Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 3245–3250
Bioorganic & Medicinal Chemistry Letters

3-(7-Azaindolyl)-4-arylmaleimides as potent, selective inhibitors of glycogen synthase kinase-3

Han-Cheng Zhang,[a,*] Hong Ye,[a] Bruce R. Conway,[b] Claudia K. Derian,[a] Michael F. Addo,[a] Gee-Hong Kuo,[b] Leonard R. Hecker,[a] Diane R. Croll,[a] Jian Li,[a] Lori Westover,[b] Jun Z. Xu,[b] Richard Look,[b] Keith T. Demarest,[b] Patricia Andrade-Gordon,[a] Bruce P. Damiano[a] and Bruce E. Maryanoff[a]

[a]*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA 19477-0776, USA*
[b]*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ 08869-0602, USA*

Received 5 February 2004; revised 26 March 2004; accepted 29 March 2004

Abstract—A novel series of acyclic 3-(7-azaindolyl)-4-(aryl/heteroaryl)maleimides was synthesized and evaluated for activity against GSK-3β and selectivity versus PKC-βII, as well as a broad panel of protein kinases. Compounds **14** and **17c** potently inhibited GSK-3β ($IC_{50} = 7$ and 26 nM, respectively) and exhibited excellent selectivity over PKC-βII (325 and >385-fold, respectively). Compound **17c** was also highly selective against 68 other protein kinases. In a cell-based functional assay, both **14** and **17c** effectively increased glycogen synthase activity by inhibiting GSK-3β.

1. Introduction

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase composed of two isoforms (α and β) with high homology (ca. 90%) at the catalytic domain.[1] GSK-3β plays a critical role in glucose homeostasis, CNS function (via the proteins tau and β-catenin), and cancer (via angiogenesis, apoptosis, and tumorigenesis).[2] Inhibition of GSK-3-dependent phosphorylation should activate insulin-dependent glycogen synthesis, thereby mimicking the action of insulin to lower plasma glucose. Thus, inhibitors of GSK-3β would afford a novel mode of treating type II diabetes.[3] Additionally, GSK-3 inhibitors have therapeutic potential for treating neurodegenerative diseases, bipolar disorder, stroke, cancer, and chronic inflammatory diseases.[4]

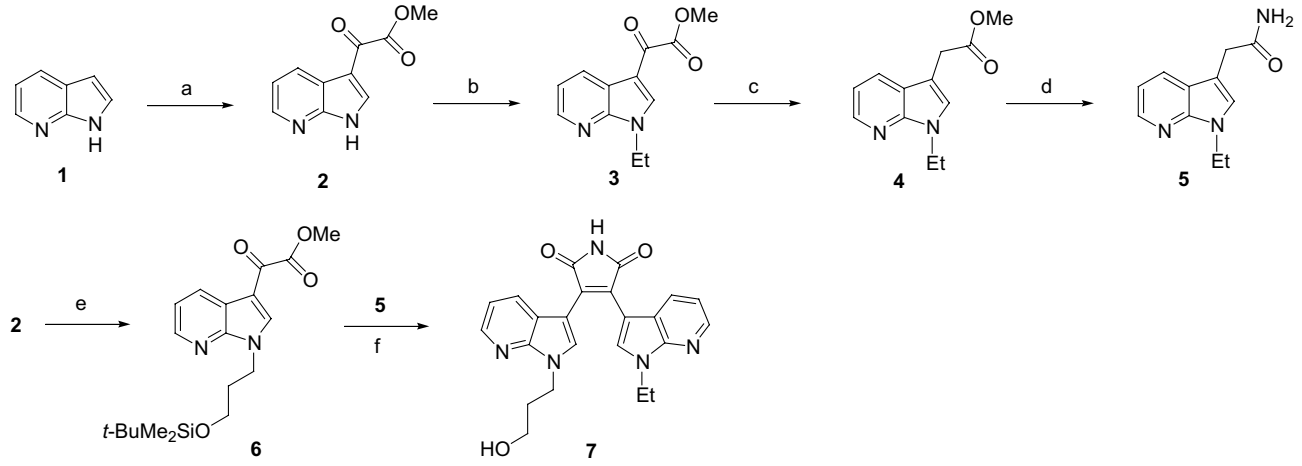
A number of GSK-3 inhibitors with various degrees of selectivity against other protein kinases have been reported in the past several years.[5] During the search for PKC-β inhibitors as potential agents for treatment of diabetic complications and other disorders,[3b,6] we identified a novel series of macrocyclic bisindolylmaleimides with potent (single-digit nanomolar IC_{50}) dual inhibition against both PKC-βII and GSK-3β,[7] indicating high homology (ca. 50%) at their ATP binding sites between these two enzymes. Replacement of both indole rings with 7-azaindole led to a series of macrocyclic bis-7-azaindolylmaleimides as GSK-3β inhibitors.[8] The compounds generally showed excellent selectivity against a broad panel of about 60 protein kinases; however, achieving high selectivity over PKC-βII proved to be a challenge. Of the many macrocyclic bis-7-azaindolylmaleimides prepared,[8] only one compound with a tetra(ethylene glycol)-linked 22-membered ring exhibited good selectivity for GSK-3β over PKC-βII (>200-fold).[8a] We were interested in expanding on this foundation. Herein, we report the synthesis and biological evaluation of a novel series of acyclic 3-(7-azaindolyl)-4-(aryl/heteroaryl)maleimides as potent GSK-3β inhibitors with excellent selectivity over PKC-βII (>300-fold), as well as a broad panel of other kinases.

2. Synthetic chemistry

Methyl 7-azaindole-3-glyoxylate **2** was prepared from commercially available **1** by deprotonation with

Keywords: GSK-3 inhibitors; Kinases; Azaindolylmaleimides.
* Corresponding author. Tel.: +1-215-628-5988; fax: +1-215-628-4985; e-mail: hzhang@prdus.jnj.com

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.03.090



Scheme 1. Reagents and conditions: (a) EtMgBr, THF, −65 °C, then MeO_2CCOCl, −78 °C, 24%; (b) EtI, Cs_2CO_3, DMF, 50 °C; (c) Et_3SiH, TFA, 55 °C; (d) NH_3, MeOH, 90 °C, 34% overall yield from **2**; (e) $Br(CH_2)_3OSiMe_2$–*t*-Bu, Cs_2CO_3, DMF, 50 °C, 44%; (f) *t*-BuOK, THF, 0 °C, then concd HCl, 39%.

ethylmagnesium bromide followed by acylation with methyl oxalyl chloride (Scheme 1). N-Alkylation of **2** with iodoethane in the presence of Cs_2CO_3 in DMF afforded intermediate **3**, which was reduced with Et_3SiH in CF_3CO_2H (TFA) at 55 °C to provide methyl ester **4**. Aminolysis of ester **4** gave amide **5**. Compound **2** was also N-alkylated with 3-(*tert*-butyldimethylsilyloxy)propyl bromide to give α-keto ester **6**. Maleimide condensation of **6** and amide **5** proceeded smoothly in the presence of *t*-BuOK at 0 °C.[9] Treatment with concd HCl removed the silyl group to yield acyclic bis-7-azaindolylmaleimide **7**.

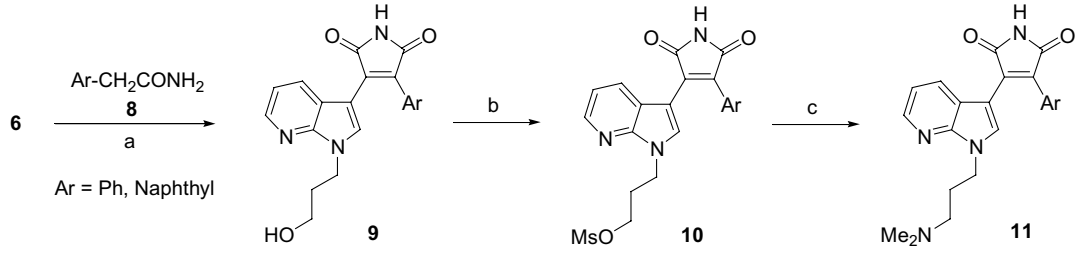
α-Keto ester **6** was also subjected to maleimide condensation with various commercially available arylacetamides **8**, following the same procedure as described above, to afford target compounds **9a**–**f** (Scheme 2).[10] The hydroxy group in **9** was further converted to the corresponding amine. Thus, treatment of **9** with Ms_2O in pyridine/THF at 50 °C selectively produced O-sulfonated product **10** with no detectable N-sulfonated isomer. Substitution of the mesylate group in **10** with excess of dimethylamine in THF afforded amine-containing products **11a**,**b**.

Alkylation of **2** with Boc-protected 3-bromopropylamine using Cs_2CO_3 as a base gave intermediate **12**, which was then condensed with 2-methoxyphenylacetamide **13** in the presence of *t*-BuOK followed by addition of concd HCl to derive maleimide **14** along with some **15** (Scheme 3). Deprotection of Boc group in **14** with TFA afforded **15**. Further functionalization of the primary amino group in **15** was conducted with various reagents. Treatment of **15** with butyl formate in DMF at 80 °C afforded formamide product **16a**. Reaction of **15** with sulfamide in dioxane at 80 °C provided **16b**, and with methanesulfonic anhydride in the presence of pyridine afforded sulfonamide **16c**.

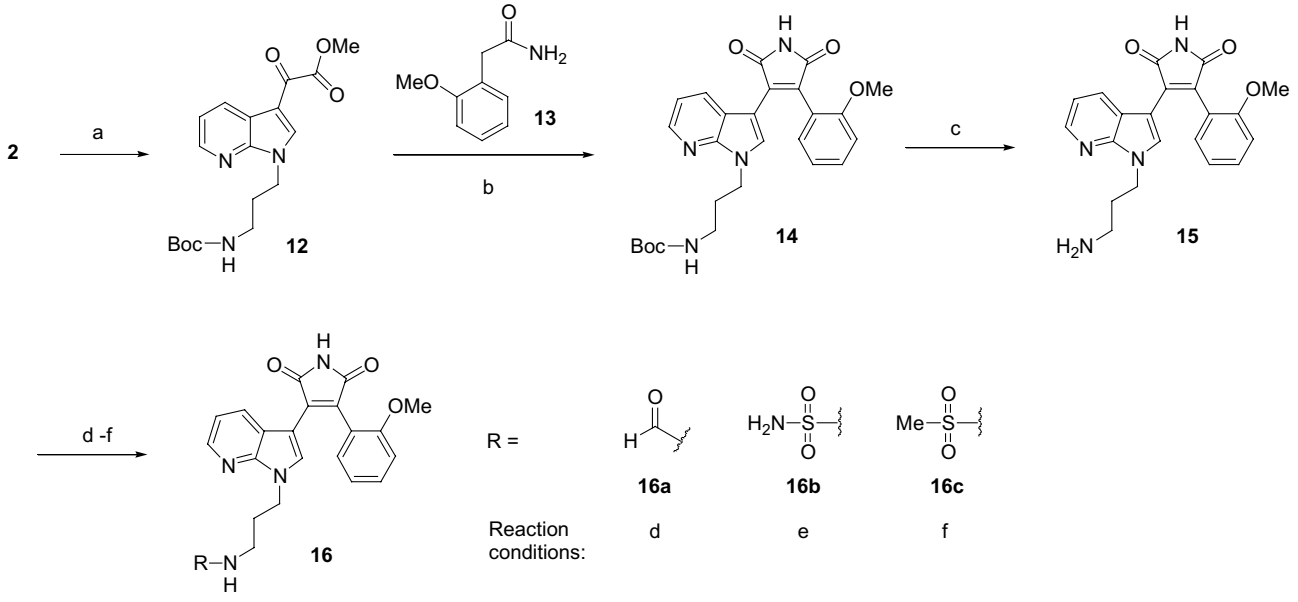
Thiophene- and pyridine-containing analogues **17a**–**c** were synthesized from α-keto ester **6** and the corresponding heteroarylacetamides under the conditions described for **9a**–**e**.

3. Enzymatic activity

Since achieving high selectivity for GSK-3β over PKC-βII proved to be the most challenging among the approximately 60 kinases screened with the macrocyclic maleimide compounds,[7,8] the 3-(7-azaindolyl)-4-(aryl/heteroaryl)maleimides were tested in enzymatic assays involving both GSK-3β and PKC-βII to determine potency and selectivity between the two key kinases

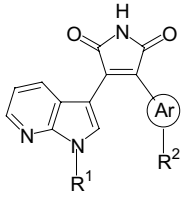


Scheme 2. Reagents and conditions: (a) *t*-BuOK, THF, 0 °C, then concd HCl, 17–62%; (b) Ms_2O, pyridine, THF, 50 °C; (c) Me_2NH, THF, 50–65 °C, 22–31% overall yield from **9**.



Scheme 3. Reagents and conditions: (a) $Br(CH_2)_3NHBoc$, Cs_2CO_3, DMF, 68 °C, 65%; (b) *t*-BuOK, THF, 0 °C, then concd HCl, 43%; (c) TFA, CH_2Cl_2, 84%; (d) HCO_2Bu, DMF, 80 °C, 60%; (e) $H_2NSO_2NH_2$, 1,4-dioxane, 80 °C, 17%; (f) Ms_2O, pyridine, THF, 50 °C, 61%.

Table 1. Enzymatic activity of 3-(7-azaindolyl)-4-(aryl/heteroaryl)maleimides[a]



Compd	R^1	Ar	R^2	GSK-3β[b] IC_{50} (μM)	PKC-βII[c] IC_{50} (μM)	PKC-α[c] IC_{50} (μM)	PKC-γ[c] IC_{50} (μM)
7	$HO(CH_2)_3$	3-(7-Azaindolyl)	N^1-Et	0.065 ± 0.010	1.07 ± 0.18	>10	>10
9a	$HO(CH_2)_3$	1-Naphthyl	H	0.031 ± 0.001	0.27 ± 0.15	3.6	ca. 10
9b	$HO(CH_2)_3$	Ph	2-Cl	0.010 ± 0.001	0.73 ± 0.12	4.4	5.5
9c	$HO(CH_2)_3$	Ph	2-CF_3	0.014 ± 0.003	1.85 ± 0.01	ca. 10	ca. 10
9d	$HO(CH_2)_3$	Ph	2-OMe	0.004 ± 0.001	1.44 ± 0.22	ca. 10	>10
9e	$HO(CH_2)_3$	Ph	2-Cl–4-F	0.006 ± 0.002	2.38 ± 1.17	4.5	>10
9f	$MeO(CH_2)_3$	Ph	2-OH	0.045 ± 0.004	4.36 ± 2.03	>10	>10
11a	$Me_2N(CH_2)_3$	1-Naphthyl	H	0.14 ± 0.003	0.24 ± 0.01	1.4	2.8
11b	$Me_2N(CH_2)_3$	Ph	2-Cl	0.015 ± 0.003	1.16 ± 0.06	4.0	3.6
14	Boc-$NH(CH_2)_3$	Ph	2-OMe	0.007 ± 0.001	2.26 ± 0.24	>10	>10
15	$H_2N(CH_2)_3$	Ph	2-OMe	0.037 ± 0.004	1.10 ± 0.49	ca. 10	>10
16a	$HC(O)NH(CH_2)_3$	Ph	2-OMe	0.008 ± 0.001	2.73 ± 0.40	>10	8.7
16b	$H_2NSO_2NH(CH_2)_3$	Ph	2-OMe	0.020 ± 0.002	0.89 ± 0.34	>10	6.0
16c	$MeSO_2NH(CH_2)_3$	Ph	2-OMe	0.014 ± 0.001	1.88 ± 0.08	4.7	8.6
17a	$HO(CH_2)_3$	2-Thienyl	H	0.031 ± 0.006	>10	>10	>10
17b	$HO(CH_2)_3$	2-Pyridyl	H	0.48 ± 0.13	>10	>10	>10
17c	$HO(CH_2)_3$	2-Pyridyl	3-Cl–5-CF_3	0.026 ± 0.007	>10	>10	>10

[a] IC_{50} values are expressed as mean ± SEM ($n \geqslant 2$; $n = 1$ for values without error limits). '>10' and 'ca. 10' mean <50% and ca. 50% inhibition at 10 μM of compound, respectively.
[b] Recombinant rabbit GSK-3β was used and protein phosphatase inhibitor-2 (PPI-2) as a substrate.[8]
[c] Recombinant human PKC-α, βII, and γ were used and histone as a substrate.[7]

(Table 1). In addition, these compounds were also screened against PKC-α and PKC-γ, two isozymes within the same PKC subfamily as PKC-βII. Bis-7-azaindolylmaleimide **7** inhibited GSK-3β and PKC-βII with IC_{50} values of 0.065 and 1.07 μM, respectively, and was highly selective over PKC-α and PKC-γ ($IC_{50} > 10$ μM). The selectivity for GSK-3β over PKC-βII with **7** decreased when compared to the corresponding macrocyclic bis-7-azaindolylmaleimides.[8] Replacement of a 7-azaindole ring in **7** with a naphthyl

(**9a**) increased the potency for both GSK-3β and PKC-βII ($IC_{50} = 0.031$ and 0.27 μM, respectively). Substitution of the hydroxyl in **9a** with dimethylamino (**11a**) led to a 5-fold loss of potency for GSK-3β, while the potency for PKC-βII was maintained. Interestingly, replacement of the naphthyl in **9a** with a 2-chlorophenyl group (**9b**) further improved activity for GSK-3β ($IC_{50} = 0.010$ μM) as well as selectivity over PKC-βII (73-fold). Modifications on the phenyl ring in **9b** led to single-digit nanomolar inhibitors of GSK-3β, **9d** and **9e**, which had excellent selectivity over PKC-βII, PKC-α, and PKC-γ. For example, **9d** inhibited GSK-3β with an IC_{50} of 0.004 μM and exhibited $\geqslant$360-fold selectivity versus PKCs βII, α, and γ. Transfer of the *O*-methyl group from phenol to hydroxypropyl side chain in **9d** (viz. **9f**) caused an 11-fold drop in potency for GSK-3β; however, good selectivity versus PKCs βII, α, and γ was maintained. Substitution of the hydroxyl in **9d** with a primary amine (**15**) decreased the potency for GSK-3β by 9-fold. Introduction of various functionalities to the amino group in **15**, such as carbamate (**14**), amide (**16a**), sulfamide (**16b**), and sulfonamide (**16c**), was well tolerated, giving potent GSK-3β inhibitors ($IC_{50} \leqslant 0.020$ μM) with various degrees of activity for PKC-βII ($IC_{50} = 0.89$–2.73 μM). The selectivity of this 7-azaindole maleimide series for GSK-3β over PKC-βII was further enhanced by replacing the phenyl with a thienyl (**17a**) or pyridyl group (**17c**), while maintaining potent GSK-3β inhibition. In this vein, pyridine-containing analogue **17c** potently inhibited GSK-3β with an IC_{50} of 0.026 μM and showed excellent (>385-fold) selectivity over PKC-βII, as well as PKC-α and PKC-γ (IC_{50}'s >10 μM).

4. Kinase selectivity

With potent inhibition of GSK-3β and excellent selectivity over PKC-βII achieved, we selected representative compounds for further screening against a broad panel of 70 protein kinases (Upstate Biotech Inc.) to assess kinase selectivity. Compound **9d**, one of the most potent GSK-3 inhibitors, showed potent inhibition (<10% of control at 10 μM of compound in the presence of 10 μM of ATP) against PKC-βII, CDK1-6, and RSK3. In addition, some activity (<50% of control) was observed with **9d** against other kinases, including AMPK, BLK, CAMK, CHK1, CK1, JNK3, LYN, MSK1, PDK1, PKC-α, PKC-ε, PKC-θ, PRK2, RSK1, and RSK2 (data not shown). Similarly, **15** and **16b** showed poor selectivity and inhibited most of the kinases listed above (data not shown). Improvement of selectivity was observed with **9f** and **14**, where the number of kinases inhibited was greatly reduced (Table 2). It appears to be a generalized effect with this acyclic 7-azaindole-based maleimide series that the CDK family is potently inhibited in addition to GSK-3β and PKC-βII.[11] With the macrocyclic bis-7-azaindolylmaleimides[8] or bisindolylmaleimides,[7] the GSK-3β selectivity relative to the CDKs was more easily achieved. Pyridyl compound **17c** exhibited a significant improvement of selectivity over the CDKs (25–62% of control). This compound was also highly selective over the remaining kinases in the panel, with very weak or no activity.[12] To further determine the actual degree of selectivity for **17c**, we obtained IC_{50} values (Table 3) for CDK1/cyclin B (5.8 μM) and CDK2/cyclin A (2.8 μM), as representatives for the CDK family, as well as MSK1 (>10 μM), which somehow failed during single-dose screening, reflecting GSK-3β selectivities of 220, 105, and >385-fold relative to these kinases, respectively. We determined IC_{50} values for **9f** and **14** against CDK1 and CDK2, representing the CDK family, and a few other kinases potently inhibited by **9f** and **14** (Table 3). The very potent GSK-3β inhibitor **14** ($IC_{50} = 0.007$ μM) also potently inhibited CDK1 and CDK2, with IC_{50} values of 0.17 and 0.068 μM, respectively.

5. Cellular activity

Selected compounds **9f**, **14**, and **17c** were tested for their ability to increase glycogen synthase (GS) activity in HEK293 cells, a direct functional assay to measure the cellular activity of GSK-3β inhibitors. The results in Table 4 indicate effective blockade of GSK-3β and increased GS activity within cells by these compounds, with EC_{50} values of 0.04–0.62 μM. LiCl, a known inhibitor of GSK-3β,[13] was basically inactive in this cell-based assay, while another GSK-3β inhibitor reference compound, SB-216763,[5k] had an EC_{50} of 0.20 μM.

6. Molecular docking

Given the X-ray structure of GSK-3β (pdb code: 1q3d),[14] a molecular docking study can be performed to probe the possible binding mode of a GSK-3β inhibitor. Figure 1 illustrates **17c** docked into the ATP binding site of GSK-3β.[15] The key interactions for this complex include two hydrogen bonds between the maleimide portion of **17c** to Asp-133 and Val-135 backbone carbonyl and amide hydrogen, respectively. The R1 hydroxyl group forms another hydrogen bond with Gln-185. The azaindole nitrogen is only about 3.6 Å from the carboxyl group of Asp-200 and may form an additional hydrogen bond depending on the protonation state of Asp-200. This binding mode is very similar to those revealed by recent X-ray structures of PDK1/bisindolylmaleimide complexes.[16] Thr-138 and Arg-141 are about 5 Å from pyridyl group, and the electrostatic interaction between pyridyl and the positively charged guanidine is energetically favorable. In contrast, the two corresponding residues on these positions in PKC-βII are Asp-97 and Tyr-100. The electrostatic interaction between the negatively charged side chains and the pyridyl group is not energetically propitious. This difference may contribute to the excellent GSK-3β over PKC-βII selectivity for **17c**.

Table 2. Activities at protein kinases assays[a]

Protein kinase	Activity (% of control)			Protein kinase	Activity (% of control)		
	9f	**14**	**17c**		**9f**	**14**	**17c**
GSK3β (h)	1	0	3	MKK4 (m)	86	101	87
Abl (m)	86	91	93	MKK6 (h)	83	95	86
AMPK (r)	68	64	74	MKK7β (h)	71	101	68
Blk (m)	75	63	67	MSK1 (h)	57	61	Fail[b]
CAMKII (r)	63	60	76	p70S6K (h)	87	82	88
CAMKIV (h)	82	91	82	PAK2 (h)	94	93	78
CDK1/cyclinB (h)	9	3	34	PDGFRα (h)	99	108	86
CDK2/cyclinA (h)	9	2	25	PDGFRβ (h)	96	93	77
CDK2/cyclinE (h)	11	3	30	PDK1 (h)	78	20	79
CDK3/cyclinE (h)	26	3	62	PKA (b)	99	112	86
CDK5/p35 (h)	9	2	25	PKA (h)	92	95	87
CDK6/cyclinD3 (h)	50	24	59	PKBα (h)	93	103	64
CDK7/cyclinH (h)	47	60	59	PKBβ (h)	82	99	69
CHK1 (h)	78	95	73	PKCα (h)	46	38	70
CHK2 (h)	75	49	92	PKCβII (h)	32	15	70
CK1 (y)	58	85	66	PKCγ (h)	59	76	72
CK2 (h)	93	103	56	PKCε (h)	49	54	67
CSK (h)	89	95	74	PKCθ (h)	46	71	66
Fes (h)	79	87	81	PRAK (h)	82	57	59
FGFR3 (h)	79	83	64	PRK2 (h)	76	68	71
Fyn (h)	94	63	89	c-RAF (h)	74	92	74
IGF-1R (h)	80	86	78	ROCK-II (h)	100	78	90
IKKα (h)	83	89	76	ROCK-II (r)	94	91	97
IKKβ (h)	81	91	83	Rsk1 (r)	48	38	66
IR (h)	88	94	95	Rsk2 (h)	54	31	77
JNK1α1 (h)	75	81	80	Rsk3 (h)	33	24	60
JNK2α2 (h)	63	84	93	SAPK2a (h)	84	109	81
JNK3 (r)	52	68	76	SAPK2b (h)	102	106	94
Lck (h)	84	67	82	SAPK3 (h)	120	122	86
Lyn (m)	81	20	85	SAPK4 (h)	97	100	86
MAPK1 (h)	78	81	66	SGK (h)	98	105	87
MAPK2 (h)	92	92	91	cSRC (h)	99	74	93
MAPK2 (m)	100	89	93	Syk (h)	86	88	76
MAPKAP-K2 (h)	97	85	85	Yes (h)	89	42	93
MEK1 (h)	94	100	74	ZAP-70 (h)	100	112	91

[a] Performed at Upstate Biotech Inc.
[b] Compound **17c** was retested against MSK1 and an IC_{50} value of >10 μM was determined.

Table 3. IC_{50} values for selected kinases[a]

Compd	Kinase	IC_{50} (μM)
9f	CDK1/cyclinB (h)	0.70
	CDK2/cyclinA (h)	0.43
	Rsk3 (h)	2.0
14	CDK1/cyclinB (h)	0.17
	CDK2/cyclinA (h)	0.068
	Lyn (h)	1.8
	PDK1 (h)	0.57
	Rsk3 (h)	0.64
17c	CDK1/cyclinB (h)	5.8
	CDK2/cyclinA (h)	2.8
	MSK1 (h)	>10

[a] Values are an average of duplicate determinations. Assays were performed at Upstate Biotech Inc.

Table 4. Glycogen synthase activity in HEK293 cells[a]

Compd	EC_{50} (μM)
9f	0.39
14	0.04
17c	0.62
LiCl	>3000
SB-216763[b]	0.20

[a] Values are an average of triplicate determinations. HEK293 cells were treated with compounds and GS activity was determined in cell extracts by measuring ^{14}C-UDP glucose incorporation into glycogen.
[b] GSK-3 inhibitor reference compound.[5k]

7. Conclusion

We identified a novel series of 3-(7-aza-indolyl)-4-(aryl/heteroaryl)maleimides as potent GSK-3β inhibitors with excellent selectivity (>300-fold) over PKC-βII, the most difficult kinase among a broad panel to achieve high selectivity over with the previously reported macrocyclic bisindolylmaleimides,[7] or bis-7-aza-indolylmaleimides.[8] Screening against a panel of 70 kinases revealed that this acyclic series potently inhibits the CDK family and has some activity against a number of other kinases. Introduction of a substituted pyridyl group led to potent GSK-3β inhibitor **17c**, with a significant improvement in selectivity over the CDKs and excellent selectivity over the remaining kinases in the panel. Representative compounds, including **17c**, were effective intracellularly, increasing glycogen synthase activity via the blockade of GSK-3β.

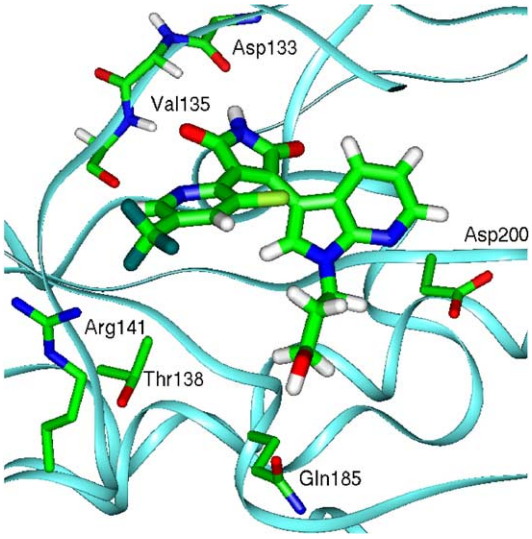


Figure 1. Docking of **17c** to GSK-3β crystal structure.

Acknowledgements

We thank Earl Danser, and Dr. Indrasena Reddy for excellent technical assistance; and Upstate Biotech Inc. for kinase screening data.

References and notes

1. (a) Embi, N.; Rylatt, D. B.; Cohen, P. *Eur. J. Biochem.* **1980**, *107*, 519; (b) Woodgett, J. R. *EMBO J.* **1990**, *9*, 2431.
2. (a) Grimes, C. A.; Jope, R. S. *Prog. Neurobiol.* **2001**, *65*, 391; (b) Kim, H.-S.; Skurk, C.; Thomas, S. R.; Bialik, A.; Suhara, T.; Kureishi, Y.; Birnbaum, M.; Keaney, J. F., Jr.; Walsh, K. *J. Biol. Chem.* **2002**, *277*, 41888; (c) Manoukian, A. S.; Woodgett, J. R. *Adv. Cancer Res.* **2002**, *84*, 203.
3. (a) Kaidanovich, O.; Eldar-Finkelman, H. *Expert Opin. Ther. Targets* **2002**, *6*, 555; (b) Wagman, A. S.; Nuss, J. M. *Curr. Pharm. Des.* **2001**, *7*, 417; (c) Bullock, W. H.; Magnuson, S. R.; Choi, S.; Gunn, D. E.; Rudolph, J. *Curr. Top. Med. Chem.* **2002**, *2*, 915.
4. (a) Eldar-Finkelman, H. *Trends Mol. Med.* **2002**, *8*, 126; (b) Dorronsoro, I.; Castro, A.; Martinez, A. *Expert Opin. Ther. Pat.* **2002**, *2*, 1527.
5. (a) Martinez, A.; Castro, A.; Dorronsoro, I.; Alonso, M. *Med. Res. Rev.* **2002**, *22*, 373; (b) Kunick, C.; Lauenroth, K.; Leost, M.; Meijer, L.; Lemcke, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 413; (c) Conde, S.; Perez, D. I.; Martinez, A.; Perez, C.; Moreno, F. J. *J. Med. Chem.* **2003**, *46*, 4631; (d) Witherington, J.; Bordas, V.; Gaiba, A.; Naylor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3059; (e) Witherington, J.; Bordas, V.; Haigh, D.; Hickey, D. M. B.; Ife, R. J.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1581; (f) Olesen, P. H.; Sorensen, A. R.; Urso, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. *J. Med. Chem.* **2003**, *46*, 3333; (g) 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; (h) 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; (i) Martinez, A.; Alonso, M.; Castro, A.; Perez, C.; Moreno, F. J. *J. Med. Chem.* **2002**, *45*, 1292; (j) 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; (k) 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; (l) Polychronopoulos, P.; Magiatis, P.; Skaltsounis, A.-L.; Myriantopoulos, V.; Mikros, E.; Tarricone, A.; Musacchio, A.; Roe, S. M.; Pearl, L.; Leost, M.; Greengard, P.; Meijer, L. *J. Med. Chem.* **2004**, *47*, 935.
6. (a) Way, K. J.; Katai, N.; King, G. L. *Diabetes Med.* **2001**, *18*, 945; (b) Goekjian, P. G.; Jirousek, M. R. *Expert Opin. Invest. Drugs* **2001**, *10*, 2117; (c) Sorbera, L. A.; Silvestre, J.; Rabasseda, X.; Castaner, J. *Drugs Future* **2000**, *25*, 1017.
7. 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.
8. (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.
9. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *Tetrahedron Lett.* **1999**, *40*, 1109.
10. We prepared **9f** by maleimide condensation of 2-(2-hydroxyphenyl)acetamide and methyl *N*-(3-methoxypropyl)-7-azaindole-3-glyoxylate.
11. Other classes of compounds inhibiting both GSK-3 and CDKs have been reported, for example, see Refs. [5d,g,l].
12. A full paper on other heteroaryl-containing analogues will be published separately: Kuo, G.-H., et al.
13. (a) Nyfeler, F.; Walter, P. *FEBS Lett.* **1979**, *108*, 197; (b) Stambolic, V.; Ruel, L.; Woodgett, J. R. *Curr. Biol.* **1996**, *6*, 1664.
14. Bertrand, J. A.; Thieffine, S.; Vulpetti, A.; Cristiani, C.; Valsasina, B.; Knapp, S.; Kalisz, H. M.; Flocco, M. *J. Mol. Biol.* **2003**, *333*, 393.
15. Software used: LigandFit: Cerius2, Version 4.9; Accelrys Inc., San Diego, CA, 2003.
16. Komander, D.; Kular, G. S.; Schuttelkopf, A. W.; Deak, M.; Prakash, K. R.; Bain, J.; Elliot, M.; Garrido-Franco, M.; Kozikowski, A. P.; Alessi, D. R.; Van Aalten, D. M. F. *Structure* **2004**, *12*, 215.