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Novel bis(indolyl)maleimide pyridinophanes that are potent, selective inhibitors of glycogen synthase kinase-3

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Abstract—Novel bis(indolyl)maleimide pyridinophanes **3**, **9a**, **9b**, **10a**, **10b**, and **11** were prepared by cobalt-mediated [2+2+2] cycloaddition of an appropriate α,ω-diyne with an *N*,*N*-dialkylcyanamide. These macrocyclic heterophanes were found to be potent, selective inhibitors of glycogen synthase kinase-3β. An X-ray structure of a co-crystal of GSK-3β and **3** (IC_{50} = 3 nM) depicts the hydrogen bonding and hydrophobic interactions in the ATP-binding pocket of this serine/threonine protein kinase.

Biologically active macrocyclic compounds have attracted much interest from synthetic and medicinal chemists, as exemplified by macrolide antibiotics,[1] inhibitors of proteases,[2] and Taxol analogues.[3] Some notable inhibitors of protein kinases (PKs) also possess a macrocyclic motif, such as bis(indolyl)maleimide **1** (ruboxistaurin; LY-333351), which is related to the natural product staurosporin (**2**).[4] In contrast to the promiscuous kinase inhibitory activity of staurosporin, **1** is a relatively selective inhibitor of the PKC-β isozyme, with a reported IC_{50} of 5 nM.[5] The much improved kinase selectivity for **1** is probably attributable to its nonplanar bis(indolyl)maleimide pharmacophore and conformationally constrained macrocyclic structure.[6] Our studies of novel inhibitors of protein kinases,[7] such as macrocycles related to **1**,[7a,b] led us to explore the construction of such compounds by a different synthetic route. Thus, we decided to apply our cobalt(I)-mediated [2+2+2] macrocyclization method[8] to the synthesis of novel bis(indolyl)maleimide pyridinophanes, such as **3**, which retain the critical pharmacophore for key interactions within the kinase ATP binding pocket. It is noteworthy that we are forming the macrocycle and the pyridine ring simultaneously, and that all three heteroaryl rings are in a 'phane' arrangement (2 *meta*-indoles and 1 *para*- or *meta*-pyridine). We found that these novel-format, pyridine-containing, macrocyclic bis(indolyl)maleimides ('multiheterophanes') are potent, highly selective inhibitors of glycogen synthase kinase-3β (GSK-3β), a serine/threonine protein kinase that plays a critical role in glucose homeostasis, CNS function (via the proteins tau and β-catenin), and cancer (via angiogenesis, apoptosis, and tumorigenesis).[9,10]

We obtained the target compounds in the following manner. Indole-3-acetamide was treated with NaH in DMF followed by 5-chloro-1-pentyne or 6-chloro-1-hexyne to afford **4a** or **4b** (Scheme 1). Indole-3-glyoxylate **5** was converted to N-alkylated derivatives **6a** or **6b** by treatment with 5-chloro-1-pentyne or 6-chloro-1-hexyne in the presence of cesium carbonate. The maleimide condensation of **4a** and **6a** proceeded smoothly in the presence of KO-*t*-Bu at 0–23 °C[11] to give α,ω-diyne substrate **7a** in 63% isolated yield. We subjected **7a** to cobalt-mediated [2+2+2] cycloaddition with cyanamide **8** using our improved reaction protocol.[8c,d] Thus, **7a** in 1,4-dioxane (0.005 M) was reacted with *N*,*N*-dimethylcyanamide (**8a**) or *N*-cyanopyrrolidine (**8b**) (5 mol equiv) and $CpCo(CO)_2$ (0.5 mol equiv; Cp = cyclopentadienide) under argon at 105–110 °C for 24 h. The volatiles were removed in vacuo and the residue was separated by flash-column chromatography (silica gel) to afford two pyridine-containing multiheterocyclophanes, 17-membered *meta*-pyridinophanes (**9a** or **9b**) and 18-membered *para*-pyridinophanes (**10a** or **10b**), in 20–25% isolated yield. These structures

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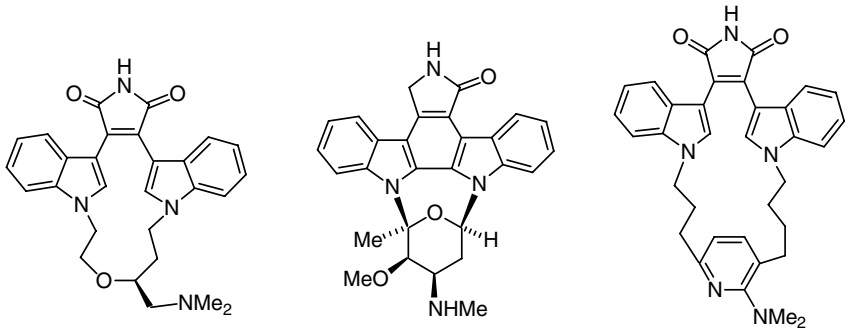
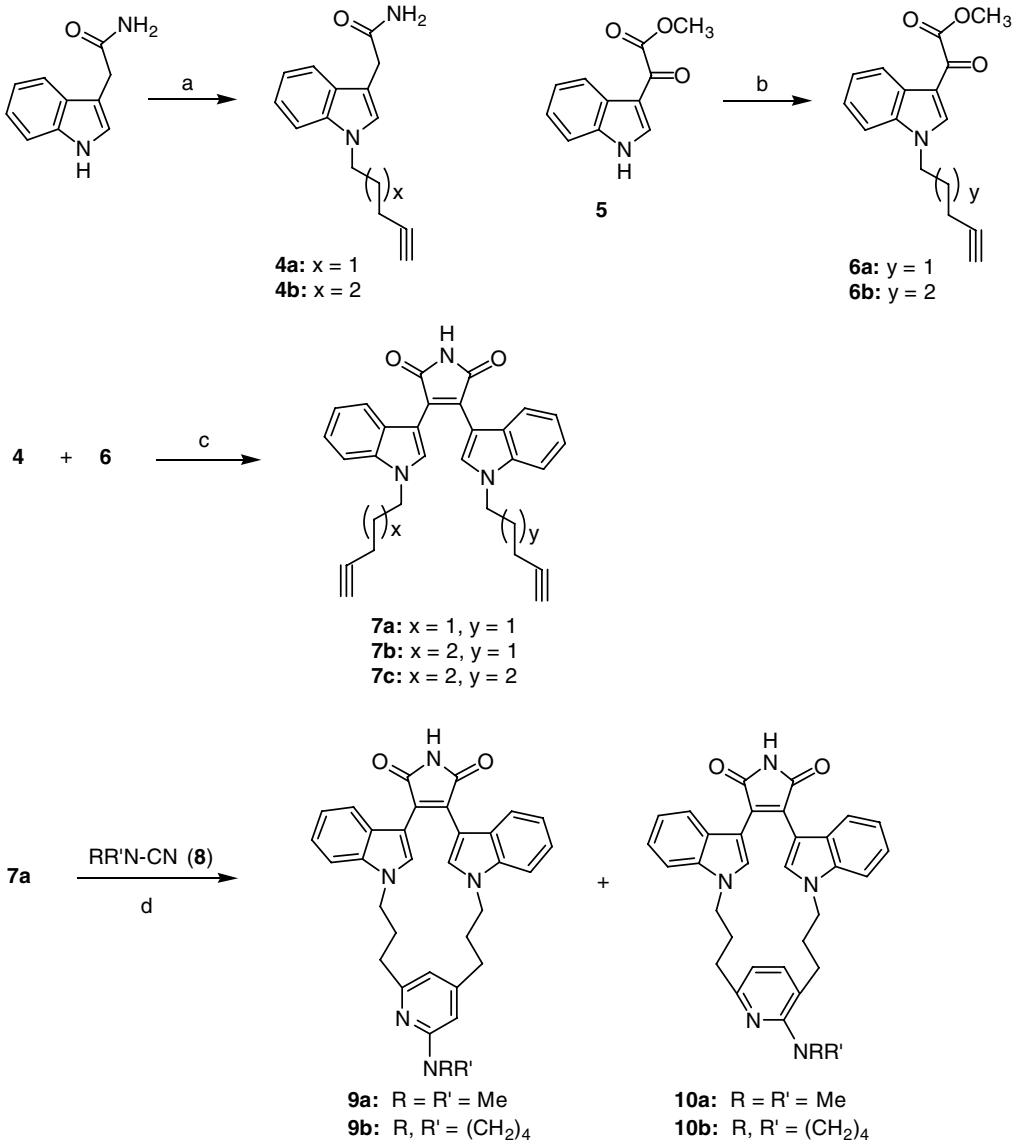


1 **2** **3**

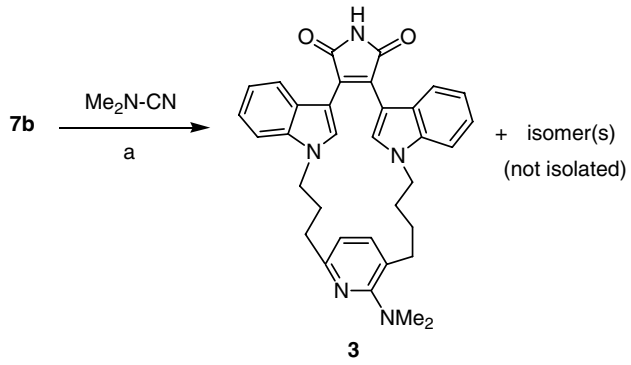
were assigned on the basis of one- and two-dimensional ^{1}H and ^{13}C NMR spectral data.[8]

Unsymmetrical α,ω-diyne **7b** was prepared in 40% yield via maleimide condensation of **4b** and **6a**. The cobalt-mediated [2+2+2] cycloaddition of **7b** and *N*,*N*-dimethylcyanamide under the above conditions afforded 19-membered *para*-pyridinophane **3** in 10% isolated yield (Scheme 2). Other minor isomer(s) were also observed in the reaction mixture, but the isolation of them as pure materials proved to be difficult.

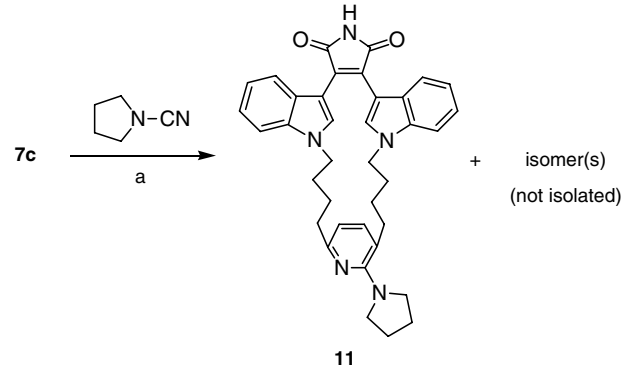
A longer chain, symmetric α,ω-diyne **7c** was prepared in 42% isolated yield from maleimide condensation of **4b**



Scheme 1. Reagents and conditions: (a) 5-chloro-1-pentyne, NaH, DMF, 0–55 °C, 90% (**4a**); (b) 5-chloro-1-pentyne, Cs_2CO_3, DMF, 59% (**6a**); (c) KO-*t*-Bu, THF, 0–23 °C, 63%; (d) $CpCo(CO)_2$, 1,4-dioxane, 105–110 °C, 24 h. Yields: **9a** and **10a**, 9% and 12%; **9b** and **10b**, 10% and 15%.



Scheme 2. Reagents and conditions: (a) $CpCo(CO)_2$, 1,4-dioxane, 105–110 °C, 24 h, 10%.



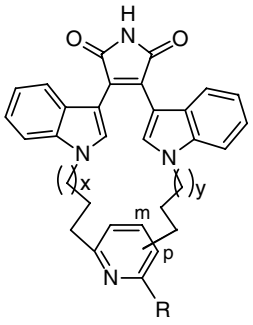
Scheme 3. Reagents and conditions: (a) $CpCo(CO)_2$, 1,4-dioxane, 105–110 °C, 24 h.

and **6b**. Treatment of **7c** with *N*-cyanopyrrolidine under cobalt-mediated [2+2+2] cycloaddition conditions provided 20-membered *para*-pyridinophane **11** (Scheme 3). Isolation of the other minor isomer(s) from the reaction mixture proved to be difficult.

The cobalt-mediated cycloaddition, as used here, generated a macrocycle (17–20 members) and a heteroaryl ring (i.e., 2-aminopyridine) simultaneously, providing considerable molecular complexity in a single step. However, the isolated yields (10–25%) in the above examples ought to be better. Indeed, the same protocol was previously shown to provide products from the cycloaddition of cyanamide with α,ω-diynes with good-to-excellent yields,[8c,d] suggesting that the lower yields may be due to the complex 'multiphane' bis(indolyl)maleimide template. To address this issue, we explored the effect of Lewis base, donor additives on the multiphane-forming reaction and discovered that the addition of PPh_3 can deliver a marked improvement. For example, a solution of **7a**, *N*,*N*-dimethylcyanamide (5 mol equiv), PPh_3 (0.5 mol equiv), and $CpCo(CO)_2$ (0.5 mol equiv) in 1,4-dioxane (0.005 M, relative to **7a**) was stirred at 110 °C for 36 h. After flash-column chromatography, we obtained two multiphane products, **9a** and **10a**, in 69% *isolated yield* with a ratio of 3:4. We are in the process of studying this enhanced cobalt-mediated [2+2+2] cycloaddition process in more detail.

The biological activity of the target compounds was investigated with an emphasis on kinase inhibition in vitro. Ruboxistaurin (**1**; 14-membered macrocycle) was reported to be a selective inhibitor of PKC-β (IC_{50} = 5 nM, PKC-βII).[5] We reported that macrocyclic bis(indolyl)maleimides with 16-membered to 22-membered rings, and linkers bearing multiple heteroatoms, also exhibit potent inhibition of PKC-βII (IC_{50} = 6–200 nM). However, unlike ruboxistaurin, our larger

Table 1. Enzymatic activity of pyridine-containing macrocycles[a]



Compound	R	*x*	*y*	*meta* or *para*	GSK-3β IC_{50} (μM)	PKC-βII IC_{50} (μM)
9a	Me_2N	1	1	*meta*	0.007	2.4
9b	$(CH_2)_4N$	1	1	*meta*	0.011	1.2
10a	Me_2N	1	1	*para*	0.037	ND
10b	$(CH_2)_4N$	1	1	*para*	0.030	2.2
3	Me_2N	1	2	*para*	0.003	1.4
11	$(CH_2)_4N$	2	2	*para*	0.024	ND
SB-216763[b]					0.007	ND

[a] Compounds were characterized by mass spectral and NMR (1D and 2D ^1H and ^{13}C)[8] data. IC_{50} values are an average of multiple determinations ($n \geqslant 2$). Assays were performed at Upstate Biotech (www.upstate.com) using a filtration assay. Recombinant human GSK-3β was used with a peptide derived from glycogen synthase as the substrate; recombinant human PKC-βII was used with histone H1 as the substrate. ND denotes not determined.

[b] GSK-3 inhibitor reference compound (Coghlan, M. P., et al. *Chem. Biol.* **2000**, *7*, 793).

macrocycles also potently inhibit GSK-3β, with low-nanomolar IC_{50} values.[7a,b] The pyridinophanes synthesized herein were first tested in enzymatic assays involving PKC-βII or GSK-3β to determine potency and selectivity for these kinases (Table 1). Although the compounds showed excellent potency against GSK-3β (IC_{50} values in the low *nanomolar* range), their ability to inhibit PKC-βII was greatly attenuated (IC_{50} values in the low *micromolar* range). For example, 19-membered macrocycle **3** inhibited GSK-3β and PKC-βII with IC_{50} values of 3 and 1400 nM, respectively (460-fold selectivity for GSK-3β over PKC-βII). Such potency and selectivity between PKC-βII and GSK-3β has not been observed for any previously reported bis(indolyl)maleimide-containing macrocycles (with ring sizes ranging from 14 to 22), indicating that the pyridine-containing linker in **3** may be playing an important role in the surprising shift in selectivity.

To further assess the selectivity over other kinases, macrocycles **9a**, **9b**, **10b**, and **3** were screened against an Upstate panel of 100 kinases (KinaseProfiler™ service) for their ability to inhibit phosphorylation of the appropriate peptide/protein substrates in the presence of 1 μM compound and 10 μM ATP (Table 2). Very significantly, GSK-3 (α and β isozymes) clearly stood out among all kinases in the panel as being effectively targeted by all four compounds, with 1–9% of control (i.e., 91–99% inhibition). Furthermore, these compounds were highly selective over the other kinases examined except for MSK1 (36–104% of control), PKC-θ (21–33% of control), and Rsk1–3 (5–85% of control). IC_{50} values for those kinases with <50% of control data were determined. Thus, **3** inhibited MSK1, PKC-θ, Rsk1, Rsk2, Rsk3, and TrkB with IC_{50} values of 510, 98, 1900, 850, 48, and >3000 nM, respectively.

An X-ray structure of a co-crystal of **3** and GSK-3β was obtained by Proteros Biostructures.[12] The diffraction data show the inhibitor ligand (**3**) within the ATP binding pocket (Fig. 1). The maleimide portion of **3** makes key hydrogen bonding contacts with residues Asp-133 (amide C═O) and Val-135 (Nα), as expected.[13] The other maleimide C═O hydrogen bonds with a water molecule that bridges to Asp-200 (Nα). Ligand **3** makes hydrophobic contacts with the side chains of Ile-62, Phe-67, Thr-138, Leu-188, and Cys-199. The 2-dimethylaminopyridine unit is largely solvent-exposed, and not involved in important interactions. Perhaps, the *para*-pyridinophane subunit may determine the conformation

Table 2. Activity in assays involving diverse protein kinases (% of control)[a]

Protein kinase	9a	9b	10b	3	Protein kinase	9a	9b	10b	3	Protein kinase	9a	9b	10b	3
Abl(h)	98	107	108	105	Fms(h)	101	99	106	94	PKBβ(h)	118	104	102	86
Abl(m)	108	104	110	98	Fyn(h)	106	106	103	103	PKBγ(h)	106	103	105	93
Abl(T315I)(h)	79	77	103	100	**GSK3α(h)**	**3**	**4**	**9**	**4**	PKCα(h)	74	82	83	68
ALK(h)	55	58	74	103	**GSK3β(h)**	**1**	**3**	**7**	**1**	PKCβII(h)	68	74	77	64
AMPK(r)	101	105	99	101	IGF-1R(h)	37	42	106	84	PKCγ(h)	107	99	102	91
Arg(m)	129	121	130	113	IKKα(h)	133	132	121	92	PKCδ(h)	100	104	91	73
Aurora-A(h)	111	111	106	109	IKKβ(h)	124	125	130	128	PKCε(h)	83	93	97	72
Axl(h)	104	106	100	97	IR(h)	102	110	87	91	PKCη(h)	109	102	97	85
Blk(m)	70	74	91	109	JNK1α1(h)	105	108	104	102	PKCι(h)	117	121	90	104
Bmx(h)	159	173	176	101	JNK2α2(h)	106	114	110	96	PKCθ(h)	27	29	33	21
BTK(h)	106	106	104	105	JNK3(h)	107	103	102	96	PKCμ(h)	118	118	113	110
c-RAF(h)	87	92	85	103	Lck(h)	100	99	90	96	PKCζ(h)	105	99	116	98
CaMKII(r)	107	109	98	92	Lyn(h)	76	87	78	107	PKD2(h)	97	103	115	100
CaMKIV(h)	113	112	99	92	Lyn(m)	102	99	104	90	PRAK(h)	96	101	102	88
CDK1/cyclinB(h)	98	80	98	78	MAPK1(h)	86	99	110	97	PRK2(h)	113	110	126	106
CDK2/cyclinA(h)	80	88	88	120	MAPK2(h)	104	92	88	102	ROCK-II(h)	103	107	104	110
CDK2/cyclinE(h)	84	88	88	54	MAPK2(m)	95	103	99	95	ROCK-II(r)	92	83	91	101
CDK3/cyclinE(h)	89	86	106	59	MAPKAP-K2(h)	101	108	95	98	Ros(h)	108	117	105	79
CDK5/p35(h)	105	99	104	99	MEK1(h)	93	91	98	76	Rsk1(h)	15	15	85	39
CDK6/cyclinD3(h)	74	82	92	86	Met(h)	132	129	132	121	Rsk1(r)	7	5	67	37
CDK7/cyclinH(h)	108	107	111	89	MKK4(m)	119	119	113	130	Rsk2(h)	10	12	63	32
CHK1(h)	101	110	106	105	MKK6(h)	86	91	85	102	Rsk3(h)	5	5	25	33
CHK2(h)	94	84	91	91	MKK7β(h)	78	97	85	88	SAPK2a(h)	92	92	93	108
CK1δ(h)	111	112	109	107	MSK1(h)	58	38	104	36	SAPK2b(h)	119	114	99	104
CK1(y)	98	99	98	91	MST2(h)	84	100	86	103	SAPK3(h)	115	103	114	78
CK2(h)	111	108	113	107	NEK2(h)	102	105	99	104	SAPK4(h)	104	102	102	101
CSK(h)	133	125	129	95	p70S6K(h)	91	95	84	98	SGK(h)	105	109	93	93
cSRC(h)	105	97	113	81	PAK2(h)	103	100	102	93	Syk(h)	101	105	109	86
EGFR(h)	96	108	104	94	PAR-1Bα(h)	100	96	101	94	Tie2(h)	109	96	107	110
EphB2(h)	114	110	114	125	PDGFRα(h)	119	126	113	107	TrkB(h)	98	105	106	Fail
EphB4(h)	103	109	100	89	PDGFRβ(h)	101	103	105	147	Yes(h)	79	58	43	96
Fes(h)	133	139	130	107	PDK1(h)	104	107	100	115	ZAP-70(h)	103	115	121	113
FGFR3(h)	84	114	117	75	PKA(h)	95	104	102	90					
Flt3(h)	71	77	85	86	PKBα(h)	114	112	106	94					

[a] These kinase inhibition assays were performed at Upstate Biotech (1 μM test compound; 10 μM ATP). A description of the kinases, along with their abbreviations, and details on the assay conditions used can be found at the website http://www.upstate.com (h, human; m, mouse; r, rat; y, yeast).

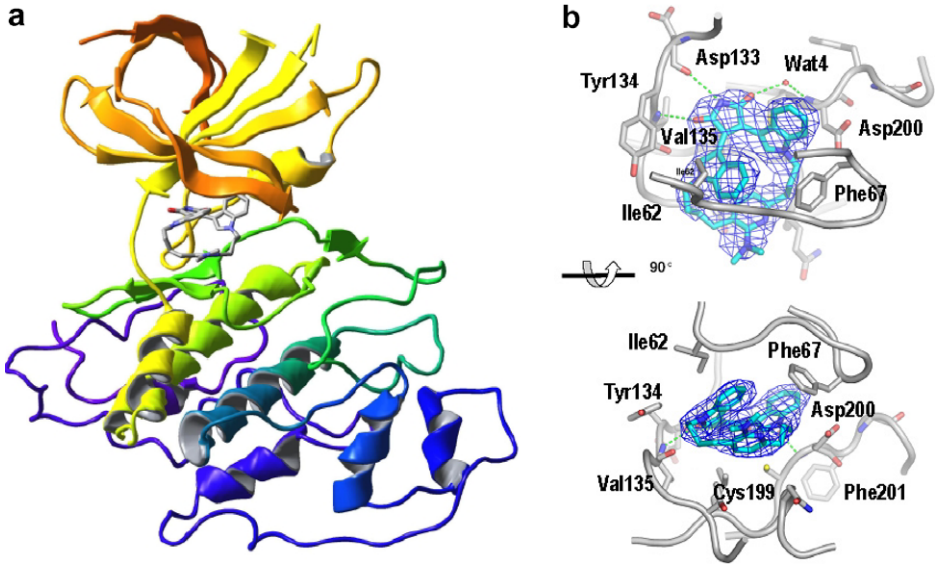


Figure 1. (a) Ribbon-and-tube diagram of the structure of **3**·GSK-3β, as determined by X-ray crystallography (2.8 Å), showing the ligand in the ATP binding pocket. (b) Two views of the complexed ligand, **3**, rotated 90° relative to each other, depicting the electron density of the ligand.

of the macrocycle, thereby conveying the high inhibitory potency for GSK-3β and influencing the selectivity over PKC-βII and the other kinases.

In conclusion, by using our cobalt-mediated [2+2+2] cycloaddition methodology,[8] we assembled novel bis(indolyl)maleimide pyridinophanes (**3**, **9a**, **9b**, **10a**, **10b**, **11**), which were found to be potent, selective inhibitors of GSK-3β. This macrocyclic multiheterophane format is quite unique for bis(indolyl)maleimide-based kinase inhibitors, and would not be easy to access via standard macrocyclization processes that rely on alkylation, esterification, or amidation reactions.

The X-ray structure of **3**·GSK-3β does not immediately reveal the source of the high kinase selectively for **3**, as the 2-dimethylaminopyridine unit in the macrocyclic linker is not involved in important contacts with the protein, and is largely solvent-exposed. However, we suggest that the conformation of the macrocyclic linker may be governed to some degree by the pyridinophane unit, which may impart the high inhibitory potency for GSK-3β and the selectivity over many other kinases.

Acknowledgments

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