Bioorganic & Medicinal Chemistry Letters 23 (2013) 4374–4380

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Development of highly selective casein kinase 1δ/1ε (CK1δ/ε) inhibitors with potent antiproliferative properties

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ARTICLE INFO

Article history:
Received 7 April 2013
Revised 20 May 2013
Accepted 21 May 2013
Available online 31 May 2013

Keywords:
Casein kinase 1δ/ε inhibitor
Selective CK1δ/ε inhibitor
Purine scaffold kinase inhibitor
Antiproliferative agent
Potent growth inhibitor of A375 melanoma cell line

ABSTRACT

The development of a series of potent and highly selective casein kinase 1δ/ε (CK1δ/ε) inhibitors is described. Starting from a purine scaffold inhibitor (SR-653234) identified by high throughput screening, we developed a series of potent and highly kinase selective inhibitors, including SR-2890 and SR-3029, which have $IC_{50} \leqslant 50$ nM versus CK1δ. The two lead compounds have ⩽100 nM EC_{50} values in MTT assays against the human A375 melanoma cell line and have physical, in vitro and in vivo PK properties suitable for use in proof of principle animal xenograft studies against human cancer cell lines.

The casein kinase 1 (CK1) family of serine/threonine-specific kinases is comprised of seven members (α, β1, δ, ε, γ1, γ2 and γ3); each isoform has a preference for pre-phosphorylated substrates.[1] CK1 kinases regulate diverse processes including Wnt signaling,[2,3] membrane trafficking,[4] the actin cytoskeleton,[5] the DNA damage response,[6] and circadian rhythms.[7] Importantly, aberrant CK1δ and CK1ε activity is implicated in human pathologies, including neurodegenerative diseases, sleep disorders and cancer. CK1 kinases are ubiquitously expressed in the central nervous system and CK1δ is thought to play roles in dopamine signaling, neurotransmitter release and the phosphorylation of neurotransmitter receptors.[8,9] Further, CK1δ expression is elevated in Alzheimer's disease tissue and CK1δ phosphorylates tau, which initiates microtubule destabilization and neuronal cell death.[5,10] These kinases may also play roles in cleavage of the amyloid precursor protein (APP),[9] as CK1 inhibitors disrupt APP cleavage and a constitutively active form of CK1ε augments APP peptide production.[9,11] Finally, the up-regulation of CK1 isoforms in Alzheimer's patients makes CK1 an attractive target for the treatment of Alzheimer's disease.[9]

Casein kinases 1δ and 1ε are highly expressed in some cancers and appear to control tumor cell growth, apoptosis, metabolism and differentiation.[10,12] For example, forced expression of kinase-impaired mutants of CK1δ blocks SV40-induced cell transformation and mammary carcinogenesis in vivo.[13] Further, CK1ε is required for the survival of breast cancer subtypes that rely on aberrant β-catenin activity, and active, myristoylated CK1ε is sufficient to provoke transformation via stabilization of β-catenin and activation of Wnt transcription targets.[14] CK1δ/ε-directed stabilization of β-catenin may occur via CK1δ/ε-directed phosphorylation of lipoprotein receptor-related protein 5/6 (Lrp5/6) and/or dishevelled (dvl/dsh).[15–18] CK1δ and CK1ε also play roles in ovarian cancer[19] and pancreatic adenocarcinoma.[20]

These important biological roles have stimulated considerable effort to develop CK1δ/ε inhibitors.[10,21–24] Included among the many small molecule inhibitors of CK1δ that have been reported are CKI-7,[25] D4476,[26,27] IC261,[28] (R)-DRF053,[22] Bischof-5[24] (compound **5** in Ref. 24) and PF-670462 (see Fig. 1).[29,30] CKI-7 is a 6 μM CK1 inhibitor, but does not readily pass cell membranes.[25,26] IC261, D4476 and (R)-DRF053 are cell-permeable yet have limitations. Specifically, D4476 is a 0.3 μM CK1 inhibitor in vitro,[26] has low activity (20–50 μM) in cell-based assays,[27,29] and also inhibits p38α, raising concerns regarding off-target effects.[10,26,27] Further,

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http://dx.doi.org/10.1016/j.bmcl.2013.05.075

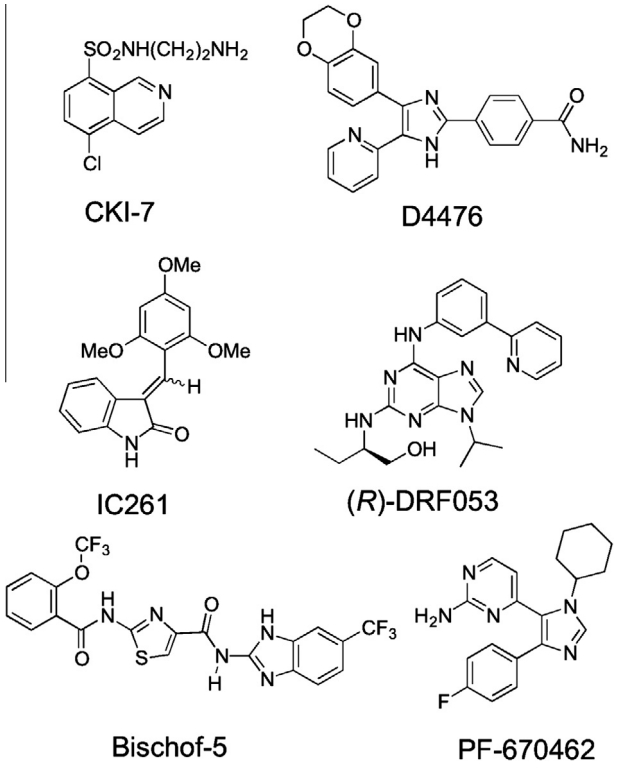
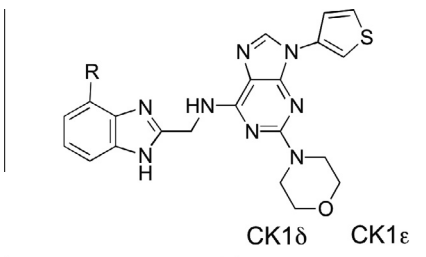


Figure 1. Representative CK1δ/ε inhibitors.

the IC_{50} of IC261 is only 1 μM for CK1 inhibition in vitro and 25 μM in cells,[10] and there are off target effects as IC261 binds to tubulin and inhibits microtubule polymerization.[28] Moreover, (R)-DRF053 is a potent, dual CK1/CDK inhibitor (14 nM vs CK1), yet only exhibits weak (EC_{50} 17.2 μM) antiproliferative activity against human neuroblastoma SH-SY5Y cells. Bischof-5 is yet another potent (48 nM) CK1δ inhibitor, but is also weakly active in cells, likely due to poor cell penetration.[29] Finally, PF-670462 is a 14 nM inhibitor of CK1δ in vitro and was initially reported to be highly selective, at least among the 45 kinases tested.[29] Subsequent studies showed that PF-670462 also potently inhibits p38 and EGFR.[30] Both PF-670462 and PF-4800567 (Pfizer's CK1ε inhibitor)[30] lack anti-cancer activity.[28]

A high-throughput screening (HTS) campaign under the auspices of the MLPCN program at Scripps Florida, targeting inhibitors of Wee1 degradation,[31] identified SR-653234 as a promising hit. Extensive mechanistic and biochemical profiling studies demonstrated that SR-653234 and especially its analog SR-1277 (Fig. 2) are highly selective CK1δ/ε inhibitors and that CK1δ plays a crucial role in regulating the activity of Wee1 at the G2/M cell cycle



	CK1δ	CK1ε
SR-653234 (R = H)	160 nM	540 nM
SR-1277 (R = NO_2)	49 nM	260 nM

Figure 2. CK1δ/ε inhibition data for SR-1277 and SR-653234.

interface.[11] These efforts led to SR-1277 being designated as Probe ML177 in the MLPCN system.[32] However, SR-1277 has poor solubility, sub-optimal PK properties and metabolic liabilities due to the thiophene unit and especially the aryl nitro substituent.[33,34] Therefore, we have performed and report herein additional SAR studies that led to the identification of several analogs (including SR-2890 and SR-3029) that are appropriate for progression into murine xenograft studies against human cancers.

We adopted the general procedure published by Schultz for synthesis of analogs of SR-653234 and SR-1277.[35–37] As depicted in Figure 3 for the synthesis of SR-653234, the *N*-thienyl intermediate **2** was accessed via a Chan–Lam coupling reaction of commercially available dichloropurine **1** and 3-thienylboronic acid.[36,38,39] A one-pot double nucleophilic substitution sequence then converted intermediate **2** into the targeted CK1δ/ε inhibitor. The regioselectivity of the latter sequence is excellent, with the first amine nucleophile adding to C(6) of the purine scaffold as has been demonstrated previously.[35–37]

The substituted 2-(aminomethyl)benzimidazoles (**6**) used in this study that are not commercially available were synthesized as summarized in Figure 4. Thus, a substituted phenylenediamine **3** (prepared by reduction of the corresponding *ortho*-nitroaniline,[40] if not commercially available) was coupled to *N*-Boc-glycine using EDC and HOBt as the coupling reagents to give a mixture of **4a** and **4b**. The mixture of these two amides was heated at 80 °C in acetic acid to effect cyclization to the *N*-Boc protected benzimidazole **5**. Finally, the Boc group was removed by treatment of **5** with a mixture of HCl (12 N in water) and dioxane at room temperature overnight. The product **6** was obtained as the HCl salt by precipitation from diethyl ether. This three-step procedure usually did not require any chromatographic purification steps, and provided the substituted benzimidazoles **6** (with a range of substituents corresponding to those in the inhibitors presented in Tables 1–3) having acceptable purity for use directly in the synthesis of the targeted CK1δ/ε inhibitors according to the procedure summarized in Figure 3.

Using this chemistry, we synthesized a series of analogs of SR-653234 with a range of substituents in the benzimidazole ring to probe the effect of this substitution on inhibitor activity. Substitution of the benzimidazole ring in either position 4 (R^1) or position 5 (R^2) led to an increase of CK1δ inhibition compared to the unsubstituted parent compound SR-653234 (Table 1). A trifluoromethyl group at R^1 modestly enhanced CK1δ inhibition (compare entries 1 and 2) while nitro and methanesulfonyl substituents at this position led to significantly more active analogs SR-1277 and SR-2805 (entries 7 and 11). Improvements of CK1δ inhibitor activity were also achieved by incorporating a range of substituents at R^2. Substitution with a trifluoromethyl group (SR-1273, entry 3), a nitro group (SR-1278, entry 8), a cyano group (SR-1276, entry 6), a methoxy group (SR-1279, entry 9) or a methanesulfonyl group (SR-2797, entry 10) led to significant improvement of CK1δ inhibitor activity.

A thiophene substituent, especially when not substituted at positions 2 and/or 4, is generally considered to be a liability in view of the potential for production of highly reactive metabolites.[41,42] To avoid this potential problem, we sought other groups that could be used at the purine 9-position (R^3) without significant loss of CK1δ inhibitory activity (Table 2).[43] Replacement of the thiophene ring of SR-653234 by a cyclopentyl group led to a more potent inhibitor, SR-2149 (entry 1). Although the furan-containing analogs SR-2850 and SR-2007 had excellent potency, the furan ring is also a known metabolic liability, especially when not substituted at positions 2 and 4.[43] On the other hand, several inhibitors bearing fluoro-substituted phenyl rings at position R^3 had very interesting properties. As depicted by the results in entries 4–7 of Table 2, the position of the fluorine substituent dramatically influenced the

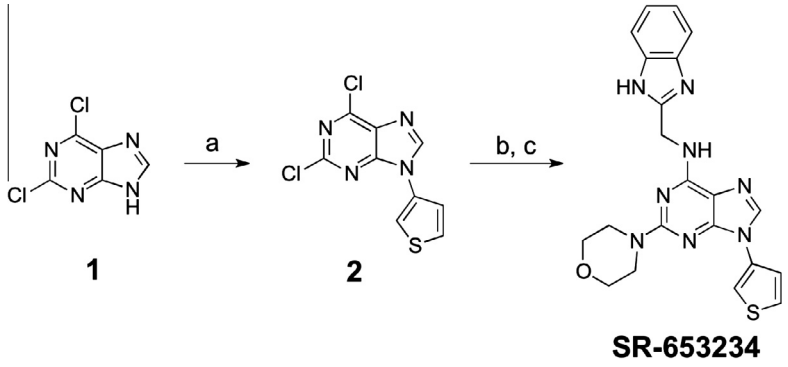


Figure 3. Strategy for synthesis of purine-scaffold CK1δ/ε inhibitors, illustrated by the synthesis of SR-653234. Conditions: (a) $ArB(OH)_2$, $CuOAc_2$, MS 4 Å, NEt_3, CH_2Cl_2, 24 h, 23 °C, 27 %; (b) 2-(aminomethyl)benzimidazole, $(i\text{-}Pr)_2NEt$, *i*-PrOH, 30 min, 90 °C, microwave; (c) morpholine, 130 °C, 30 min, microwave, 70%.

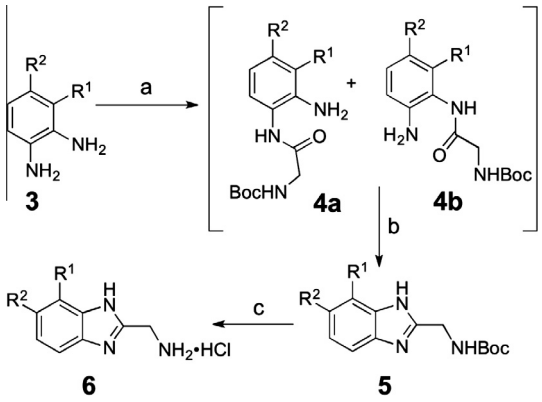
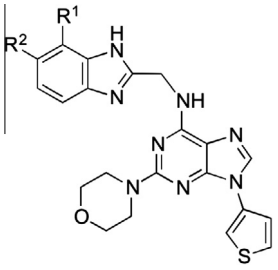


Figure 4. General method for synthesis of substituted 2-(aminomethyl)benzimidazoles. Conditions: (a) EDC·HCl, HOBt·H_2O, Boc-GlyOH, CH_2Cl_2, 23 °C, 2 h; (b) AcOH (neat), 80 °C, 2 h; (c) HCl (12 N), dioxane, (1/1), overnight, 23 °C.

Table 1
Structure–activity relationship data for CK1δ inhibitors with substituted benzimidazole units

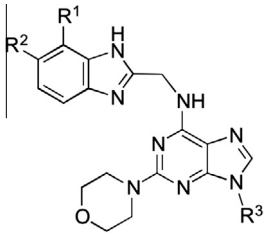


Entry	Compound number	R^1	R^2	IC_{50} CK1δ[a] (nM)
1	SR-653234	H	H	160
2	SR-1272	CF_3	H	128
3	SR-1273	H	CF_3	13
4	SR-1274	H	Cl	105
5	SR-1275	H	F	50
6	SR-1276	H	CN	11
7	SR-1277	NO_2	H	49
8	SR-1278	H	NO_2	21
9	SR-1279	H	OMe	17
10	SR-2797	H	SO_2Me	10
11	SR-2805	SO_2Me	H	16

[a] CK1δ inhibition data obtained by Reaction Biology Corp.

CK1δ inhibitor activity. The 4-fluorophenyl analog SR-2362 was essentially inactive whereas inhibitors with 2-fluorophenyl (SR-2366, entry 6) and 3-fluorophenyl (SR-2364, entry 5) substitutions gave potent CK1δ inhibitors, with the 3-fluorophenyl compound SR-2364 having an IC_{50} value of 57 nM versus CK1δ. The 3,5-difluorophenyl analog SR-2368 was also a reasonably potent CK1δ inhibitor (entry 7).

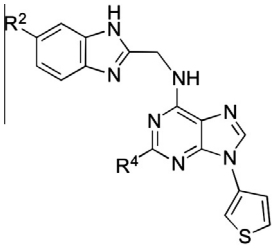
Table 2
Activity of CK1δ inhibitors with other substituents at N-9 (R^3)



Entry	Compound number	R^1	R^2	R^3	IC_{50} CK1δ[a] (nM)
1	SR-2149	H	H	Cyclopentyl	57
2	SR-2850	H	Cl	3-Furyl	23
3	SR-2007	NO_2	H	3-Furyl	19
4	SR-2362	NO_2	H	4-F-Phenyl	>1000
5	SR-2364	NO_2	H	3-F-Phenyl	57[b]
6	SR-2366	NO_2	H	2-F-Phenyl	114[b]
7	SR-2368	NO_2	H	3,5-DiF-phenyl	75[b]

[a] CK1δ inhibition data obtained by Reaction Biology Corp., unless indicated otherwise.
[b] CK1δ inhibition data determined from an in-house kinase inhibition assay.

Table 3
Activity of CK1δ inhibitors with other substituents at purine C-2 (R^4)



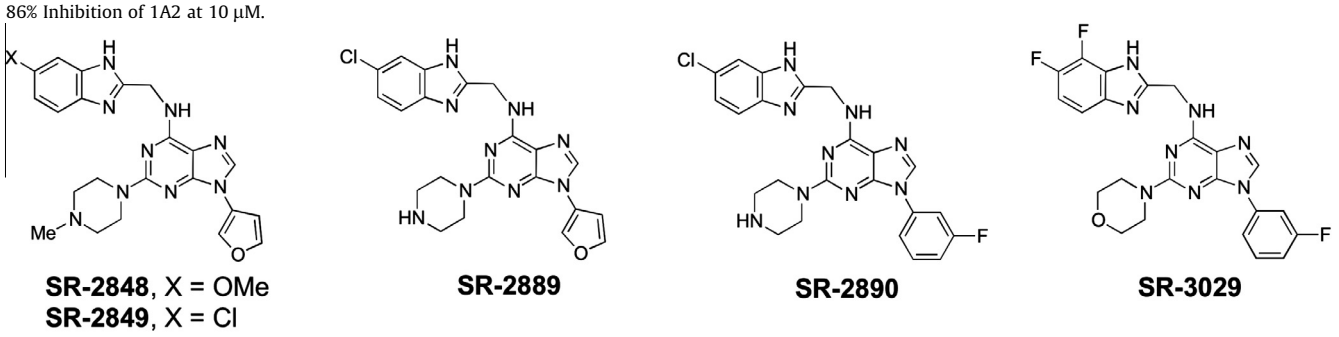
Entry	Compound number	R^4	R^2	IC_{50} CK1δ (nM)
1	SR-1292	*N*-Piperazine	H	3[a]
2	SR-1294	4-(*N*-Me)-piperazine	H	11[a]
3	SR-2876	*N*-Piperazine	Cl	51[b]
4	SR-2875	4-Amino-piperidine	Cl	119[b]
5	SR-2915	3-Methyl-piperazine	H	199[b]

[a] CK1δ inhibition data obtained by Reaction Biology Corp.
[b] CK1δ inhibition data determined from an in-house assay.

Table 4
IC_{50} data, cell-based activity and in vitro PK data for selected CK1δ inhibitors

Compound	Biochemical[a]		Cell activity	In vitro PK properties		
	CK1δInh IC_{50} (nM)	CK1εInh IC_{50} (nM)	MTT assay A375 EC_{50} (nM)	Microsome stability (h/r/m) T1/2[b] (min)	Solublity[c] (μM)	Cyp inhibition[d]
SR-653234	160	540	111	11/6/1	28	e
SR-1277	49	260	22	7/5/2	1	>10 μM
SR-2848	30		89	31/26/15	25	>10 μM
SR-2849	11		3	6/5/1	18	>10 μM
SR-2889	5		2	25/NA/8	71	>10 μM
SR-2890	4		38	44/NA/11	60	>10 μM
SR-3029	44	260	86	18/NA/5	13	>10 μM
PF-670462	13	90	>10,000			
D4476	167	350	10,000			
Bischof-5	29	199	2300			
AC220	—	—	1570			
Sunitinib				54/21/21		

[a] Data obtained by Reaction Biology Corporation (RBC).
[b] Microsome stability using human, rat, and mouse liver microsomes, with sunitinib as the reference. 'NA' = data not obtained.
[c] Solubility in DMEM/10% FBS.
[d] Cyp assay versus 1A2, 2C9, 2D6, and 3A4.
[e] 86% Inhibition of 1A2 at 10 μM.



Another liability of lead compound SR-1277 is its low solubility (1 μM in PBS buffer). In an attempt to address this problem, additional analogs with piperazine and piperidine substituents R^4 were synthesized (see Table 3). Inhibitor SR-1292 with an unsubstituted piperazine ring at this position is a 3 nM inhibitor of CK1δ (entry 1), approximately sixteen-fold more potent than SR-1277. The *N*-methylpiperazine derivative (SR-1294) was also highly potent (11 nM inhibitor of CK1δ, entry 2). However, use of several other amines at this position led to loss of inhibitor activity (SR-2875 and SR-2915, entries 4 and 5). The data for these compounds suggests that the positioning or the steric environment of the piperazine ammonium group (protonated at physiological pH) is critical for high CK1δ inhibitor activity. Not surprisingly, solubility of SR-1292 and SR-2876 (75 μM and 54 μM in PBS, respectively) was substantially greater than that for analogous compounds with morpholine substituents at R^4.

A number of additional, potent analogs were synthesized by combining two or more of the structure elements highlighted in Tables 1–3. Data for several such analogs are summarized in Table 4.

Kinetic analysis demonstrated that the purine scaffold CK1δ/ε inhibitors that are the subject of this paper are ATP competitive; Ki's measured for SR-1277, SR-2890, and SR-3029 are 69 nM, 14 nM, and 97 nM, respectively. This insight enabled us to perform modeling studies of inhibitors bound to CK1δ using the published CK1δ-PF670462 co-crystal structure as the template for structure-based design.[44] Docking poses of SR-1277 and SR-1292 in the CK1δ-PF670462 active site are shown in Figure 5. Our working hypothesis is that the ability of the substituents on the benzimidazole unit (either R^1 or R^2, as defined in Table 1) to interact with Arg-13 is responsible for the significant improvement in CK1δ inhibition activity associated with these substitutions, leading to enhanced selectivity versus FLT3, which is the most significant off-target activity of our CK1δ/ε inhibitors (vida infra). The significant increase in inhibitor activity associated with use of piperazine or *N*-methyl piperazine as the R^4 substituent (e.g., SR-1292 and SR-1294, Table 3) is consistent with the positively charged ammonium unit of these agents interacting with the amide carbonyl of Asp-132. Finally, the R^3 thiophene, furan, and 3-fluorophenyl groups that are associated with high inhibitor potency (Table 2) bind in a relatively tight recognition pocket deep in the ATP binding site.

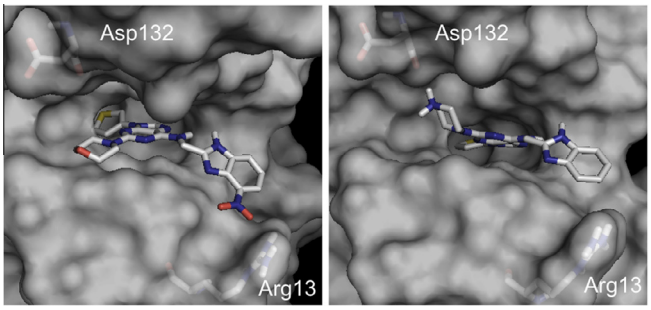


Figure 5. Poses of SR-1277 (left) and SR-1292 (right) docked into the CK1δ active site.

Throughout the progression of this work, new inhibitors were subjected to an MTT assay against the human melanoma A375 cell line.[45] Those compounds that exhibited significant anti-proliferative activity in this assay (EC_{50} <200 nM) were taken forward to a core set of in vitro DMPK assays (microsome stability, inhibition of cytochrome P450 1A2, 2C9, 2D6, and 3A4) to assess the drug-like characteristics of the increasingly optimized candidates.[46] The data summarized in Table 4 demonstrates that we have accomplished the synthesis of a number of very potent CK1δ inhibitors (e.g., SR-2848, SR-2849, SR-2889, SR-2890, and SR-3029),

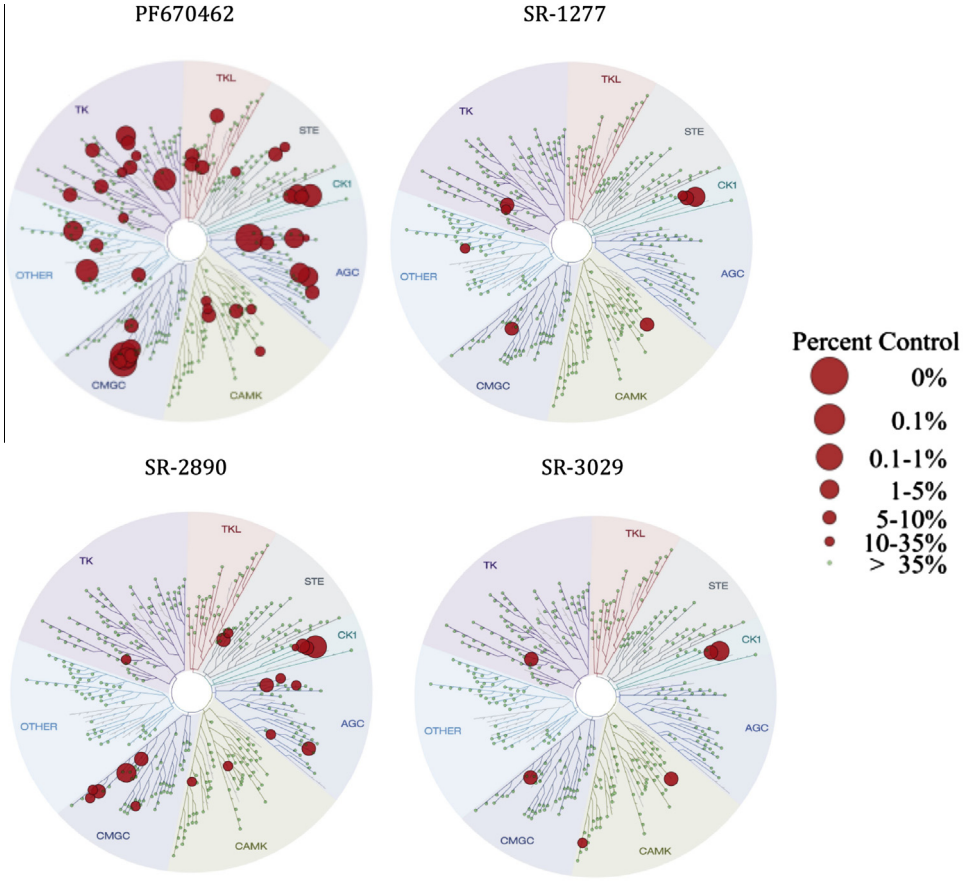


Figure 6. Dendrogram presentation of results of DiscoverRX® KINOMEscan® kinase binding selectivity analysis of PF-670462, SR-1277, SR-2890 and SR-3029. Data are presented for all kinases that have <10% control activity at 10 μM (% control is the percentage of kinase remaining bound to the bead-bound active-site ligand in the presence of the inhibitor).

Table 5
Kinases showing less than 10% activity in the presence of 10 μM SR-1277, SR-2890 or SR-3029

Target	SR-1277	SR-2890	SR-3029
BMP2K	6.2	68	39
CDK4/cyclin D1	56	0.2	4.4
CDK4/cyclin D3	56	10	19
CDK7	72	1.5	38
CDK13	1	88	100
CSNK1A1	63	10	22
CSNK1A1L	9.6	2.5	22
CSNK1D [CK1δ]	4.2	1.6	1.5
CSNK1E [CK1ε]	0.5	0.1	0.4
FLT3	3.4	13	3.7
FLT3 (D835H)	7.3	37	42
FLT3 (D835Y)	11	10	41
FLT3 (ITD)	3.7	15	19
FLT3 (K663Q)	5.2	13	12
FLT3 (N841L)	11	13	44
LATS2	100	3.1	26
MARK2	100	96	7.3
MAST1	100	6.2	23
MELK	47	7.1	22
MYLK4	2.6	85	2.1
NLK	38	5.6	98
PCTK3	62	6.6	37
PDGFRB	8.2	9.4	91
PFTAIRE2	47	9.3	20
PFTK1	40	4.6	55
PRKCQ	100	5	88
ROCK2	100	8.8	54
RIOK3	9.6	99	100
SGK	57	1	24
TAOK2	84	7.4	35
TAOK3	85	4.8	34

some of which have low nM EC_{50}'s as inhibitors of melanoma A375 cell growth. The data in Table 4 indicates that inhibitors with high microsome stability—approaching that of the reference compound sunitinib—are those that have piperazine derivatives at R^4. In addition, the new CK1δ/ε inhibitors presented in Table 4 consistently demonstrate less than 50% inhibition of cytochrome P450 1A2, 2C9, 2D6, and 3A4 at a 10 μM test concentration.

The exceptional activity of the purine scaffold CK1δ/ε inhibitors in MTT assays versus human melanoma A375 cells is striking (Table 4), especially since other potent CK1δ inhibitors are much less active in this cell-based assay. For example, we have determined that the EC_{50}'s of PF-670462,[29,30] D4476,[26,27] and Bischof-5[24] in the A375 melanoma MTT assay is >10 μM, 10 μM, and 2.3 μM, respectively (see Table 4). The significantly reduced activity of D4476 and Bischof-5 may be rationalized by poor cell penetration, as has been noted elsewhere.[24,27] However, the lack of anti-mela-

Table 6
IC_{50} values (nM) for inhibition of off-target kinases by SR-1277, SR-2890 and SR-3029[a,b]

Off-Target Kinase	SR-1277 (nM)	SR-2890 (nM)	SR-3029 (nM)
FLT3	305	809	3000
CDK4/cyclin D1	1340	283	576
CDK4/cyclin D3	—	391	368
CDK6/cyclin D1	—	1240	428
CDK6/cyclin D3	311	4420	427
CDK9/cyclin K	109	—	—

[a] Data obtained by Reaction Biology Corporation (RBC).
[b] Comparative data, also from RBC, for inhibition of CK1δ and CK1ε are provided in Table 4.

Table 7
Mouse PK data for selected CK1δ/ε inhibitors (IV dosing, 1 mg/kg, 10/10/80 DMSO/Tween/water)

Compound	C_{max} (μM)	Cl (ml/min/kg)	AUC (μM h)	T1/2 (h)	%F	Brain penetration (%)
SR-653234	3.2	2.2	1.75	0.73	0	13
SR-1277	1.2	2.8	1.26	1.42	0	24
SR-2890	4.6	8.4	4.16	1.50	10	<1
SR-3029	7.3	5.5	6.35	0.90	13	12

noma activity for PF-670462 is a concern, as this compound is widely believed to be a highly selective kinase inhibitor.

To address the question of kinase selectivity, and especially to investigate if our compounds are hitting other kinase target(s) that might be responsible for the potent antiproliferative effects, SR-1277, SR-2890, and SR-3029 were subjected to the DiscoverRX® KINOMEscan® analysis of 442 kinases. The Pfizer inhibitor PF-670462 was also tested. This assay, run at 10 μM, assesses the degree to which the inhibitor competitively displaces a bead-bound active-site ligand from a DNA-tagged kinase using quantitative PCR. It is clear from the dendrogram depiction of these kinome selectivity analyses (Fig. 6, which includes all kinases inhibited ⩾90% at 10 μM) that PF-670462 is a very non-selective kinase inhibitor. Among the 44 kinases that are inhibited ⩾90% by 10 μM PF-670462 are the pro-apototic kinases JNK, p38, and EGFR isoforms (and strongly so). In contrast, these studies established the high selectivity of SR-1277, SR-2890, and SR-3029 as CK1δ/ε inhibitors, with only 6 off-target kinases inhibited ⩾90% at 10 μM by SR-3029, and that SR-2890 is less kinase selective than either SR-1277 or SR-3029. A higher resolution snapshot of those kinases with less than 10% activity in the presence of SR-1277, SR-2890, or SR-3029 is provided in Table 5, with data for the kinases inhibited ⩾90% by specific inhibitors (i.e., less than 10% of active kinase remaining at 10 μM) highlighted in blue. These data show that the selectivity profile of each inhibitor is different, and that there are only three kinases that are strongly inhibited by all three inhibitors: CK1δ, CK1ε and FLT3, plus several FLT3 mutants.

Because the DiscoverRX® KINOMEscan® kinase binding assay is a competitive active site probe displacement assay, with different binding affinities of the active site probe for the range of kinases studied, these data do not, and are not intended to correlate with IC_{50} values. Therefore, to assess the inhibition potency of SR-1277, SR-2890, and SR-3029 against the most important off-target kinases identified, IC_{50} values were obtained by Reaction Biology Corporation (Table 6). These data suggest that the most important off-target kinase, FLT3, is only weakly inhibited by SR-1277, SR-2890, and SR-3029. These data, together with the results summarized in Table 4 for the MTT assay of the known FLT3 inhibitor AC220[47] against the A375 melanoma cell line, indicate that inhibition of FLT3 or FLT3 mutants is not responsible for the potent antiproliferative effects demonstrated for the purine-based CK1δ/ε inhibitors described in this paper. [AC220 is a low nM inhibitor of the FLT3 mutants identified in Table 5].[47] Moreover, co-treatment of A375 cells with PF-670462 (which is only weakly active against FLT3 and FLT3 mutants) and AC220 (which is inactive against CK1δ/ε) was ineffective in inducing a significant antiproliferative effect, indicating that the lack of FLT3 activity is not responsible for the inactivity of PF-670462 in the A375 MTT assay. Finally, data summarized in Table 6 for inhibition of the various CDK's also indicates that inhibition of these targets does not significantly contribute to the potent antiproliferative properties of SR-1277, SR-2890 and SR-3029.

Finally, mouse PK studies for a select group of CK1δ/ε inhibitors were performed (Table 7). These data show that SR-2890 and SR-3029 have PK properties sufficient to be advanced into xenograft studies of human tumors. The modest level of brain penetration of SR-3029 suggests that this compound could be useful in animal studies of brain cancers.

In summary, we have developed a series of potent and highly selective CK1δ/ε inhibitors with potent antiproliferative activity by optimization of HTS-derived SR-653234. These efforts led to the identification of SR-2890 and SR-3029 that have in vitro and in vivo PK properties suitable for use in xenograft studies of human cancers, including brain cancers in the case of SR-3029. Further studies on the development of these compounds as novel anticancer agents, as well as studies targeting their use in appropriate models of Alzheimer's disease, will be reported in due course.

Acknowledgments

This research was supported by the NIH Molecular Library Screening Center Network grant U54MH074404 (Dr. Hugh Rosen, Principal Investigator), the Rendina Family Foundation, and funds from the State of Florida to Scripps Florida. S. Nakanishi was supported by a Marie Mayer Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.05.075.

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