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The development of potent and selective bisarylmaleimide GSK3 inhibitors

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Abstract—Many 3-aryl-4-(1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-7-yl)maleimides exhibit potent GSK3 inhibitory activity (<100 nM IC_{50}), although few show significant selectivity (>100 ×) versus CDK2, CDK4, or PKCβII. However, combining 3-(imidazo[1,2-*a*]pyridin-3-yl), 3-(pyrazolo[1,5-*a*]pyridin-3-yl) or aza-analogs with a 4-(2-acyl-(1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-7-yl)) group on the maleimide resulted in very potent inhibitors of GSK3 (⩽5 nM) with >160 to >10,000-fold selectivity versus CDK2/4 and PKCβII. These compounds also inhibited tau phosphorylation in cells and were effective in lowering plasma glucose in a rat model of type 2 diabetes (ZDF rat).

Glycogen synthase kinase 3 (GSK3) is an integral component of the insulin signaling pathway as a modulator of glycogen synthase (GS), the enzyme that catalyzes the last, and rate-limiting, step in glycogen biosynthesis.[1] GSK3 is a constituently active negative regulator of GS; that is, phosphorylation of GS by GSK3 turns off GS.[2] Thus, inhibitors of GSK3 are expected to leave GS in an active state stimulating the conversion of glucose to glycogen (mimicking the effect of insulin), and have potential utility for treatment of type 2 diabetes.[3] A variety of bis-aryl maleimides (BAMs) have been reported as potent GSK3 inhibitors. Early studies afforded BAMs that also inhibited PKCs[4,7] and CDKs,[3d,e] a property common to many other structurally distinct GSK3 inhibitors;[5,7] for example, **1**,[6] **3**[5b] (Fig. 1). Further SAR has produced potent inhibitors of GSK3 that demonstrate increased selectivity;[3] for example, **2**[8] and **4**.[5b]

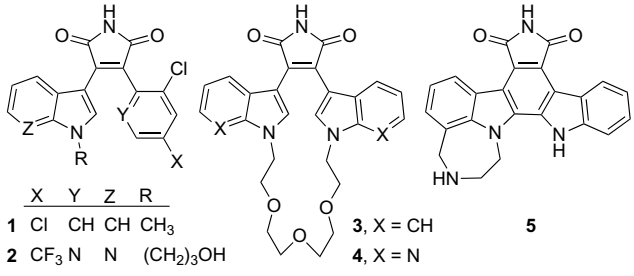

Figure 1. Selected maleimide kinase inhibitors.

Lilly has a history of maleimide kinase inhibitors. Ruboxistaurin mesylate[9a,b] and enzastaurin[9c–e] are potent and selective inhibitors of PKCβ and are currently under clinical evaluation for the treatment of diabetic complications and cancer, respectively. Efforts toward the design of cyclin-dependant kinase inhibitors have not only afforded a rich SAR on the maleimido-indolocarbazoles **5**[10a] but also a large array of BAMs[10b–e] to evaluate the inhibition of other kinases.

Since cross-reactivity with PKCs and CDKs is a feature common to many GSK3 inhibitors, we postulated that

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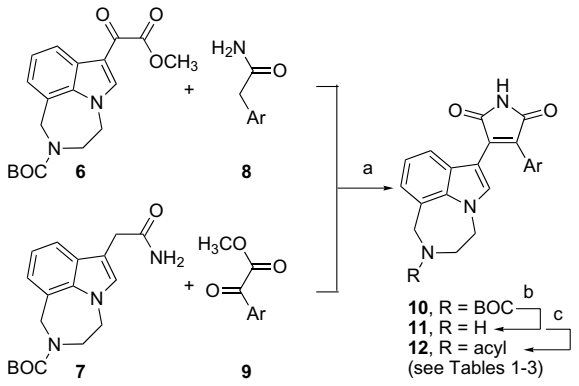


Scheme 1. Reagents and conditions: (a) KO-*t*-Bu, DMF, 73%; (b) 4 N HCl/EtSH/dioxane, 86%; (c) *N*,*N*-dimethylcarbamoyl chloride, TEA, MeOH, 80%. Yields shown are for **31** as a representative compound.

spanning the 1,7-indole positions of a 3-aryl-4-(3-indolyl)maleimide with a ring system, as in **5**, could be used to design novel, potent and selective inhibitors. Initially, we focused attention on the 3-aryl-4-[1,7-aza-annulated-indol-3-yl]maleimides **11/12** (Scheme 1); preference was given to bicyclic heteroaromatic Ar groups.

Maleimides **12** were prepared as shown in Scheme 1. Condensation[11] of indole 3-glyoxylate **6** or 3-acetamide **7** with the corresponding aryl acetamide **8** or aryl glyoxylate **9** gave maleimides **10**. The 1,7-aza-annulated indole–gyloxylate **6** and –acetamide **7** were prepared by routes reported by Al-awar and co-workers.[10] Acetamides **8** were synthesized by hydrolysis of the corresponding nitriles.[12] The glyoxylates **9** were prepared from the corresponding arylbromides via Li–halogen exchange followed by reaction with dimethyl oxalate. Removal of the *tert*-butyl carbamate protecting group in **10** under acidic conditions and acylation of the resulting secondary nitrogen under standard conditions gave **12**.

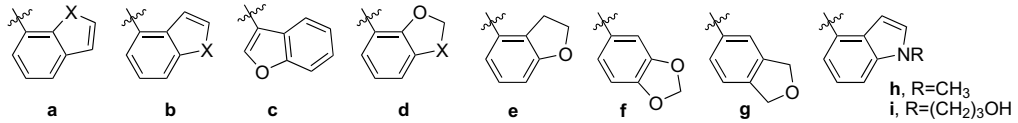
As summarized in Table 1, maleimides with a diverse array of Ar substituents were examined. Of these, the '*ortho*-oxo fused' aromatics **13**, **16**, **18**, **26**–**28**, and **30**–**31** exhibited the best GSK3 inhibition (IC_{50} 1–13 nM).[15] They also potently inhibited PKCβII and CDK2/4. With highly potent inhibitors in hand, our attention focused on selectivity, which emerged as a more significant challenge for SAR. Notably, some of the *N*-acylated derivatives, for example, **27**–**28** and **30**–**31**, showed somewhat improved selectivity against PKCβII, CDK2, and CDK4.

As an approach to improved selectivity, we explored isosteric replacement of CH═ to N═ in the benzofuran series with encouraging results (Table 2). Compound **32a** was synthesized starting from 7-bromo-5*H*-furo[3,2-*c*]pyridin-4-one,[13] which was converted to the 2-(furo[3,2-*c*]pyridin-7-yl)acetamide.[14] The resulting acetamide was condensed with glyoxylate **6** and deprotected using 4 N HCl/dioxane/EtSH. The 3-furo-[3,2-*c*]pyridin-7-yl series **32** consistently gave excellent GSK3 activity and the *N*-acyl derivatives **32b**–**f** demonstrated on average somewhat improved selectivity against CDK4 and PKCβII (Table 2; for example, **26** versus **32b**, **30** versus **32d**).

The promising activity of the 3-furo[3,2-*c*]pyridin-7-yl series suggested a search for other aza-heterocycles

Table 1. Kinase inhibition of 3-aryl-4-[1,7-aza-annulatedindol-3-yl]maleimides **12**

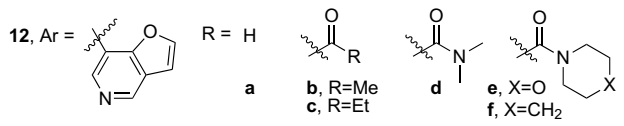
12, Ar =



a **b** **c** **d** **e** **f** **g**

Compound	R	Ar	GSK3 IC_{50} (nM)	Ratio of IC_{50}s		
				$\frac{CDK2}{GSK3}$	$\frac{CDK4}{GSK3}$	$\frac{PKC\beta II}{GSK3}$
13	H	**a**, X = O	3.4	3	5	183
14	H	**b**, X = O	41	5	1	39
15	H	**c**	64	—	—	37
16	H	**d**, X = CH_2	3.3	10	7	53
17	H	**e**	130	—	—	35
18	H	**d**, X = O	13	7	2	103
19	H	**a**, X = S	45	2	1	15
20	H	**b**, X = S	34	—	—	24
21	H	**f**	27	42	18	202
22	H	**g**	83	—	—	47
23	H	**a**, X = NH	150	—	—	15
24	H	**h**	33	11	1	28
25	H	**i**	27	11	1	9
26	COMe	**a**, X = O	1.5	7	25	80
27	COMe	**d**, X = CH_2	1.1	16	77	133
28	COMe	**d**, X = O	2.5	24	50	240
29	COMe	**a**, X = S	19	4	7	7
30	$CONMe_2$	**a**, X = O	2.7	25	35	89
31	$CONMe_2$	**d**, X = O	3.2	139	89	190

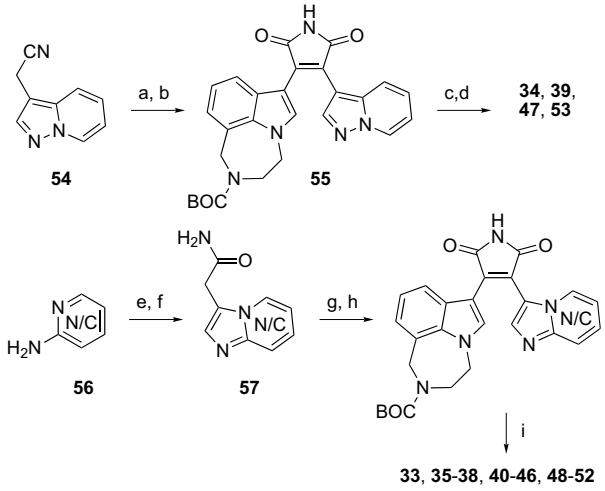
Table 2. Kinase inhibition of 3-furo[3,2-*c*]pyridin-7-yl-maleimides **32**



Compound	R	GSK3 IC_{50} (nM)	Ratio of IC_{50}s		
			CDK2/GSK3	CDK4/GSK3	PKCβII/GSK3
32a	**a**	3.2	2	6	54
32b[a]	**b**	0.9	9	60	422
32c[a]	**c**	1.0	13	98	375
32d[a]	**d**	1.2	13	112	—
32e[a]	**e**	0.8	49	158	—
32f[a]	**f**	2.1	17	92	108

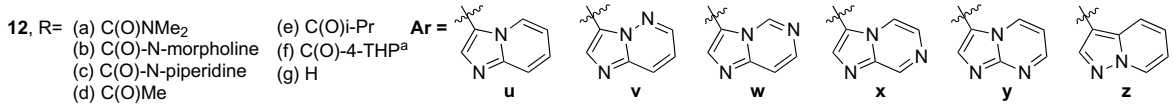
[a] HCl salt.

incorporating a nitrogen in a similar orientation as in **32**. We focused on imidazo[1,2-*a*]pyridine **48**,[15] aza-analogs **49**–**52**, and pyrazolo[1,5-*a*]pyridine **53** (Table 3). Maleimides **12z** (Table 3) were prepared as shown in Scheme 2. Pyrazolo[1,5-*a*]pyridin-3-yl-acetonitrile[16] **54** was hydrolyzed to the acetamide, condensed with **6** to give **55**, deprotected, and acylated. To prepare maleimides **12u**–**y**, the appropriate 2-amino pyridines **56** (Scheme 2) were condensed with ethyl (*E*)-4-oxo-but-2-enoate,[17] generated in situ via an acid catalyzed hydrolysis of ethyl (*E*)-4,4-dimethoxy-but-2-enoate. The resulting ethyl esters were converted to acetamides **57**,



Scheme 2. Yields shown for **39** are representative: Reagents and conditions: (a) KOH, *t*-BuOH, reflux, 30 min, 82%; (b) **6**, KO-*t*-Bu, DMF, 64%; (c) 4 N HCl/dioxane, EtSH, rt, 92%; (d) morpholine–4-carbonyl chloride, TEA, MeOH, 68%. Yields shown for **33** are representative: (e) ethyl (*E*)-4,4-dimethoxy-but-2-enoate, CH_3CN, H_2O, TsOH, reflux; (f) NH_3, MeOH, 100 °C, ~20–30% for two steps; (g) **6**, KO-*t*-Bu, DMF, 60%; (h) 4 N HCl/dioxane, EtSH, rt, quant.; (i) *N*,*N*-dimethylcarbamoyl chloride, TEA, MeOH, 78%.

Table 3. In vitro and in vivo activities of imidazo[1,2-*a*]pyridinyl, and pyrazolo[1,5-*a*]pyridinyl maleimides



Compound	R	Ar	GSK3 IC_{50} (nM)	Ratio of IC_{50}s			pTau[b] IC_{50} (nM)	In vivo glucose lowering[c] (ZDF rat, 10 mpk)
				CDK2/GSK	CDK4/GSK	PKCβ/GSK		
33[15]	a	**u**	1.6	1284	907	635	12	104
34	a	**z**	4.7	469	370	235	38	69
35[15]	b	**u**	1.3	2491	1308	893	2.6	119
36	b	**w**	71	>282	>282	>282	—[d]	—
37	b	**x**	3.2	>6300	4551	>6300	11	−2[f]
38	b	**y**	1.7	>11,800	8575	>11,800	297	−43[f]
39	b	**z**	1.3	2332	1900	576	—	66
40[15]	c	**u**	2.0	2680	2420	281	1.6	124
41	c	**v**	0.7	620	1327	1305	0.3	137
42	c	**x**	2.1	>9500	8916	>9500	8.7	64
43	c	**y**	1.9	>10,500	10,022	>1507	53	−61[f]
44	d	**u**	1.9	331	483	457	111	—
45	e	**u**	1.8	1977	2024	522	5	109
46	f	**u**	0.8	6880	2653	1745	7.7	—
47	e	**z**	3.5	466	309	160	13	10
48[e]	g	**u**	12	63	13	28	—	—
49[e]	g	**v**	4.8	14	15	133	—	—
50	g	**w**	330	23	14	3	—	—
51[e]	g	**x**	60	93	19	>334	—	—
52[e]	g	**y**	120	73	20	112	—	—
53[e]	g	**z**	30	25	10	18	—	—

[a] THP = tetrahydropyranyl.
[b] Inhibition of tau phosphorylation.
[c] % of insulin (10 units) response.
[d] Not tested.
[e] HCl Salt.
[f] Glucose levels higher than vehicle control.

condensed with glyoxylate **6**, and acylated. Although some of the parent NH compounds **48**–**53** were potent GSK3 inhibitors, most showed only modest potency and selectivity. However, the acylated derivatives **33**–**35** and **37**–**47** proved significant breakthroughs. These compounds not only demonstrated very good GSK3 inhibition but also dramatically improved selectivity versus PKCβII, CDK2, and CDK4.

Having identified numerous single digit nM inhibitors, we suspected that this was the lower limit of the assay. This was shown to be the case using **33**.[15] Kinetic analysis revealed a K_i considerably lower than the biochemical IC_{50}. The K_i was determined either though traditional kinetics ($K_i = 0.38$ nM) or using Biacore technology ($K_i = 0.23$ nM). In addition, the IC_{50} varied with GSK3 enzyme concentration consistent with tight binding inhibition. Thus, we suspect that inhibitors with IC_{50}s < 3–5 nM likely have K_i's in the pM range and greater selectivity than the biochemical IC_{50}s imply.

To differentiate the selective inhibitors, we relied on a cell-based assay measuring inhibition of Ser396 phosphorylation of tau, a natural substrate of GSK3 in SY5Y cells.[18] This assay was quite effective in differentiating compounds (Table 3).

Finally, the selective inhibitors were examined in an animal model of type 2 diabetes.[15] Zucker diabetic fatty (ZDF)[19] rats were dosed via oral gavage with 10 mg/kg of inhibitor and 4 h post-dose plasma glucose levels were compared to vehicle and insulin (10 units) treated controls, with results expressed as a percentage of the positive control insulin response. Taken with the PKC/CDK selectivity data, the in vivo data (Table 3) clearly established a superior profile for the imidazopyridine series **u** and **v** (e.g., **33**, **35**, **40**–**41**, and **45**) relative to the other aza-imidazopyridines **w**–**y** and the pyrazolopyridine series **z**.

In conclusion, the development of a series of very potent and highly selective GSK3 inhibitors is reported. These compounds inhibit tau phosphorylation in a neuronal cell line, lower plasma glucose in the ZDF rat model of type 2 diabetes, and hold considerable promise as potential therapeutic agents for diabetes and Alzheimer's disease.

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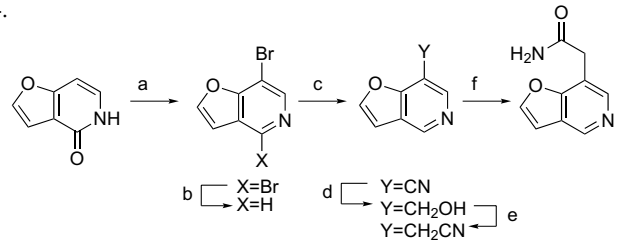
14. 

(a) (i) NBS, 75%; (ii) $POBr_3$, 50%; (b) $Pd(PPh_3)_4$, NaO_2CH, 75%; (c) CuCN, CuI, DMF, 94%; (d) (i) NH_4OH, 150 °C, 100%; (ii) BH_3·THF, 73%; (e) (i) HCl, Et_2O; (ii) $SOCl_2$; (iii) NaCN, EtOH, H_2O, 67%; (f) KOH, *t*-BuOH, 85%.
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