.18 (dd, $J = 7.7$, 1.3 Hz, 1H), 8.02 (ddd, $J = 8.3$, 4.5, 1.5 Hz, 2H), 7.74 (dd, $J = 7.5$, 1.1 Hz, 1H), 7.51 (m, 1H), 7.32 (m, 2H), 7.17 (m, 1H), 6.64 (dd, $J = 7.9$, 1.5 Hz, 1H), 6.53 (dd, $J = 8.1$, 4.7 Hz, 1H), 4.50 (t, $J = 6.6$ Hz, 2H), 3.49 (m, 2H), 2.04 (m, 2H); MS (ES) m/z 438 (M+H$^+$); FAB-HRMS (M+H$^+$). Calcd 438.1454, found 438.1455.

5.1.36. 3-Hydroxy-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (41). TBAF (0.29

mL, 0.29 mmol, 1 M in THF) at 20 °C was added to a THF (10 mL) solution of **4** (0.1 g, 0.19 mmol). The mixture was stirred at 20 °C for 18 h, and then concentrated under reduced pressure. The residue was purified by column chromatography eluting with $MeOH/CH_2Cl_2$ to give 0.05 g (90%) of compound **41** as a yellow solid: ^1H NMR (400 MHz, CD_3OD) δ 9.27 (dd, $J = 8.1$, 1.1 Hz, 1H), 8.46 (dd, $J = 5.7$, 0.8 Hz, 1H), 8.26 (s, 1H), 7.57 (dd, $J = 8.1$, 5.9 Hz, 1H), 4.57 (m, 2H), 3.56 (m, 2H), 2.12 (m, 2H); MS (ES) m/z 288 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 288.0984, found 288.0984.

5.1.37. 4-[1-(3-Hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile (42). To a solution of **5** (54 mg, 0.1 mmol) in DMF (3 mL) under N_2 was added $Pd(Ph_3P)_4$ (12 mg, 0.01 mmol), LiCl (13 mg, 0.3 mmol), and $Zn(CN)_2$ (23 mg, 0.2 mmol). The reaction mixture was heated to 120 °C and stirred for 3 h. After cooling, the reaction mixture was diluted with EtOAc, filtered through Celite, washed with water (3×), dried with $MgSO_4$, filtered, and concentrated to give 6 mg (11%) of silylated product as a yellow solid. This solid was dissolved in THF (2 mL), TBAF (17 μL, 0.01 mmol) was added and the mixture was stirred for 8 h then concentrated and purified by column chromatography to give 3 mg (92%) of **42** as a yellow solid: ^1H NMR (300 MHz, acetone-d_6) δ 8.72 (s, 1H), 8.65 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.37 (dd, $J = 4.8$, 1.5 Hz, 1H), 7.29 (dd, $J = 8.1$, 4.6 Hz, 1H), 4.52 (m, 2H), 3.47 (m, 2H), 2.03 (m, 2H); MS (ES) m/z 297 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 297.0988, found 297.0978.

5.1.38. 3-Butyl-4-[1-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (44). Method B: using 2,4-dimethoxy-5-tributylstannanyl-pyrimidine **43** (1.5 equiv) and following the same procedure as in the preparation of **7** gave **34** (36%, see above) and **44** (21%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, $J = 4.6$ Hz, 1H), 8.06 (d, $J = 8.1$, 1H), 7.65 (s, 1H), 7.21 (dd, $J = 8.1$, 4.8 Hz, 1H), 4.51 (m, 2H), 3.47 (m, 2H), 2.64 (m, 2H), 2.04 (m, 2H), 1.62 (m, 2H), 1.37 (m, 2H), 0.88 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z 328 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 328.1661, found 328.1675.

5.1.39. 2-[1-(3-Phenyl-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetamide (45). To a solution of the amide **2** (0.5 g, 2.7 mmol) in DMF (10 mL) was added Cs_2CO_3 (2.65 g, 8.1 mmol) and 3-phenyl-propyl bromide (0.8 g, 4.05 mmol). The reaction was heated at 70 °C for 2 h. After cooling down, the solution was diluted with EtOAc and washed with H_2O. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica to give 0.412 g (49%) of compound **45** as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.88 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.22 (m, 6H), 7.10 (m, 1H), 4.32 (m, 2H), 3.70 (s, 2H), 2.66 (m, 2H); MS (ES) m/z 316 ($M+H^+$).

5.1.40. 3-Hydroxy-4-[1-(3-phenyl-propyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (46). To a solution of **45** (0.412 g, 1.3 mmol) in DMF (10 mL) at 0 °C was added $(CO_2Et)_2$ (0.38 g, 2.6 mmol), and then KO*t*-Bu (2.6 mL, 2.6 mmol, 1 M in THF) dropwise. The resulting red solution was stirred for 15 min and concentrated. The product was purified by column chromatography to give 0.393 g (81%) of **46** as a yellow solid: ^1H NMR (300 MHz, acetone-d_6) δ 9.11 (s, 1H), 8.75 (m, 1H), 8.10 (m, 1H), 7.97 (s, 1H), 7.12 (m, 5H), 6.88 (m, 1H), 4.15 (m, 2H), 2.45 (m, 2H), 2.04 (m, 2H); MS (ES) m/z 374 ($M+H^+$).

5.1.41. 3-Chloro-4-[1-(3-phenyl-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (47). To a solution of **46** (0.393 g, 1.05 mmol) in DMF and CH_2Cl_2 (1:1) was added $(COCl)_2$ (0.4 g, 3.15 mmol) in one portion at 0 °C. The reaction was followed by TLC until starting material disappeared (~1 h), then $NaHCO_3$ solution was added. The mixture was diluted with EtOAc and washed with water, dried, concentrated, and chromatographed on silica gel to give 0.372 g (89%) of **47** as a yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.43 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.75 (s, 1H), 7.24 (m, 7H), 4.41 (m, 2H), 2.70 (m, 2H), 2.30 (m, 2H); MS (ES) m/z 366 ($M+H^+$).

5.1.42. 3-(2,4-Dimethoxy-pyrimidin-5-yl)-4-[1-(3-phenyl-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (48). To a solution of **47** (30 mg, 0.082 mmol) and $Pd(^tBu_3P)_2$ (4 mg, 0.008 mmol) in THF (1 mL) was added the organo-tin **43** (53 mg, 0.123 mmol) at 23 °C under nitrogen. The reaction mixture was refluxed for 18 h. Upon cooling, the mixture was diluted with EtOAc (10 mL) and washed with H_2O, KF, brine, and dried. After concentration, the crude product was purified by column chromatography (SiO_2) to give 6 mg (16%) of compound **48**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.31 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.09 (s, 1H), 7.59 (s, 1H), 7.31 (m, 2H), 7.20 (m, 4H), 7.05 (dd, $J = 7.9$, 1.3 Hz, 1H), 6.90 (dd, $J = 7.9$, 4.7 Hz, 1H), 4.41 (m, 2H), 4.04 (s, 3H), 3.43 (s, 3H), 2.69 (m, 2H), 2.29 (m, 2H); MS (ES) m/z 470 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 470.1829, found 470.1838.

5.1.43. 3-[1-(3-Phenyl-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-4-pyrimidin-5-yl-pyrrole-2,5-dione (49). Method A: using pyrimidine-5-boronic acid (2 equiv) and following the same procedure as in the preparation of **48** gave **49** (36%) as a yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.89 (s, 2H), 8.33 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.16 (s, 1H), 7.23 (m, 6H), 6.90 (dd, $J = 7.9$, 4.7 Hz, 1H), 6.74 (dd, $J = 8.1$, 1.3 Hz, 1H), 4.42 (m, 2H), 2.73 (m, 2H), 2.35 (m, 2H); MS (ES) m/z 410 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 410.1617, found 410.1620.

5.1.44. 3-Chloro-1-methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione (50). A solution of EtMgBr (26.6 mL, 79.8 mmol, 3 M in Et_2O) was added dropwise under argon to a well-stirred solution of 7-azaindole

(9 g, 76 mmol) in dry toluene (270 mL) at room temperature. After 1 h, a solution of the 2,3-dichloro-*N*-methylmaleimide (4.5 g, 38 mmol) in toluene (240 mL) was slowly added. After 15 min, anhydrous CH_2Cl_2 (300 mL) was added and the reaction mixture was heated at 50 °C for 24 h. Hydrolysis was performed by a saturated solution of NH_4Cl till pH 7. After extraction with EtOAc (2×400 mL), the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Compound **50** was precipitated from methanol, filtered, washed with methanol, and dried under vacuum. Compound **50** was obtained as an orange solid (2.12 g, 21%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 1H), 8.34 (m, 2H), 8.21 (s, 2H), 7.21 (m, 1H), 2.98 (s, 3H); MS (ES) m/z 262 ($M+H^+$).

5.1.45. 3-Chloro-1-methyl-4-(1-phenethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione (51). To a solution of **50** (250 mg, 0.96 mmol) in anhydrous DMF (15 mL) was added NaH (5 equiv, 60% dispersion in oil) under N_2. After stirring 10 min, (2-bromo-ethyl)-benzene (355 mg, 1.92 mmol) was added and the reaction mixture was heated at 70 °C for 90 min. Water (15 mL) was added at 20 °C followed by EtOAc (50 mL). The aqueous layer was acidified with 1 N HCl, extracted with EtOAc (three times), and organic layers were combined, dried, and concentrated. The product was purified by column chromatography to give 37 mg (11%) of **51**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.43 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.90 (s, 1H), 7.26–7.20 (m, 3H), 7.14–7.06 (m, 3H), 4.62 (t, $J = 7.2$ Hz, 2H), 3.22 (t, $J = 7.2$ Hz, 2H), 3.14 (s, 3H); MS (ES) m/z 366 ($M+H^+$).

5.1.46. 3-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-chloro-1-methyl-pyrrole-2,5-dione (52). Using benzyl bromide (3 equiv) and following the same procedure as in the preparation of **51** gave **52** (76%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.44 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.14 (s, 1H), 7.32–7.28 (m, 5H), 7.26–7.21 (m, 1H), 5.58 (s, 2H), 3.14 (s, 3H); MS (ES) m/z 352 ($M+H^+$).

5.1.47. 3-(2,4-Dimethoxy-pyrimidin-5-yl)-1-methyl-4-(1-phenethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione (53). Compound **51** (38 mg, 0.1 mmol), $Pd_2(dba)_3$ (10.4 mg, 0.01 mmol), organo-tin **43** (64 mg, 0.15 mmol), and $P(^tBu)_3$ (10.2 mg, 0.02 mmol) were mixed in anhydrous THF and DMF (10:1 by volume). The mixture was sealed in a tube and microwaved for 350 s at 200 °C. The reaction mixture was concentrated and the product was purified by column chromatography to give 27 mg (55%) of **53**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.31 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.91 (s, 1H), 7.31–7.23 (m, 3H), 7.18–7.15 (m, 2H), 7.01 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.91–6.87 (m, 1H), 4.62 (t, $J = 7.3$ Hz, 2H), 4.07 (s, 3H), 3.44 (s, 3H), 3.24 (t, $J = 7.1$ Hz, 2H); MS (ES) m/z 470 ($M+H^+$).

5.1.48. 3-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-pyrrole-2,5-dione (54). Compound **52** (51 mg, 0.145 mmol), $Pd_2(dba)_3$ (14.5 mg, 0.014 mmol), organo-tin **43** (93.6 mg, 0.218 mmol), and $P(^tBu)_3$ (14.3 mg, 0.028 mmol) was mixed in anhydrous THF and DMF (10:1 by volume). The mixture was sealed in a tube and microwaved for 350 s at 200 °C. The reaction mixture was concentrated and the product was purified by column chromatography to give 47 mg (71%) of **54**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.32 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.02 (s, 1H), 7.32–7.29 (m, 5H), 7.09 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.93–6.89 (m, 1H), 5.55 (s, 2H), 4.04 (s, 3H), 3.34 (s, 3H), 3.14 (s, 3H); MS (ES) m/z 456 ($M+H^+$).

5.1.49. 3-(2,4-Dimethoxy-pyrimidin-5-yl)-4-(1-phenethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione (55). To a solution of **53** (27 mg, 0.058 mmol) in EtOH (2 mL) was added KOH aqueous solution (1 mL, 10 N) and the reaction was stirred for 2 h. Water (5 mL) was added and the mixture was acidified with 10% citric acid. After extraction with CH_2Cl_2 (three times), the organic layers were dried and concentrated to give the crude anhydride (23 mg). To this crude anhydride in anhydrous DMF (1.5 mL) was added HMDS (93.6 mg, 0.58 mmol) in MeOH (0.8 mL). The reaction mixture was heated at 80 °C for 2 h and then cooled down slowly. The solvent was removed and the residue was purified by column chromatography to give 9.2 mg (35%) of compound **55**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.35 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.98 (s, 1H), 7.28–7.23 (m, 3H), 7.14–7.12 (m, 2H), 6.99–6.95 (m, 2H), 4.64 (t, $J = 7.2$ Hz, 2H), 4.05 (s, 3H), 3.41 (s, 3H), 3.24 (t, $J = 7.2$ Hz, 2H); MS (ES) m/z 456 ($M+H^+$).

5.1.50. 3-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-(2,4-dimethoxy-pyrimidin-5-yl)-pyrrole-2,5-dione (56). Using compound **54** and following the same procedure as in the preparation of **55** gave **56** (26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.33 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.02 (s, 1H), 7.46 (s, 1H), 7.33–7.29 (m, 5H), 7.09 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.94–6.90 (m, 1H), 5.56 (s, 2H), 4.04 (s, 3H), 3.34 (s, 3H); MS (ES) m/z 442 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 442.1516, found 442.1532.

5.1.51. 2-[1-(3-Phenoxy-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetamide (57). Using 3-phenoxyl-propyl bromide (1.5 equiv) and following the same procedure as in the preparation of **45** gave **57** (27%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (dd, $J = 4.6$, 1.3 Hz, 1H), 7.89 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.26 (m, 2H), 7.16 (s, 1H), 7.08 (dd, $J = 7.9$, 4.6 Hz, 1H), 6.94 (m, 1H), 6.86 (m, 2H), 4.49 (m, 2H), 3.92 (m, 2H), 3.64 (s, 2H), 2.36 (m, 2H); MS (ES) m/z 310 ($M+H^+$).

5.1.52. 3-Hydroxy-4-[1-(3-phenoxy-propyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (58). Using compound **57** and following the same procedure as in the

preparation of **46** gave **58** (53%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (m, 1H), 8.41 (m, 1H), 8.17 (s, 1H), 7.25 (m, 4H), 7.21 (m, 1H), 6.86 (m, 2H), 4.62 (m, 2H), 3.98 (m, 2H), 2.44 (m, 2H); MS (ES) m/z 364 ($M+H^+$).

5.1.53. 3-Chloro-4-[1-(3-phenoxy-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (59). Using compound **58** and following the same procedure as in the preparation of **47** gave **59** (78%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, $J = 4.9$, 1.5 Hz, 1H), 7.97 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.25 (m, 4H), 7.14 (dd, $J = 7.9$, 4.9 Hz, 1H), 6.95 (m, 1H), 6.86 (m, 2H), 4.53 (m, 2H), 3.95 (m, 2H), 2.35 (m, 2H); MS (ES) m/z 382 ($M+H^+$).

5.1.54. 3-(2,4-Dimethoxy-pyrimidin-5-yl)-4-[1-(3-phenoxy-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione (60). Method B: using compound **59** and following the same procedure as in the preparation of **48** gave **60** (23%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.32 (d $J = 4.6$ Hz, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.28 (m, 2H), 7.08 (d, $J = 7.9$ Hz, 1H), 6.92 (m, 4H), 4.61 (m, 2H), 4.06 (s, 3H), 4.01 (m, 2H), 3.43 (s, 3H), 2.44 (m, 2H); MS (ES) m/z 486 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 486.1778, found 486.1775.

5.1.55. 2-[1-(3-Cyano-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetamide (61). Using 3-cyano-propyl bromide (1.5 equiv) and following the same procedure as in the preparation of **45** gave **61** (42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.91 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.20 (s, 1H), 7.13 (dd, $J = 7.9$, 4.7 Hz, 1H), 4.47 (m, 2H), 3.71 (s, 2H), 2.38 (m, 2H), 2.29 (m, 2H); MS (ES) m/z 243 ($M+H^+$).

5.1.56. 4-[3-(4-Hydroxy-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-pyrrolo[2,3-*b*]pyridin-1-yl]-butyronitrile (62). Using compound **61** and following the same procedure as in the preparation of **46** gave **62** (73%) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.65 (dd, $J = 8.1$, 1.7 Hz, 1H), 8.17 (dd, $J = 4.8$, 1.5 Hz, 1H), 7.69 (s, 1H), 7.06 (dd, $J = 7.9$, 4.8 Hz, 1H), 4.38 (m, 2H), 2.43 (m, 2H), 2.21 (m, 2H); MS (ES) m/z 297 ($M+H^+$).

5.1.57. 4-[3-(4-Chloro-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-pyrrolo[2,3-*b*]pyridin-1-yl]-butyronitrile (63). Using compound **62** and following the same procedure as in the preparation of **47** gave **63** (77%) as an orange solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.39 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.32 (s, 1H), 7.26 (dd, $J = 8.1$, 4.7 Hz, 1H), 4.53 (m, 2H), 2.51 (m, 2H), 2.28 (m, 2H); MS (ES) m/z 315 ($M+H^+$).

5.1.58. 4-{3-[4-(2,4-Dimethoxy-pyrimidin-5-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-pyrrolo[2,3-*b*]pyridin-1-yl}-butyronitrile (64). Method B: using compound **63** and following the same procedure as in the preparation of **48** gave **64** (43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.29 (dd, $J = 4.7$, 1.5 Hz, 1H), 8.07 (s, 1H), 7.07 (dd, $J = 7.9$, 1.5 Hz, 1H), 6.92 (dd, $J = 7.9$, 4.7 Hz, 1H), 4.50 (s, 2H), 4.04 (s, 3H), 3.48 (s, 3H), 2.36 (m, 4H); MS (ES) m/z 419 ($M+H^+$).

5.1.59. 4-[3-(2,5-Dioxo-4-pyrazin-2-yl-2,5-dihydro-1*H*-pyrrol-3-yl)-pyrrolo[2,3-*b*]pyridin-1-yl]-butyronitrile (65). Method B: using 2-tributylstannylpyrazine (1.5 equiv) and following the same procedure as in the preparation of **64** gave **65** (68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.57 (s, 2H), 8.30 (m, 2H), 7.82 (s, 1H), 6.89 (dd, $J = 7.9$, 4.4 Hz, 1H), 6.75 (d, $J = 7.9$ Hz, 1H), 4.52 (m, 2H), 2.44 (m, 2H), 2.37 (m, 2H); MS (ES) m/z 359 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 359.1256, found 359.1257.

5.1.60. 4-{3-[4-(1-Methyl-1*H*-pyrazol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-pyrrolo[2,3-*b*]pyridin-1-yl}-butyronitrile (66). Method B: using 2-1-methyl-3-tributylstannanyl-1*H*-pyrazole (1.5 equiv) and following the same procedure as in the preparation of **64** gave **66** (33%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (m, 2H), 7.45 (m, 2H), 7.22 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.99 (dd, $J = 8.1$, 4.8 Hz, 1H), 6.80 (d, $J = 2.4$ Hz, 1H), 4.51 (s, 2H), 3.85 (s, 3H), 2.44 (m, 2H), 2.36 (s, 2H); MS (ES) m/z 361 ($M+H^+$); FAB-HRMS ($M+H^+$). Calcd 361.1413, found 361.1419.

5.2. Biology

5.2.1. GSK-3 kinase assay. Compounds were tested for the ability to inhibit recombinant rabbit GSK-3β (New England Biolabs) using the following protocol. Protein phosphatase inhibitor-2 (PPI-2, Calbiochem) phosphorylation was measured using a standard filtration assay (MultiScreen-DV/Millipore). Briefly, the test compounds were added to a reaction mixture containing PPI-2 (45 ng), GSK-3β (0.75 units), and ^{33}P-ATP (1 μCi) in 50 mM Tris–HCl (pH 8.0), 10 mM $MgCl_2$, 0.1% BSA, 1 mM DTT, and 100 μM activated Sodium Orthovanadate. The total ATP concentration was 25 μM. After 90 min incubation at 30 °C, the phosphorylated PPI-2 was precipitated using one volume of 20% trichloroacetic acid (TCA). Filter plates were subsequently washed with 10% TCA and radioactivity was quantified using a TopCount Scintillation Counter (Packard). IC_{50} values were determined from at least three separate experiments and the K_i values ±SEM were calculated using the Cheng-Prussof equation.

5.2.2. Protein kinase selectivity panel (Upstate Biotech Inc.). Protein kinase selectivity assays were performed as previously described.[36,39] Briefly, protein kinases were assayed for their ability to phosphorylate the appropriate peptide/protein substrates in the presence of 10 μM compound. Assays were done using 100 μM ATP and were linear with respect to time.

5.2.3. Glycogen synthase assay. Compounds were tested for the ability to increase glycogen synthase (GS) activity in living cells (HEK293 cells). To do this, cell extracts were prepared from cells treated with compounds or vehicle and GS activity measured using a modified protocol.[15b] Briefly, cells were serum (and glucose) starved for 3 h and treated with the appropriate compounds for 90 min at 37 °C. Cells were then washed, scraped, and collected by centrifugation prior to lysis using three freeze/thaw cycles. Lysates were then clarified by centrifugation and the supernatants assayed for GS activity. To do this, ^{14}C-UDP glucose incorporation into glycogen was measured in the absence or presence of glucose 6-phosphate. The EC_{50} for GS activation was then determined and compared with lithium.

5.2.4. Metabolism, human liver microsomes. Human liver microsomes were obtained from Xenotech (Kansas City, KS). The microsomal reaction composition was prepared as: microsomes, 1 mg/mL; NADPH, 1 mM; potassium phosphate (pH 7.4), 100 mM; magnesium chloride, 10 mM; test compound, 5 μM, and equilibrated at 37 °C for 3 min. The reaction was initiated by addition of NADPH, and then incubated in a shaking water bath at 37 °C. Aliquots (100 μL) were withdrawn in duplicate at 0, 15, 30, and 60 min and combined with 400 μL of ice-cold 50/50 acetonitrile/dH_2O to terminate the reaction. Several controls (testosterone, propranolol, and atenolol) were run simultaneously with the test compounds. The percent compound remaining in the incubation mixture were plotted as a function of time; a first-order exponential equation was fit to the observed data. The elimination half-lives associated with the disappearance of test and control compounds were determined to compare their relative metabolic stability. The $T_{1/2}$ of testosterone = 5.4 min, propranolol = 29 min, and atenolol > 100 min.

5.2.5. Abbreviations. GSK-3β, glycogen synthase kinase-3β; Abl, the product of the abl proto-oncogene; AMPK, AMP-activated protein kinase; Arg, the product of the c-abl-related gene; Axl, the product of the axl proto-oncogene; Blk, B lymphocyte kinase; Bmx, bone marrow tyrosine kinase gene in chromosome X; CAMKII, calmodulin-dependent protein kinase II; CAMKIV, calmodulin-dependent protein kinase IV; CDK1/cyclinB, cycline-dependent protein kinase 1; CDK2/cycA, cyclin-dependent protein kinase 2; CDK5/p35, cyclin-dependent protein kinase 5; CDK6/cyclin D3, cyclin-dependent protein kinase 6; CDK7/cyclin H, cyclin-dependent protein kinase 7; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CK1, casein kinase 1; CK2, casein kinase 2; CSK, carboxy-terminal Src kinase; Fes, cellular product of the *fes* proto-oncogene; Fyn, product of *fyn* proto-oncogene; FGFR3, FGF receptor kinase 3; IGF-1R, insulin-like growth factor-1 receptor kinase; IKK, I kappa B kinase; IR, insulin receptor kinase; JNK1α 1, c-Jun N-terminal kinase 1α1; JNK2α2, c-Jun N-terminal kinase 2α2; JNK3, c-Jun N-terminal kinase 3; Lck, lymphocyte kinase; Lyn, Lck/Yes-related tyrosine kinase; MAPK1, mitogen-activated protein kinase 1; MAPK2, mitogen-activated protein kinase 2; MAPKAP-K2, MAPK-activated protein kinase 2; MEK1, MAPK/ERK kinase 1; MKK4, MAPK kinase 4; MKK6, MAPK kinase 6; MKK7β, MAPK kinase 7β; MSK1, mitogen- and stress-activated protein kinase 1; PAK2, p21-activated protein kinase-2; PDGFR, platelet-derived growth factor receptor; PDK1, 3-phosphoinositide-dependent protein kinase 1; PKA, camp-dependent protein kinase; PKBα, protein kinase B α (also called Akt); PKBβ, protein kinase B β; PKC, protein kinase C; PRAK, p38-regulated/activated kinase; PRK2, protein kinase c-related protein kinase-2; c-Raf, cellular product of *raf* proto-oncogene; RsK, ribosomal S6 kinase; SAPK2b, stress-activated protein kinase 2b (also known as p38β 2); P70S6K, p70 ribosomal protein S6 kinase; c-SRC, cellular product of *src* oncogene, Syk, splenic tyrosine kinase; TrkB, tyrosine receptor kinase-B; Yes, cellular product of the *yes* proto-oncogene; ZAP-70, zeta-associated protein kinase-70. m = mouse, h = human.

Acknowledgements

We thank Earl Danser for sending the compounds to UBI for selectivity testing.

References and notes

1. Embi, N.; Rylatt, D. B.; Cohen, P. *Eur. J. Biochem.* **1980**, *107*, 519.
2. Welsh, G. I.; Proud, C. G. *Biochem. J.* **1993**, *294*, 625.
3. Woodgett, J. R. *EMBO. J.* **1990**, *9*, 2431.
4. Grimes, C. A.; Jope, R. S. *Prog. Neurobiol.* **2001**, *65*, 391.
5. Eldar-Finkelman, H. *TRENDS Mol. Med.* **2002**, *8*, 126.
6. Kaidanovich, O.; Eldar-Finkelman, H. *Expert Opin. Ther. Targets* **2002**, *6*, 555.
7. (a) Lovestone, S.; Reynolds, C. H.; Latimer, D.; Davis, D. R.; Anderton, B. H.; Gallo, J.-M.; Hanger, D.; Mulot, S.; Marquardt, B.; Stabel, S.; Woodgett, J. R.; Miller, C. C. J. *Curr. Biol.* **1994**, *4*, 1077; (b) Pap, M.; Cooper, G. M. *J. Biol. Chem.* **1998**, *273*, 19929; (c) Lucas, J. J.; Hernandez, F.; Gomez-Ramos, P.; Moran, M. A.; Hen, R.; Avila, J. *EMBO. J.* **2001**, *20*, 27.
8. Cross, D.; Cubert, A. A.; Chalmers, K. A.; Facci, L.; Skaper, S. D.; Reith, A. D. *J. Neurochem.* **2001**, *77*, 94.
9. Castro, A.; Martinez, A. *Expert Opin. Ther. Patents* **2000**, *10*, 1519.
10. Phiel, C. J.; Klein, P. S. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 789.
11. Hoeflich, K. P.; Luo, J.; Rubie, E. A.; Tsao, M.-S.; Jin, O.; Woodgett, J. R. *Nature* **2000**, *406*, 86.
12. Bray, A. M.; Schultz, P.; Ring, D. B.; Harrison, S. D. Chiron Corp. WO9816528, 1998.
13. (a) Dorronsoro, I.; Castro, A.; Martinez, A. *Expert Opin. Ther. Patents* **2002**, *12*, 1527; (b) Martinez, A.; Castro, A.; Dorronsoro, I.; Alonso, M. *Med. Res. Rev.* **2002**, *22*, 373; (c) Olesen, P. H.; Sorensen, A. R.; Urso, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. *J. Med. Chem.* **2003**, *46*, 3333.
14. Ring, D. B.; Johnson, K. W.; Henriksen, E. J.; Nuss, J. M.; Goff, D.; Kinnick, T. R.; Ma, S. T.; Reeder, J. W.; Samuels, I.; Slabiak, T.; Wagman, A. S.; Hammond, M.-E. W.; Harrison, S. D. *Diabetes* **2003**, *52*, 588.

15. (a) Smith, D. G.; Buffet, M.; Fenwick, A. E.; Haigh, D.; Ife, R. J.; Saunders, M.; Slingsby, B. P.; Stacey, R.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 635; (b) Coghlan, M. P.; Culbert, A. A.; Cross, D. A. E.; Corcoran, S. L.; Yates, J. W.; Pearce, N. J.; Rausch, O. L.; Murphy, G. J.; Carter, P. S.; Cox, L. R.; Mills, D.; Brown, M. J.; Haigh, D.; Ward, R. W.; Smith, D. G.; Murray, K. J.; Reith, A. D.; Holder, J. C. *Chem. Biol.* **2000**, *7*, 793.
16. Martinez, A.; Alonso, M.; Castro, A.; Perez, C.; Moreno, F. J. *J. Med. Chem.* **2002**, *45*, 1292.
17. (a) Kuo, G.-H.; Prouty, C.; DeAngelis, A.; Shen, L.; O'Neill, D. J.; Shah, C.; Connolly, P. J.; Murray, W. V.; Conway, B. R.; Cheung, P.; Westover, L.; Xu, J. Z.; Look, R. A.; Demarest, K. T.; Emanuel, S.; Middleton, S. A.; Jolliffe, L.; Beavers, M. P.; Chen, X. *J. Med. Chem.* **2003**, *46*, 4021; (b) Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Look, R. A.; Chen, X.; Beavers, M. P.; Roberts, J.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem.* **2004**, *12*, 1239.
18. Both compound A and compound B have $T_{1/2} = 2$ min metabolic stability in human liver microsomes. We preferred to see a compound that has $T_{1/2} = 30$ min or longer metabolic stability in human liver microsomes.
19. A manuscript of acyclic 3-(7-azaindolyl)-4-(aryl or heteroaryl)maleimides as potent, selective inhibitors of glycogen synthase kinase-3 was submitted separately: Zhang, H.-C. et al. *Bioorg. Med. Chem. Lett.* **2004**.
20. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
21. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.
22. Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1956**, *78*, 1247.
23. Rooney, C. S.; Randall, W. C.; Streeter, K. B.; Ziegler, C.; Cragoe, E. J.; Schwam, H.; Michelson, S. R.; Williams, H. W. R.; Eichler, E.; Duggan, D. E.; Ulm, E. H.; Noll, R. M. *J. Med. Chem.* **1983**, *26*, 700.
24. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053.
25. Allerton, C. M. N.; Blagg, J.; Bunnage, M. E.; Steele, J. PCT Int. Appl. WO 0214285 A1 20020221, 2002.
26. Jones, R. G.; Mann, M. J. *J. Am. Chem. Soc.* **1953**, *75*, 4048.
27. Wang, T.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Yin, Z. PCT Int. Appl. WO 0262423 A1 20020815, 2002.
28. Zimmerman, S. C.; Korthals, J. S.; Cramer, K. D. *Tetrahedron* **1991**, *47*, 2649.
29. Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.
30. Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621.
31. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A.; Sullivan, K. A.; Gillig, J. R.; Need, D. A.; Rito, C. J.; Jirousek, M. R. *J. Org. Chem.* **1998**, *63*, 1961.
32. (a) Hers, I.; Tavare, J. M.; Denton, R. M. *FEBS Lett.* **1999**, *460*, 433; (b) Hu, H. *Drug Discovery Today* **1996**, *1*, 438.
33. Nyfeler, F.; Walter, P. *FEBS Lett.* **1979**, *108*, 197.
34. Stambolic, V.; Ruel, L.; Woodgett, J. R. *Curr. Biol.* **1996**, *6*, 1664.
35. Klein, P. S.; Melton, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8455.
36. Bain, J.; McLauchlan, H.; Elliott, M.; Cohen, P. *Biochem. J.* **2003**, *371*, 199.
37. (a) Leost, M.; Schultz, C.; Link, A.; Yong-Zhong, W.; Biernat, J.; Mandelkow, E.-M.; Bibb, J. A.; Snyder, G. L.; Greengard, P.; Zaharevitz, D. W.; Gussio, R.; Senderowicz, A. M.; Sausville, E. A.; Kunick, C.; Meijer, L. *Eur. J. Biochem.* **2000**, *267*, 5983; (b) Leclerc, S.; Garnier, M.; Hoessel, R.; Marko, D.; Bibb, J. A.; Snyder, G. L.; Greengard, P.; Biernat, J.; Wu, Y. Z.; Mandelkow, E. M.; Eisenbrand, G.; Meijer, L. *J. Biol. Chem.* **2001**, *276*, 251; (c) Mettey, Y.; Gompel, M.; Thomas, V.; Garnier, M.; Leost, M.; Ceballos-Picot, I.; Noble, M.; Endicott, J.; Vierfond, J.-M.; Meijer, L. *J. Med. Chem.* **2003**, *46*, 222.
38. Zhang, H.-C.; White, K. B.; Ye, H.; McComsey, D. F.; Derian, C. K.; Addo, M. F.; Andrade-Gordon, P.; Eckardt, A. J.; Conway, B. R.; Westover, L.; Xu, J. Z.; Look, R.; Demarest, K. T.; Emanuel, S.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3049.
39. Davies, S. P.; Reddy, H.; Caivano, M.; Cohen, P. *Biochem. J.* **2000**, *351*, 95.