

**Identification of a Maleimide-Based Glycogen Synthase Kinase-3 (GSK-3)
Inhibitor, BIP-135, that Prolongs the Median Survival Time of $\Delta 7$ SMA KO
Mouse Model of Spinal Muscular Atrophy.**

Supporting Information

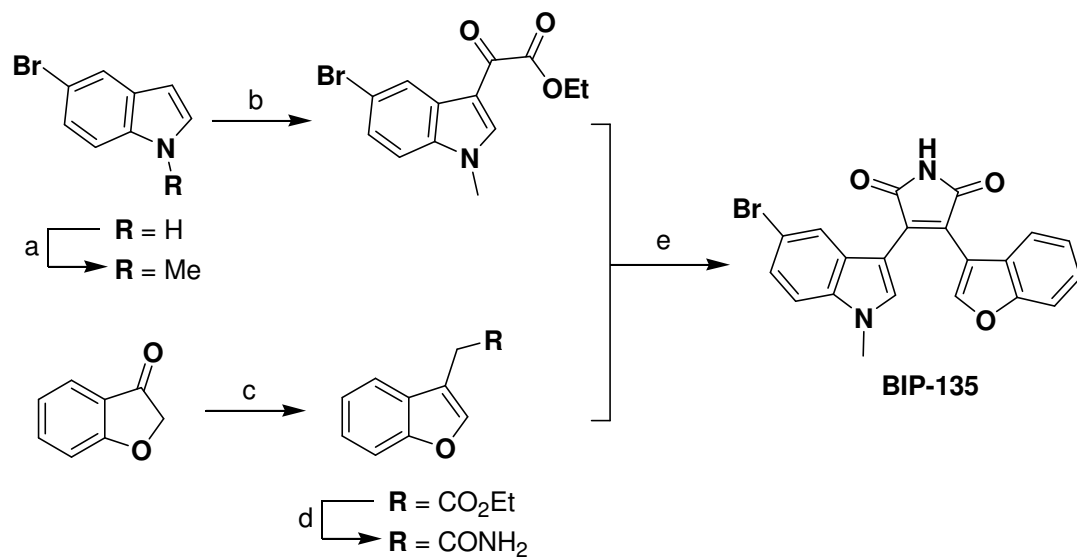
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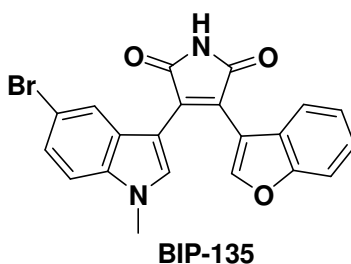
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Synthetic Scheme of BIP-135	S2
Kinase Functional Assays and Selectivity Profile of BIP-135	S3



Scheme 1. Previously reported synthetic sequence of **BIP-135** used in scale up. Reagents and conditions: (a) NaH, MeI, DMF; (b) Et_2OCCOCl , Et_2O ; (c) $\text{Ph}_3\text{P}=\text{CH}_2\text{CO}_2\text{Et}$, toluene, 110°C ; (d) $\text{NH}_3(\text{gas}) / \text{MeOH}$, 60°C ; (e) 1.0 M *t*-BuOK in THF, THF, 0°C .

Table 1. Kinase Functional Assays and Selectivity Profile of **BIP-135**.



Kinases	IC ₅₀ (nM) ^{a,b}	SI ^c	Kinases	IC ₅₀ (nM) ^{a,b}	SI ^c
GSK-3β	21		JNK1*	NI	>500
GSK-3α	16		KDR*	NI	>500
Akt	NI	>500	LCK	NI	>500
AMPK(A1/B1/G1)	12890	615	MEK1	NI	>500
Aurora A	11320	538	MKK6	NI	>500
Axl*	NI	>500	MSK1/RPS6KA5	4930	235
c-Abl*	NI	>500	NIK/MAP3K14	NI	>500
c-Abl-T315I*	NI	>500	P38α/MAPK14	NI	>500
CAMK2δ	9980	475	P38γ	NI	>500
CDK1/cyclin B	7210	343	p70S6K/RPS6KB1	14100	671
CDK2/cyclin A*	3980	190	PHKγ1	17400	829
CDK2/cyclin E	1950	93	PKA*	NI	>500
CDK4/cyclin D1	3090	147	PKB*	NI	>500
CDK5/p25	4010	191	PDK1*	NI	>500
CHK2	28700	1370	PI3Kα	870	41
			(p110α/p85α)		
CK2α	NI	>500	PKCα*	61400	2920
c-Met*	NI	>500	PKCβ1	980	47
CSK	NI	>500	PKCβ2	219	10
c-Src*	NI	>500	PKCμ/PRKD1	NI	>500
DDR2	NI	>500	PKCν/PRKD3	NI	>500
DYRK1B	590	28	PKD2/PRKD2	NI	>500
EphB4*	NI	>500	PKG1a	4260	203
ERK2/MAPK1	NI	>500	PLK3	NI	>500
FAK*	NI	>500	β-Raf-V599E*	NI	>500
FGFR3	NI	>500	Ret*	NI	>500
FGFR3*	NI	>500	ROCK2	NI	>500
(K650E)					
Flt-3*	NI	>500	RSK2	1490	71
HER-1*	NI	>500	SGK1	NI	>500
HIPK4	13960	662	Tek*	NI	>500
IGF-1R*	NI	>500	TRKA	14500	690
IR	NI	>500	TRKB	9150	436
JAK-2*	NI	>500	TRKC	1840	876

^[*] These kinases were previously screened and reported in our *J. Am. Chem. Soc.* Paper from 2006.¹⁶

^[a] The ability of the enzymes to phosphorylate the substrate (20 μM final concentration) was assayed in the presence of 10 μM of ATP (Reaction Biology, Inc at www.reactionbiology.com)

^[b] NI means no inhibition or compound activity (maximum concentration used = 10 μM)

^[c] Kinase selectivity index (SI) of BIP-135 for GSK-3β over other kinases tested