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Discovery of Dinaciclib (SCH 727965): A Potent and Selective Inhibitor of Cyclin-Dependent Kinases

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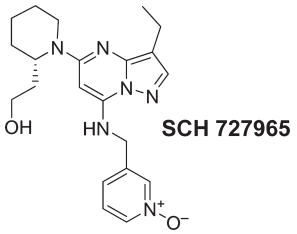
ABSTRACT Inhibition of cyclin-dependent kinases (CDKs) has emerged as an attractive strategy for the development of novel oncology therapeutics. Herein is described the utilization of an in vivo screening approach with integrated efficacy and tolerability parameters to identify candidate CDK inhibitors with a suitable balance of activity and tolerability. This approach has resulted in the identification of SCH 727965, a potent and selective CDK inhibitor that is currently undergoing clinical evaluation.

KEYWORDS Cyclin-dependent kinase, oncology therapeutics, SCH 727965



The mammalian cell cycle is a nonredundant process that integrates extracellular signaling, DNA synthesis, and mitosis.[1] Loss of cell cycle control is a hallmark of all human cancers and is frequently associated with aberrant activation of cyclin-dependent kinases (CDKs).[2,3] The CDKs are a well-characterized family of serine/threonine kinases that regulate cell cycle progression by phosphorylation and inactivation of the retinoblastoma tumor suppressor gene product (Rb) throughout late-G1, S, and G2/M phases as well as playing a role in the G2/M checkpoint and progression through mitosis.[4−9] Other members of the CDK family have also been shown to have functions beyond cell cycle regulation. For example, CDK5 is involved in neuronal function and τ phosphorylation,[10] and CDK7, CDK8, and CDK9 have been implicated in transcriptional regulation.[11,12]

Inhibition of multiple members of the CDK family has been shown to induce therapeutically desirable phenotypes such as inhibition of proliferation and apoptosis. For example, expression of dominant negative forms of CDK2 and combinatorial silencing of CDK1 and CDK2 via siRNA generates cell cycle arrest and apoptosis.[13−17] Likewise, inhibition of the noncell cycle-related CDKs, CDK7 and CDK9, depress transcriptional regulation a variety of targets including several antiapoptotic proteins.[8,17] Moreover, inhibition of CDK8 modulates B-catenin function, resulting in decreased proliferation of colon cancer cells.[18,19] Thus, inhibition of the essential, rate-limiting activities of multiple members of the CDK family represents an attractive therapeutic strategy for oncology indications.

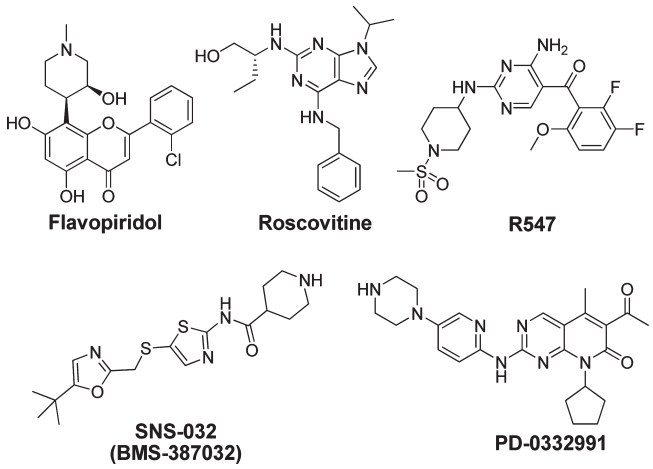


Figure 1. Representative CDK inhibitors in clinical trials.

A number of diverse CDK inhibitors have progressed into clinical development (Figure 1).[20−23] Flavopiridol has been the most clinically studied CDK inhibitor, and several phase II trials targeting a variety of indications have been completed. Thus far, the most significant activity has been reported in chronic lymphocytic leukemia.[24] Efforts in applying an in

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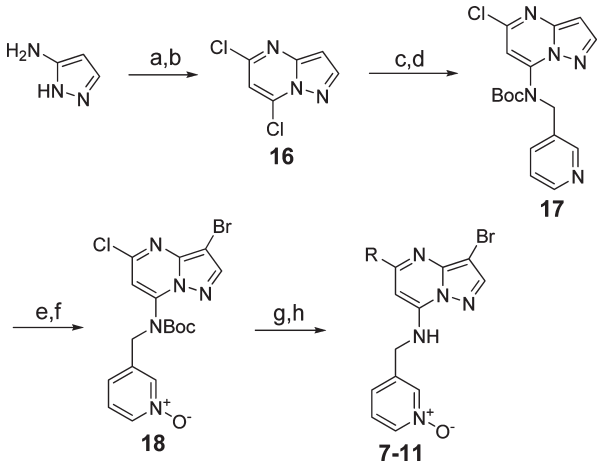
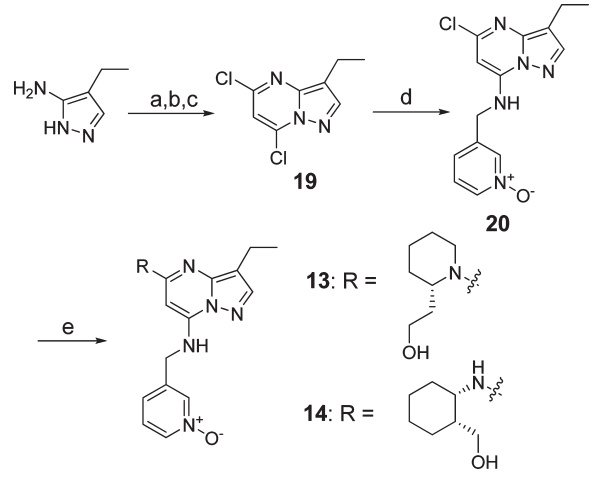
Scheme 1. Preparation of 3-Bromo Derivatives **7**−**11**[a]



[a] Reagents and conditions: (a) Na, EtOH, diethylmalonate, reflux. (b) $POCl_3$, dimethylaniline, 60 °C. (c) 3-Aminomethyl pyridine, DIPEA, dioxane. (d) Boc_2O, DMAP, CH_2Cl_2. (e) NBS, CH_3CN, 0 °C. (f) MCPBA, CH_2Cl_2. (g) HNR_1R_2, DIPEA, dioxane, 90 °C. (h) KOH, EtOH/H_2O, 100 °C.

Scheme 2. Preparation of 3-Ethyl Aminoalcohol Derivatives **13** and **14**[a]

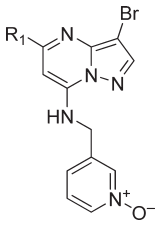


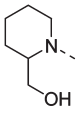
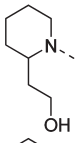
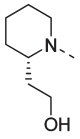
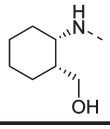
[a] Reagents and conditions: (a) Dimethylmalonate, reflux. (b) NaOMe, MeOH, reflux. (c) $POCl_3$, dimethylaniline, reflux. (d) 3-Aminomethyl pyridine *N*-oxide hydrochloride, $NaHCO_3$, CH_3CN, reflux. (e) HNR_1R_2, $NaHCO_3$, NMP, 150 °C.

vivo screening system to select candidate CDK inhibitors with the optimal combination of potency, pharmacokinetic, efficacy, and safety parameters are herein described. This functional approach allowed rapid differentiation within a discrete series of compounds as well as benchmarking against flavopiridol. Ultimately, this approach led to the identification of SCH 727965, which is currently in phase II clinical trials.

The utility of the pyrazolo[1,5-a]pyrimidine scaffold as a basis for the development of novel CDK inhibitors has previously been described.[25,26] From these efforts, compound **6** was identified as a novel CDK inhibitor, which

Table 1. Optimization in the 5-Position[a]



Compound	R_1	A/CDK2[a] IC_{50} (uM)	In-cell[b] IC_{50} (uM)
6		0.03	0.2
7		0.03	0.2
8		0.018	0.025
9		0.001	0.003
10		0.001	0.004
11		0.001	0.003

[a] Dose−response curves were generated from duplicate 8-point serial dilutions of inhibitory compounds. IC_{50} values were derived by nonlinear regression analysis. [b] Thymidine uptake growth inhibition assay in A2780 cells. Percentage inhibitions, relative to vehicle controls, were calculated and plotted on log−linear plots to allow derivation of IC_{50} values.[25,26]

was effective at reducing tumor burden in vivo upon oral delivery. In an effort to further expand the understanding of the impact of positional substitution on activity, structure−activity relationship development was expanded around each position in the pyrazolo[1,5-a]pyrimidine core.

The preparation of these novel pyrazolo[1,5-a]pyrimidine CDK inhibitors is outlined in Schemes 1 and 2. The synthesis of these analogues for the 3-bromo series began with treatment of 3-aminopyrazole with diethylmalonate under basic conditions followed by chlorination to afford **16**. Treatment with 3-aminomethylpyridine followed by Boc protection afforded intermediate **17**. Bromination with NBS followed by oxidation yielded **18**, which was treated with commercially available amines and deprotected under basic conditions to afford the

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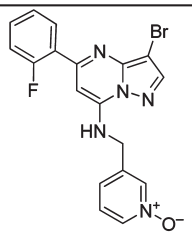
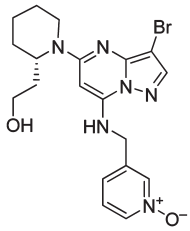
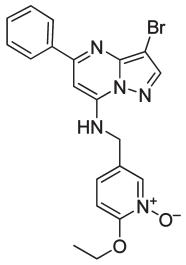
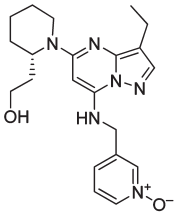
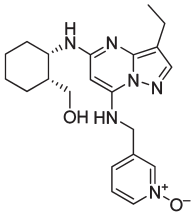
Table 2. Relative Therapeutic Indices from the in Vivo Screening Paradigm

Compound		A/CDK2 IC_{50}[a] (uM)	In-Cell IC_{50}[b] (uM)	MTD[c] (mg/kg)	MED[c] (mg/kg)	TI[c] (MTD/MED)
6		0.03	0.2	40 (po)	20 (po)	2
10		0.001	0.003	20	4	5
12		0.018	0.025	5	5	1
13		0.001	0.004	60	5	>10
14		0.001	0.003	<20	ND	ND
15	Flavopiridol	0.012	0.07	<10	10	<1

[a] Dose−response curves were generated from duplicate 8-point serial dilutions of inhibitory compounds. IC_{50} values were derived by nonlinear regression analysis. [b] Thymidine uptake growth inhibition assay in A2780 cells. Percentage inhibitions, relative to vehicle controls, were calculated and plotted on log−linear plots to allow derivation of IC_{50} values. [c] Relative therapeutic indices following intraperitoneal (IP) dosing using the in vivo screening paradigm (MTD = 20% weight loss; MED = 50% inhibition of tumor growth; and QDx7 = once a day dosing for 7 consecutive days).[25,26]

title compounds **7**−**11**. The corresponding 3-ethyl derivatives were prepared by cyclization of 3-amino-4-ethyl pyrazole with dimethylmalonate under basic conditions followed by chlorination, which afforded **19** (Scheme 2). Treatment of **19** with 3-(aminomethyl)pyridine *N*-oxide monohydrochloride under basic conditions yielded **20** followed by treatment with known amino alcohols, which afforded title compounds **13** and **14**. The preparation of **6** and **12** has been previously described.[26,27]

As illustrated in Table 1, a key observation made in the 3-bromo series was the marked improvement in potency by replacement of the aryl functionality at the 5-position of **6** with N-linked motifs bearing hydroxy substitution such as **8**. Furthermore, with correct positioning of this functionality, additional improvements in both kinase activity as well as inhibition of cell growth were observed in **9**−**11**.

The structural basis for these improvements in activity can be readily explained by interactions revealed in the X-ray crystal structure of this series of compounds bound to CDK2 and the CDK2/cyclin A complex.[28] A detailed description of these findings will be published in due course.

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Table 3. Exposure Parameters[a]

compd	AUC[b] (μM h)	C_{max}[c] (μM)
6	8	6
10	1.4	6
12	10	8
13	0.8	0.8
14	0.5	0.9
15	N/A	N/A

[a] Plasma samples from mice were collected at various times after intraperitoneal administration at 5 mg/kg and analyzed by liquid chromatography−tandem mass spectrometry. Pharmacokinetic variables were estimated from the plasma concentration data. [b] The area under the plasma concentration vs time curve (AUC) was calculated using the linear trapezoidal rule. [c] C_{max} values (maximum plasma concentration) were taken directly from the plasma concentration−time profiles.[26,29]

The initial goal of these efforts was to identify a novel inhibitor of CDK1 and CDK2. Because of the high degree of homology within the CDK family, inhibition of additional CDKs within this series of compound was also observed (data not shown). Thus, there exists a realistic likelihood that these small molecule inhibitors of the CDKs would exert their effects via compound-specific, combinatorial inhibition of multiple members of the family. This expected multitargeted nature of CDK inhibitors places a premium on maintaining an adequate therapeutic index in vivo. In this context, a critical issue in the development of CDK inhibitors is the relationship between desirable on-target effects and the onset of off-target tolerability issues that might adversely affect clinical dose escalation.

Ultimately, a screening system reminiscent of the historical standard paradigm for cytotoxic drug discovery, which evaluated the tolerability versus activity in vivo, was implemented. Simply, this in vivo system sought to establish the ratio of maximally tolerated and minimally effective doses in the A2780 ovarian carcinoma xenograft model. It was reasoned that through the application of this screening system, a compound could be identified that might give the best opportunity to achieve pharmacologically relevant doses clinically before the manifestation of toxicity. Hence, the maximally tolerated dose (MTD) was determined by intraperitoneal administration of compound to nude mice on a fixed, QDx7 schedule at varying dose levels. In these experiments, the MTD was defined as the dose on the QDx7 schedule required to reduce body weight by 20%. In parallel, the minimum effective doses (MEDs) were established on the same schedule. The MED was defined as the dose given QDx7 that was associated with >50% tumor growth inhibition. Pharmacokinetic parameters were also established to enable calibration of effects on the basis of systemic exposure. Thus, a series of compounds comprised of diverse structures, potency, and pharmacokinetic parameters were selected in an attempt to identify the optimal profile for a CDK inhibitor within this class of compound.

Through the application of this in vivo screen, clear trends emerged among compounds of diverse structures and ranges of potency (Table 2). Compound **12**, an analogue with improved in-cell activity relative to the previously described **6**, was found to have an MED of 5 mpk with an MTD of 5 mpk, giving a putative therapeutic index of 1. In contrast, the more highly potent compound **10** displayed a relative therapeutic index of 5. Interestingly, simple modification of substitution within this highly potent series of inhibitor induced significant differences in relative therapeutic indices. For example, incorporation of a 3-ethyl substituent as in **13** resulted in an improved overall profile relative to **10**. Conversely, the aminocyclohexyl methyl alcohol **14** gave a decreased tolerability profile relative to the piperidine ethanol derivative **13**. Notably, these compounds displayed no significant differences in pharmacokinetic profile (Table 3) or kinase cross-reactivity across a set of diverse kinases (data not shown). We also benchmarked flavopiridol **15**. The ratio of MTD to MED for flavopiridol was <1, indicating that in this screening system minimal antitumor efficacy was attained before the onset of toxicity. While ramifications of these findings are unknown, it is compelling to hypothesize that a compound such as **13** may have increased potential to achieve a more robustly active dose range prior to the manifestation of dose-limiting toxicities.

Several unexpected trends emerged from the utilization of this screening system. Namely, compounds with very high levels of potency tended to give improved therapeutic indices relative to those with lower affinity. Interestingly, these compounds displayed lower exposure and higher clearance rates relative to those with lower therapeutic indices. Taken together, short exposures to highly potent CDK inhibitors appear to induce long-lasting effects and have the potential to do so with improved tolerability. This stands in contrast to efforts in earlier stages of the program, which had been more focused on chronic exposure to induce continual CDK inhibition. Additionally, within this series of compounds, small changes in substitution had a large impact on overall activity and tolerability relationships that were not predictable from simple in vitro and pharmacokinetic profiling.

In summary, a series of pyrazolo[1, 5-*a*]pyrimidine CDK inhibitors, which display a range of potency and pharmacokinetic parameters, were identified. Utilizing a functional in vivo screen, compounds were readily differentiated on the basis of efficacy versus tolerability profiles even in those structures with remarkably similar substitution and in vitro and pharmacokinetic profiles. A key observation arising from the application of this approach was that highly potent, rapidly cleared CDK inhibitors appear to give an optimal balance between efficacy and tolerability. Within compounds of this profile, **13** was selected as a candidate CDK inhibitor suitable for progression. In-depth evaluation of the in vitro and in vivo properties further supported the conclusion that **13** had the appropriate qualities for a development candidate.[29] Compound **13** (SCH 727965) is currently undergoing phase II clinical trials.

SUPPORTING INFORMATION AVAILABLE

Experimental procedures and characterization data for **6**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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