Design, Synthesis, and Biological Activity of 5,10-Dihydro-dibenzo[*b,e*][1,4]diazepin-11-one-Based Potent and Selective Chk-1 Inhibitors

Le Wang,* Gerard M. Sullivan, Laura A. Hexamer, Lisa A. Hasvold, Reema Thalji,† Magdalena Przytulinska, Zhi-Fu Tao, Gaoquan Li, Zehan Chen, Zhan Xiao, Wen-Zhen Gu, John Xue, Mai-Ha Bui, Philip Merta, Peter Kovar, Jennifer J. Bouska, Haiying Zhang, Chang Park, Kent D. Stewart, Hing L. Sham, Thomas J. Sowin, Saul H. Rosenberg, and Nan-Horng Lin

R47B, Cancer Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, Illinois 60064

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A novel series of 5,10-dihydro-dibenzo[*b,e*][1,4]diazepin-11-ones have been synthesized as potent and selective checkpoint kinase 1 (Chk1) inhibitors via structure-based design. Aided by protein X-ray crystallography, medicinal chemistry efforts led to the identification of compound **46d**, with potent enzymatic activity against Chk1 kinase. While maintaining a low cytotoxicity of its own, compound **46d** exhibited a strong ability to abrogate G2 arrest and increased the cytotoxicity of camptothecin by 19-fold against SW620 cells. Pharmacokinetic studies revealed that it had a moderate bioavailabilty of 20% in mice. Two important binding interactions between compound **46b** and Chk1 kinase, revealed by X-ray cocrystal structure, were hydrogen bonds between the hinge region and the amide bond of the core structure and a hydrogen bond between the methoxy group and Lys38 of the protein.

Introduction

Checkpoint kinase 1 (Chk1) is a serine/threonine kinase that is closely involved in the regulation of the cell cycle.[1] Upon damage by either DNA damaging agents or ionic irradiation, two major weapons for current cancer treatment, Chk1 is activated via activation of the upstream ATM/ATR[a] pathway.[2] Activation of Chk1 results in phosphorylation of Cdc25A at Ser123 and several other serine residues and Cdc25C at Ser216. The phosphorylation of Cdc25 thus inhibits dephosphorylation and activation of cyclin-dependent kinases (CDKs) via the ubiquitin-proteosome pathway, arresting DNA-damaged cells at various checkpoints so that the cells' repair mechanism can be carried out to avoid mitotic catastrophe.[3] While normal cells can depend on G1 checkpoint arrest to repair their damaged DNA,[4] cancer cells with p53 deficiency can only use the S and G2 checkpoints for DNA repair.[5] It is rationalized that the inhibition of Chk1 would abrogate the S/M or the G2/M checkpoint so that cancer cells would enter mitosis/chromosome condensation prematurely with damaged DNA, eventually leading to cell death.[6] Chk1 knock-down experiments, either with Chk1 antisense or siRNA, revealed a significant enhancement of cytotoxicity of chemotherapeutics against p53-deficient cancer cell lines.[7] Thus, Chk1 inhibitors may be useful in cancer therapy as sensitizing agents.[8]

Several natural products are found to be potent Chk1 inhibitors, such as indolocarbazole analogues,[9] isogranulatimide,[10] debromohymenialdisine,[11] and 7-hydroxystaurosporine (UCN-01), which is reported to be in phase II clinical trials.[12] Synthetic Chk1 inhibitors with various core structures have also been reported in literature and in patent applications. For example, PF-00394691, bearing diazepinoindolone as the core, showed potent enzymatic activity against Chk1, with a K_i of 0.34 nM.[13] It also potentiated antitumor activity of irinotecan in Colo205 mouse xenograft. CHIR-124 is a benzoimidazole-quinolinone based Chk1 inhibitor with potent activity against the Chk1 enzyme (IC_{50} = 0.3 nM).[14] A patent application filed by Millennium disclosed pyrazole-based tricyclic Chk1 inhibitors.[15] A series of *N*-aryl-*N*′-pyrazinylurea-based Chk1 inhibitors have been disclosed recently through patent applications and publications.[16]

Human Chk1 is a nuclear protein of 476 amino acids. It contains a highly conserved N-terminal kinase domain (residues 1−265), a flexible linker region, and a less-conserved C-terminal region that may negatively regulate Chk1 kinase activity. The crystal structures of the human Chk1 kinase domain and its complexes with AMP-PNP, an ATP analogue, staurosporine, UCN-01, and SB-218078 have been solved.[17] It appears that the active binding site of Chk1 can be roughly divided into four regions. The highly conserved kinase hinge region consists of Cys87 and Glu85. Tyr20, Lys38, Glu55, and Asp148 are the major components of the polar region. There is also a ribose pocket made of hydrophilic amino acids, such as Glu91, Glu134, and Asn135. A solvent-exposed region is located only a few amino acids away from the hinge region. Thus, a solid foundation for structure-based inhibitor design has been laid out.

8-Chloro-5,10-dihydro-dibenzo[*b,e*][1,4]diazepin-11-one, compound **1a** (A-45444; Chart 1), was identified to be weakly active against human Chk1 kinase during a high-throughput screen. The co-X-ray structure of Chk1 kinase and compound **1a** revealed several important binding characteristics. The amide bond of compound **1a** formed two hydrogen bonds with the carbonyl and NH of Cys87 in the hinge region. The chlorine pointed to the solvent front and did not appear to have any interaction with the binding pocket. There was also a large space between the right-hand side phenyl ring with the carbonyl group and the polar region in the binding site. We felt that compound

* To whom correspondence should be addressed. Phone: (847) 935-4952. Fax: (847) 935-5165. E-mail: le.wang@abbott.com.

† Summer student from the Department of Chemistry at U.C., Berkeley. Current address: GlaxoSmithKline Co. in Philadelphia.

[a] Abbreviations: AMP-PNP, adenyl-5′-yl imidodiphosphate; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3 related; CPT, camptothecin; DCI, direct chemical ionization, dppf, 1,1′-bis(diphenylphosphino)ferrocene; DTT, dithiothreitol; EDTA, ethylenediaminetetraacetic acid; FACS, fluorescence-activated cell sorting; HATU, *O*-(7-azabenzotrizol-1-yl)-*N*,*N*,*N*′,*N*′ tetramethyluronium hexalfluorophosphate; HEPES, *N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid; HTRF, homogeneous time-resolved fluorescence; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium; RNase, ribonuclease; SEMCl, 2-(trimethylsilyl)ethoxymethyl chloride; siRNA, small interfering ribonucleic acid; $TMSCHN_2$, (trimethylsilyl)diazomethane.

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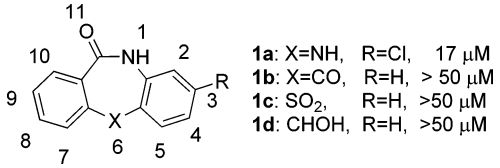
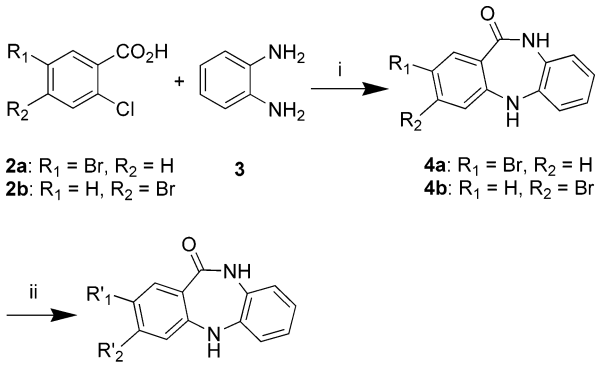
Chart 1



1a: X=NH, R=Cl, 17 μM
1b: X=CO, R=H, > 50 μM
1c: SO_2, R=H, >50 μM
1d: CHOH, R=H, >50 μM

Scheme 1[a]

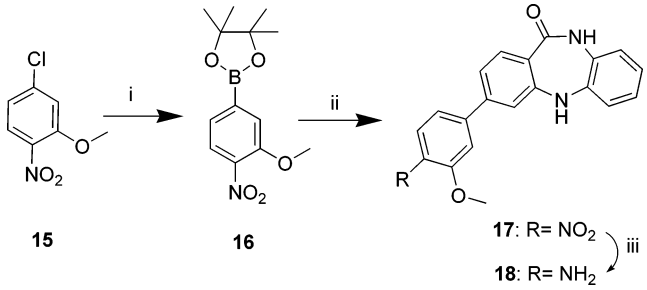


2a: R_1 = Br, R_2 = H
2b: R_1 = H, R_2 = Br
3
4a: R_1 = Br, R_2 = H
4b: R_1 = H, R_2 = Br

5-14: R'_1 = H, R'_2 = various phenyl groups
25: R'_1 = 4-OH-3-OMe-phenyl, R'_2 = H

[a] Reagents and conditions: (i) Cu, PhCl, reflux; (ii) MeOH/DME (1:2), CsF, $Pd(PPh_3)_4$, $ArB(OH)_2$, reflux.

Scheme 2[a]



15 **16**
17: R= NO_2
18: R= NH_2
iii

[a] Reagents and conditions: (i) Bis(pinacolato)diboron, $Pd_2(dba)_3$, CyMap, KOAc, dioxane, 85 °C; (ii) MeOH/DME (1:2), $Pd(PPh_3)_4$, **4b**, CsF; (iii) Pd/C, H_2, MeOH.

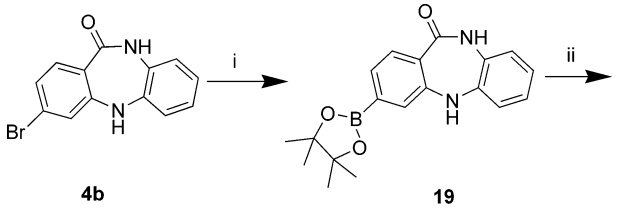
1a was a good starting point for our Chk1 program in that it was structurally simple and had interesting binding characteristics with the Chk1 enzyme. Furthermore, despite the fact that 5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one has been known for a long time, it was never used as a temple for a kinase inhibitor. In this paper, we wish to report the synthesis, SAR study, and pharmacokinetic evaluation of a series of Chk1 inhibitors based on 5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one. Through the X-ray cocrystal structures, the binding modes of several potent Chk1 inhibitors will be discussed as well.

Chemistry

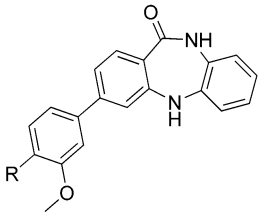
The synthesis of compounds **5**−**14** and **25** is illustrated in Scheme 1. Thus, compounds **4a**,**b** were obtained in modest yields by heating compounds **2a** or **2b** with compound **3** in chlorobenzene in the presence of copper.[18] The Suzuki coupling of **4a** and **4b** with various phenyl boronic acids yielded the desired compounds **5**−**14** and **25**.

Scheme 2 depicts the synthesis of compounds **17** and **18**. Compound **16**, a key intermediate made from **15** using palladium-mediated borylation,[19] was coupled with compound **4b** to give compound **17**, which was then reduced by hydrogenation to afford compound **18**. Alternatively, the pinacol arylboronate

Scheme 3[a]



4b **19**



20: R = CN
21: R = Cl
22: R= $COCH_3$
23: R = CO_2CH_3
24: R = $CONH_2$

[a] Reagents and conditions: (i) Bis(pinacolato)diboron, $Pd_2(dba)_3$, PCy_3, KOAc, dioxane, 85 °C; (ii) ArBr, $Pd(PPh_3)_4$, CsF, MeOH/DME (1:2).

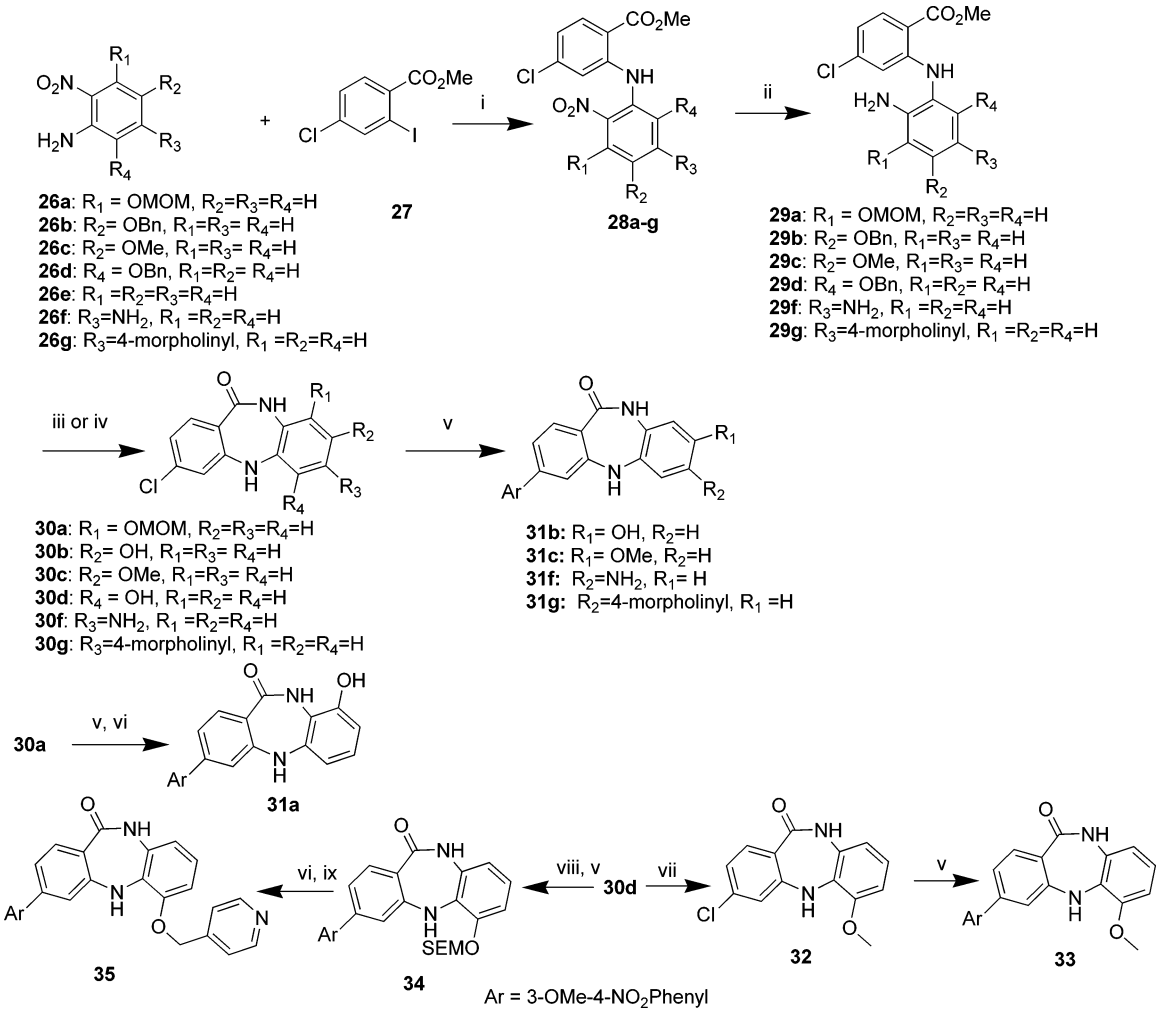
19, synthesized in a similar manner to that of compound **16**, was coupled with various aryl bromides to give compounds **20**−**24**, as shown in Scheme 3.

The synthesis of compounds **31a**−**c**, **31f**,**g**, **33**, and **35** proceeded as shown in Scheme 4. An Ullmann-type aryl amination between nitroaniline **26** and methyl 4-chloro-2-iodobenzoate in the presence of copper and K_2CO_3 resulted in formation of diaryl amine **28** in good to excellent yields. The nitro group of compound **28** were reduced by hydrogenation using platinum on carbon to provide diamines **29**, which were cyclized under acidic conditions in refluxing toluene to form compounds **30**. During the cyclization, the benzyl ethers were cleaved to give the corresponding phenols (**30b** and **30d**). Alternatively, diamines **29a** and **29f**,**g** were hydrolyzed and cyclized in the presence of HATU to give compounds **30a** and **30f**,**g**, respectively. The Suzuki coupling of compounds **30** with pinacol arylboronate **16** afforded compounds **31b**,**c** and **31f**,**g**. Treatment of the Suzuki coupling product from **30a** and **16** with HCl in MeOH and THF resulted in compound **31a**. The phenol **30d** was allowed to react with MeI in acetone to give compound **32**, which was coupled with **16** to afford compound **33**. The hydroxyl group of **30** was protected with SEMCl and then reacted with **16** to give compound **34**. Deprotection followed by alkylation with 4-chloromethylpyridine yielded compound **35**.

Scheme 5 details the formation of compounds **39** and **41**. The amino group para to the nitro group of **36** reacted with compound **27** exclusively in the presence of K_2CO_3 and copper. It seemed that the base, K_2CO_3, did not just function to neutralize HI, since without it, a mixture was generated. Reduction followed by acid-catalyzed cyclization resulted in compound **37**. Compound **38**, obtained from the Suzuki reaction of compounds **37** and **16**, was allowed to react with 3-chloropropanesulfonyl chloride in pyridine to provide the corresponding sulfonamide, which was cyclized upon treatment of sodium ethoxide in ethanol to yield **39**. Reaction of compound **37** with 4-chlorobutanoyl chloride in pyridine followed by treatment of sodium ethoxide in ethanol resulted in compound **40**. Compound **41** was prepared by the Suzuki coupling of **40** and **16**.

Compounds **46a**−**h** were prepared as shown in Scheme 6. Nitroanilines **42** were coupled with compound **27** using a palladium-mediated diaryl amine formation protocol to give compounds **43** in excellent yields. It appeared that the reaction temperature was critical for a clean transformation in that the chlorine became quite reactive at higher temperatures, leading

Scheme 4[a]



[a] Reagents and conditions: (i) Cu, K_2CO_3, PhCl, reflux; (ii) Pt/C, H_2, MeOH; (iii) (a) LiOH, THF, H_2O; (b) H_3O^+; (c) HATU, Et_3N, DMF, for **29a**, **29f**, and **29g**; (iv) p-TsOH·H_2O, $PhCH_3$, Dean−Stark trap, for **29b**, **29c**, and **29d**; (v) $Pd(OAc)_2$, Cy-Map, MeOH/DME (1:2), CsF, **16**; (vi) HCl, THF, MeOH; (vii) K_2CO_3, acetone, MeI; (viii) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, MeCN; (ix) K_2CO_3, DMF, 4-chloromethylpyridine.

to the formation of several byproducts. Hydrogenation of **43** followed by acid-catalyzed cyclization in refluxing toluene led to formation of compounds **44**. Further modifications such as Suzuki coupling and amide formation gave final compounds **46a**−**h**.

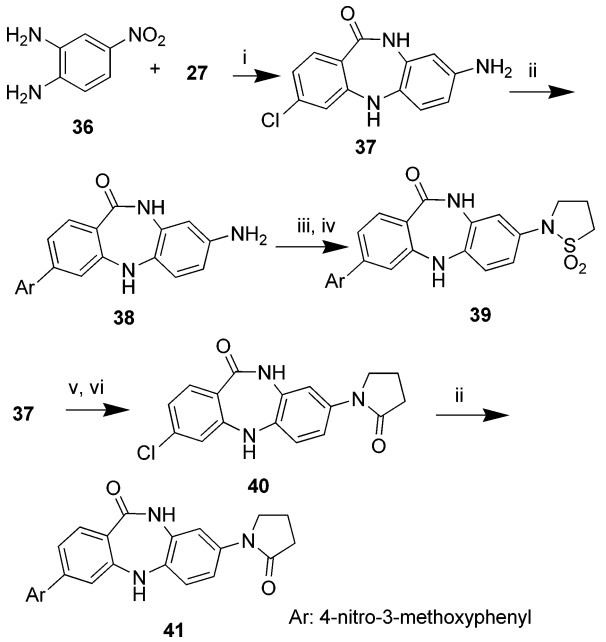
Schemes 7 and 8 describe the synthesis of two close analogues of 5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one. *N*-Methylation of compound **28e** gave compound **47**. Preparation of compound **49** was conducted in a similar manner to that of compound **31c**. Acid **50** was sequentially treated with $SOCl_2$ and $TMSCHN_2$ to form a diazo ketone, which underwent a Wolff rearrangement in the presence of silver benzoate and triethylamine in MeOH to give the homologized methyl ester **51**. Displacement of the fluorine of **51** with methyl 4-chloro-2-hydroxyl-benzoate led to the formation of biaryl ether **52**. Compound **54** was synthesized in a similar manner to that of compound **45a**.

Results and Discussion

Position 8 of the compound **1a** was explored first because the X-ray cocrystal structure with the active site of the Chk1 enzyme had shown a large space between this position and the polar region of the active site. The results are summarized in Table 1. It appeared that substitution at the *meta*-position of the benzene ring was important for the enzymatic activity, as demonstrated by compounds **6**−**14**. Replacement of the methoxy group with a slightly larger ethoxy group caused more than a 20-fold loss in activity, as shown by compounds **7** and **8**, suggesting that the space around the methoxy group was limited. It was somewhat gratifying to see that the introduction of a hydroxyl group next to the methoxy group gave rise to compound **14** with a 6-fold increase in the enzymatic activity compared to compound **7**. Encouraged by this result, a number of functional groups were investigated (compounds **17**−**24**). It appeared that electron-withdrawing groups were important for the activity. Compound **17**, bearing a strong electron-withdrawing nitro group next to the methoxy, showed the most potent activity against the Chk1 enzyme. Introduction of an amine group rendered compound **18** completely inactive. Not surprisingly, because position 9 of **1a** had been shown to point away from the polar region, compound **25**, a regioisomer of **14**, did not exhibit any enzymatic activity.

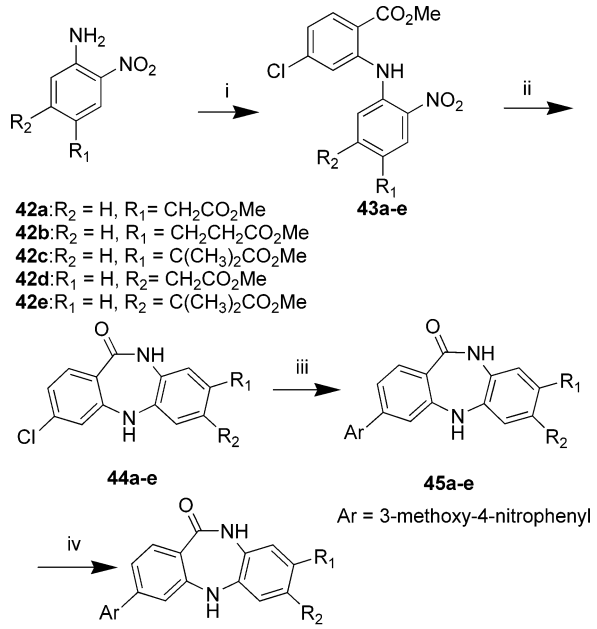
Once we identified the best substituent, 3-methyl-4-nitrophenyl, for the polar region of the active binding site of the Chk1 enzyme, we moved our attention to the other phenyl ring, pointing to the solvent-exposed region according to the X-ray cocrystal structure. The results are listed in Table 2. It was clear that the space around R_1 was rather limited because even a small hydroxyl group caused a significant loss in enzymatic activity, as shown by compounds **17** and **31a**. Because the amide bond

Scheme 5[a]



[a] Reagents and conditions: (i) (a) Cu, K_2CO_3, PhCl, reflux; (b) Pt/C, H_2, MeOH; (c) p-TsOH·H_2O, $PhCH_3$, Dean-Stark trap; (ii) $Pd(OAc)_2$, Cy-Map, MeOH/DME (1:2), CsF, **16**; (iii) 3-chloropropyl sulfonyl chloride, pyridine; (iv) NaOEt, EtOH, reflux; (v) 4-chlorobutanoyl chloride, pyridine; (vi) NaOEt, EtOH, rt, overnight.

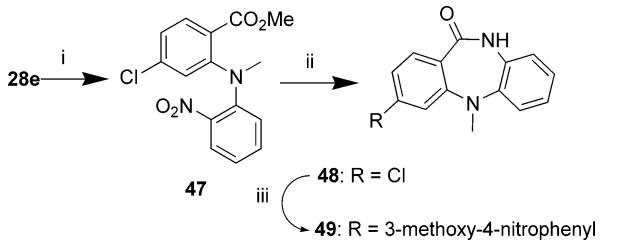
Scheme 6[a]



[a] Reagents and conditions: (i) **27**, $Pd(OAc)_2$, dppf, Cs_2CO_3, $PhCH_3$, 95 °C; (ii) (a) Pt/C, H_2, MeOH; (b) $PhCH_3$, p-TsOH·H_2O, Dean−Stark trap; (iii) $Pd(OAc)_2$, Cy-Map, MeOH/DME (1:2), CsF, **16**; (iv) (a) LiOH, MeOH/H_2O; (b) HCl; (c) HATU, Et_3N, DMF, amines.

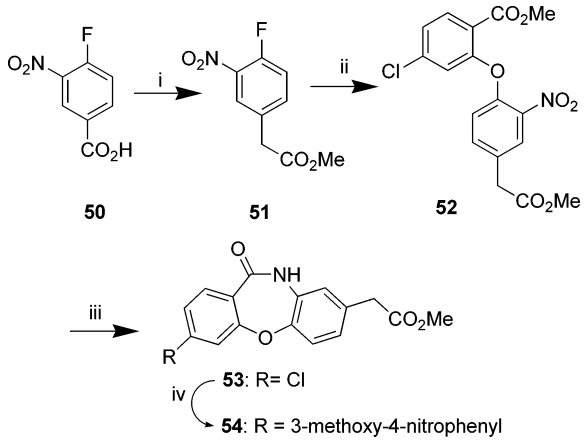
of the core forms two hydrogen bonds with the hinge binding site, the steric bulk of a substituent next to the NH of the amide bond is detrimental to that interaction, resulting in a great loss in activity. Position 5 was able to tolerate some small groups,

Scheme 7[a]



[a] Reagents and conditions: (i) MeI, NaH, DMF; (ii) (a) Pt/C, H_2, MeOH; (b) p-TsOH·H_2O, $PhCH_3$, Dean−Stark trap; (iii) $Pd(OAc)_2$, Cy-Map, MeOH/DME (1:2), CsF, **16**.

Scheme 8[a]

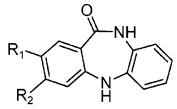


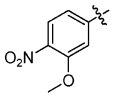
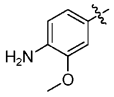
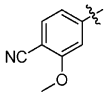
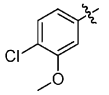
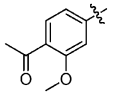
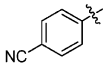
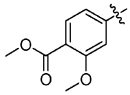
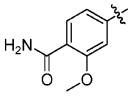
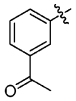
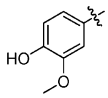
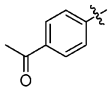
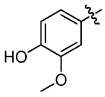
[a] Reagents and conditions: (i) (a) $SOCl_2$; (b) $TMSCHN_2$; (c) silver benzoate, Et_3N, MeOH; (ii) K_2CO_3, DMA, methyl 4-chloro-2-hydroxylbenzoate, 80 °C; (iii) (a) Pt/C, H_2, MeOH; (b) p-TsOH·H_2O, $PhCH_3$, Dean−Stark trap; (iv) $Pd(OAc)_2$, Cy-Map, MeOH/DME (1:2), CsF, **16**.

such as a methoxy, without a significant loss in activity, as demonstrated by compounds **33**. However, a larger group at position 5 caused a 10-fold drop in activity as shown by compounds **17** and **35**. In contrast to the limited tolerability at positions 2 and 5, a wide variety of functional groups were accommodated at both position 3 and position 4. It seemed that a five-membered ring lactam or sultam conferred better activity relative to the amino group at position 2, as suggested by compounds **38**, **39**, and **41**. A slightly more potent compound **45a** was obtained when position 3 was occupied by a methyl acetate compared to compound **17**. Change of the ester to amides did not affect the enzymatic activity regardless of their sizes, as suggested by compounds **46b** and **46c**. Compound **46e**, a homolog of **46b**, exhibited slightly better potency. The center NH functionality was very important for the activity. Even small changes, such as replacement of the NH group with either a NCH_3 or an oxygen atom, resulted in a dramatic loss in activity. This was likely caused by a change in the dihedral angle of the two phenyl rings when X was either NCH_3 or an oxygen atom.

The cellular activities of potent Chk1 inhibitors were evaluated in two routine assays. An MTS assay was used to determine the antiproliferative EC_{50} of compounds against HeLa cells both alone and with doxorubicin (at 150 nM), a topoisomerase II inhibitor known to induce G2/M checkpoint arrest. An ideal Chk1 inhibitor should not have any toxicity by itself. However, when it is utilized with DNA-damaging agents, such as doxorubicin, it should show high antiproliferative activity. A FACS analysis was also performed to monitor Chk1 specific and nonspecific cellular activities of potent inhibitors. In this assay, H1299 cells were treated with 0.5 to 10 μM of a Chk1 inhibitor in the presence or absence of 500 nM doxorubicin. A

Table 1. Structure−Activity Relationship for the Polar Region[a]

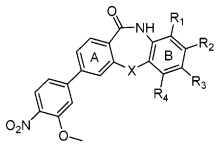


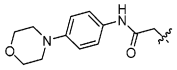
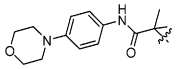
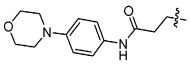
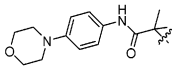
No.	R_1	R_2	IC_{50} (μM)	No.	R_1	R_2	IC_{50} (μM)
5	H		>10	**17**	H		0.010
6	H		3.6	**18**	H		>10
7	H		0.50	**20**	H		0.033
8	H		>10	**21**	H		0.091
9	H		0.97	**22**	H		0.048
10	H		>10	**23**	H		0.053
11	H		8.0	**24**	H		0.088
12	H		2.1	**25**		H	>10
13	H		>10				
14	H		0.082 (2)				

[a] IC_{50} value was calculated from 11 concentrations. All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses. The assay's reproducibility was within ±50%.

specific Chk1 inhibitor was expected not to alter cell distributions at all doses as a single agent. In the presence of doxorubicin, a Chk1 inhibitor was expected to abrogate G2/M arrest induced by doxorubicin in a dose-dependent manner. Therefore, cell population in G2/M phase would decrease after the treatment of Chk-1 inhibitor, while the cell populations in other phases, such as apotosis, G1, and S, would increase substantially (see Figure 1 in the Supporting Information). The results are detailed in Table 3. Although compound **41** showed a reasonable combination activity in the MTS assay, its ability to abrogate G2 arrest was quite weak, as suggested in the FACS analysis. Compound **39** showed a potent combination activity. However, it also had significant toxicity as a single agent. Compound **45a** exhibited an interesting property: potent single agent, but weaker combination activity. Change from an *N*,*N*-dimethyl amide to a 4-morpholinyl phenyl amide removed the single agent activity, as shown by compounds **46b** and **46c**. Installation of a gem-dimethyl functionality gave rise to compound **46d** with a significantly increased combination activity while maintaining its low single agent activity. Compound **46d** also exhibited a better capability of abrogating G2 arrest relative to compound **46c** as demonstrated in the FACS analysis. Compound **46e** showed the most potent abrogating ability. However, closer examination revealed that it caused significant alteration of cell distribution as a single agent just above 10 μM. This made compound **46e** much less desirable. A homolog of compound **46c**, compound **46f**, did not show any improvement. Compound **31f** showed good cellular activities both in the MTS assay and the FACS analysis. However, replacement of the NH_2 group with a morpholinyl group resulted in compound **31g** with significant non-Chk1 toxicity as suggested by the FACS analysis. It is worthwhile to point out that compound **46h**, a regioisomer of compound **46d**, had weaker cellular activities even though their enzymatic activities were

Table 2. Structure−Activity Relationship for the B-Ring[a]



No.	X	R_1	R_2	R_3	R_4	IC_{50} (μM)	No.	X	R_1	R_2	R_3	R_4	IC_{50} (μM)
31a	NH	OH	H	H	H	0.072 (2)	**46b**	NH	H		H	H	0.006
31b	NH	H	OH	H	H	0.011	**46c**	NH	H		H	H	0.007
31c	NH	H	OCH_3	H	H	0.014	**46d**	NH	H		H	H	0.0067 (3)
33	NH	H	H	H	OCH_3	0.016 (2)	**46e**	NH	H		H	H	0.002
35	NH	H	H	H		0.104	**46f**	NH	H		H	H	0.010 (2)
38	NH	H	NH_2	H	H	0.017	**46g**	NH	H	H		H	0.006
39	NH	H		H	H	0.002	**46h**	NH	H	H		H	0.010
41	NH	H		H	H	0.004	**49**	NCH_3	H	H	H	H	1.64
31f	NH	H	H	NH_2	H	0.006	**54**	O	H		H	H	0.91
31g	NH	H	H		H	0.004 (3)							
45a	NH	H		H	H	0.003 (2)							

[a] IC_{50} value was calculated from eleven concentrations. All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses. The assay's reproducibility was generally within ± 50%.

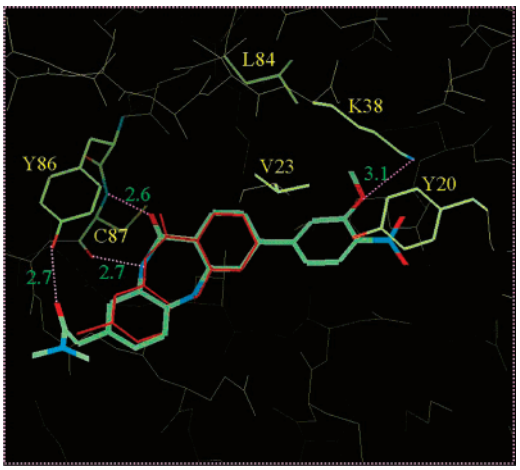
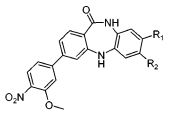


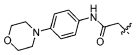
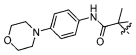
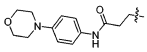
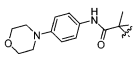
Figure 1. X-ray cocrystal structures of **1a** (red) and **46b** (green) bound to Chk-1 active site.

comparable. When FACS analysis was run with camptothecin (CPT) instead of doxorubicin, compound **46d** also showed potent ability to abrogate S phase arrest induced by CPT (see Figure 2 in the Supporting Information).

Several potent Chk1 inhibitors were further evaluated using a potentiation MTS assay in which the antiproliferative EC_{50}'s of a DNA-damaging agent, CPT, were measured in the presence of a fixed concentration of Chk1 inhibitor against SW620 cells. The results are listed in Table 4. It was clear that compound **46d** was the best for potentiating CPT compared to the others. The EC_{50} of CPT against SW620 was around 381 nM. In the presence of 3 μM and 10 μM of compound **46d**, the EC_{50}'s of CPT were measured to be 42 nM and 20 nM, a 12- and 19-fold increase, respectively. The potentiation of SW620 cells to CPT by compound **46d** was confirmed by a soft agar colony growth assay that was believed to be the best in vitro cell-based system for predicting in vivo activity. Compound **46d** itself did not show any inhibition of colony growth at concentrations up to 10 μM. In the presence of 10 μM of compound **46d** in the soft agar, the SW620 cells became much more sensitive to CPT. The EC_{50} of CPT itself was measured to be 1.75 nM. In the presence of 10 μM of compound **46d**, the EC_{50} decreased to 0.224 nM, suggesting a 9-fold potentiation. Even at a lower concentration of compound **46d** (3 μM), a 6.5-fold potentiation was also observed in this assay format (see Figure 3 in the Supporting Information).

Table 3. Cellular Activity of Potent Chk1 Inhibitors[a]



No.	R_1	R_2	IC_{50} (μM)	MTS (EC_{50}) (μM)		FACS (EC_{50}) (μM)	
				Single	Combo	Single	Combo
31b	OH	H	0.011	>59.3	37.3	Nd[b]	
31c	OCH_3	H	0.014	>59.3	21.7	>10	6.7
39		H	0.002	9.0	0.76 (2)	>10	3.43
41		H	0.004	49.5	2.2	>10	8.2
45a		H	0.003 (2)	0.89	2.1	Nd	
46b		H	0.006	2.63	0.92 (2)	Nd	
46c		H	0.007	>59.3	3.4 (2)	>10	3.0
46d		H	0.0067 (2)	>59.3	0.54 (10)	>10	0.48 (3)
46e		H	0.002	51.9	0.43 (25)	>10	0.11 (3)
46f		H	0.010 (2)	>59.3	2.34 (3)	>10	2.2
31f	H	NH_2	0.006	49.9	1.08 (3)	>10	0.75
31g	H		0.004 (3)	46.1 (3)	0.67 (3)	2.1	0.37
46g	H		0.006	32.5 (2)	1.4 5 (2)	>10	3.76
46h	H		0.010	>59.3	1.1	>10	0.39

[a] Each EC_{50} value for MTS was performed with 16 concentrations, and each assay point was determined in duplicate. Each EC_{50} value for FACS analysis was performed with six concentrations, and each assay point was determined once. All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses. Reproducibility for both MTS and FACS assays was generally within ±50%. [b] Not determined.

The selectivity profiles of compounds **46c** and **46d** were evaluated against a panel of Ser/Thr kinases in the radiometric assay using 5 μM ATP. The results are summarized in Table 5. Compound **46c** was rather weak against the kinases screened, except Akt1, which still showed a selectivity of more than 100-fold. Compound **46d** was essentially inactive against all the kinases tested. This high degree of selectivity may be one of the reasons that contributed to its superior potentiating capability and low single agent toxicity.

The pharmacokinetic study of several potent Chk1 inhibitors was conducted in mice. The results are listed in Table 6. When dosed intraperitoneally, compound **46d** exhibited a good drug concentration in blood as suggested by an AUC of 14.9. It also showed a reasonable absorption when dosed orally with a 20% bioavailability. Compounds **46e** and **46f** did not have a good AUC when dosed intraperitoneally. It is interesting to note that poor oral absorption was observed when the 4-morpholinyl phenyl amide moiety was moved from position 3 to position 4, as shown by compounds **46h** and **46d**.

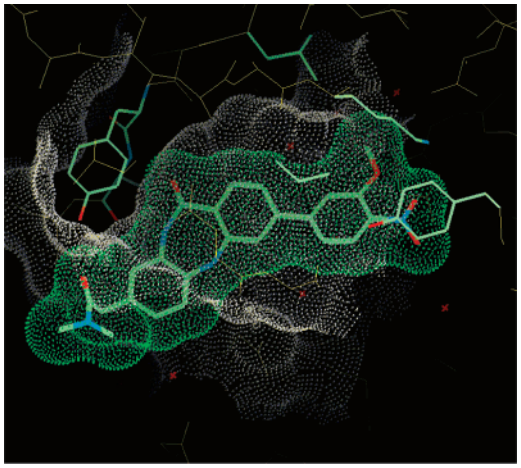


Figure 2. X-ray cocrystal structure around Chk-1 active site with the surface of the protein and **46b**.

Table 4. Potentiation Assay for Potent Chk1 Inhibitors[a]

	potentiation ratio (3 μM)	potentiation ratio (10 μM)
46d	12 (3)	19 (3)
46e	11	9.7
46f	6	6.8
46h	11	13
31d	7	8

[a] All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses.

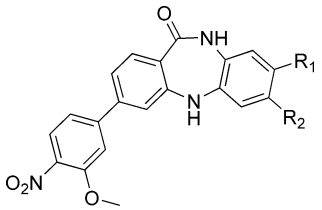
Table 5. Selectivity Profiles of Compounds **46c** and **46d**[a]

		IC_{50} (μM)	
		46c	**46d**
serine/threonine kinase panel	AMPK	>50	>10
	Aur2	8.62	>50
	cTAK	3.65	>10
	Emk	13.86	>10
	Chk2	13.45	>50
	Akt1	0.88	>10
	CDC2	>50	>10
	CK2	Nd	>10
	ERK2	5.0	>10
	Gsk3b	Nd	>10
	Ikkb	Nd	5.8
	MAPKAPKA	Nd	>10
	PKA	>50	>10
	PKCδ	>50	>10
	PKCγ	>50	>10
	Plk1	Nd	>10
	Rsk2	Nd	>10
	SGK	>50	>10
tyrosine kinase panel	SRC	>50	>10
	cKit	31.8	>10
	CSF1R	Nd	>10
	Flt1	>50	>10
	Flt3	>50	>10
	Kdr	>50	>10
	FGFR1	>50	>10
	EGFR	Nd	>10
	PDGFR	Nd	>10

[a] Both compounds were assayed once. The assay's reproducibility was within ±50%.

X-ray Crystallography. A number of potent Chk1 inhibitors were soaked into the native Chk1 crystals and their complex structures were determined by X-ray crystallography. Figure 1

Table 6. Pharmacokinetic Properties of Selected Chk1 Inhibitors[a]



	IP	IV				PO			
No.	AUC (μmol·hr/L)	AUC (μmol·hr/L)	Cl (L/hr/kg)	V_d (L/kg)	$t_{1/2}$ (h)	AUC (μmol·hr/L)	C_{max} (μM)	T_{max} (h)	F (%)
46d	14.9	3.4	1.45	3.40	1.6	2.2	0.39	2.0	20
46e	3.9				Nt[b]				
46f	2.8				Nt[b]				
31g	18.8				Nt[b]				
46h	7.5	2.4	2.0	5.0	1.7	0.16	0.09	0.67	2

[a] At least two animals were used for each dosing group. The dose for the oral and IP groups were 10 mg/kg. The dose for the IV group was 3 mg/kg; the parameters reported here were the averages of the animals. [b] Not tested.

shows the complex structures of Chk1 compound **1** and **46b**. Figure 2 shows compound **46b** in the Chk1 active binding site, with boundaries of the protein and compound **46b**. As expected, the amide bond of the 5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one formed two hydrogen bonds, with the backbone protein in the hinge region. Specifically, one hydrogen bond formed between the NH of the amide bond and the carbonyl group of Cys87 with a distance of 2.66 Å. The other was between the carbonyl group of the amide and NH of Cys87 with a distance of 2.54 Å. This hinge binding pattern was different from that of *N*-aryl-*N*′-heterocycle urea-based Chk1 inhibitors. The carbonyl of the amide bond of the urea formed a hydrogen bond with the NH of Cys87, while the NH of the amide bond formed a hydrogen bond with the carbonyl of Glu85.[20] The same hinge binding properties were also observed in a series of 3-ethylidene-1,3-dihydro-indol-2-one-based Chk1 inhibitors.[21] The 3-methoxy group played an important role in conferring the activity. The oxygen of the methoxy hydrogen-bonded strongly with NH_3^+ of Lys38 in the polar region with a distance of 3.08 Å. The methyl of the methoxy was in the vicinity of Leu84 with a distance of 3.99 Å, suggesting a perfect van der Waals contact. This may explain why even a slightly larger ethoxy could not be tolerated at this position. The role of the nitro group in the binding pocket was not entirely clear. It may have a π-electron stacking interaction with the phenyl ring of Tyr20 in the polar region because the distance between one of the oxygen atoms of the nitro group and the phenyl was around 3.6 Å. It may also exert activity via its strong electron-withdrawing ability because Val23 was directly over the 3-methoxy-4-nitrophenyl moiety with a distance of about 3.95 Å.

The nonamide NH of 5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one did not appear to have any direct interaction with the protein. However, it was essential for the activity in that it provided a perfect dihedral angle between the aryl rings. Because this type of molecule is rather rigid, a small change to that dihedral angle would cause a substantial alteration to the part of the molecule that interacted with the polar region, leading to a significant loss in activity, as demonstrated by compounds **49** and **54**.

N,*N*-Dimethyl acetamide of compound **46b** pointed to the solvent-exposed region. It is worthwhile to point out that, although there was a strong hydrogen bond observed between the carbonyl of the acetamide and the hydroxyl group of Tyr86, as the distance of 2.68 Å suggested, compound **46b** was only slightly more potent than compound **17**. The X-ray structure of Chk1 complexed with compound **46d** was also solved. Both compound **46b** and compound **46d** shared the same binding characteristics except for the 4-morpholinyl phenyl amide moiety. Its electron density could not be detected in the X-ray cocrystal structure, suggesting that it did not have any solid interaction with the protein and moved around in the solvent-exposed region.

Conclusion

A novel series of 5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one-based Chk1 inhibitors have been identified. Aided by X-ray cocrystal structures, the medicinal chemistry efforts led to the discovery of a number of potent and selective Chk1 inhibitors. Specifically, compound **46d** was shown to have the best cellular profiles. It did not possess any single-agent toxicity, yet it increased the activity of CPT by 19-fold in a potentiation MTS assay against SW620 cells. Compound **46d** exhibited high selectivity against a number of Ser/Thr kinases. It also had moderate oral absorption with a bioavialability of 20% in mice. Several important binding interactions between compound **46b** and the Chk1 kinase were revealed by X-ray cocrystal structure, which paved the way for further exploration.

Experimental Section

All commercially available solvents and reagents were used without further treatment as received unless otherwise noted. DMF (*N*,*N*-dimethylformamide), DME (1,2-dimethoxyethane), methylene chloride, toluene, methanol, and THF (tetrahydrofuran) were commercial anhydrous solvents from Aldrich. FT-NMR spectra were obtained on Bruker MHz 300 MHz (75 MHz for ^{13}C) or 500 MHz (1250 MHz for ^{13}C) spectrometers. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Thin layer chromatography (TLC) was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed on Merck silica gel 60 (230−400 mesh) using reagent grade solvents. All reactions were performed under a nitrogen atmosphere. Reverse-phase Prep high performance liquid chromatography (HPLC) was performed by a Gilson HPLC machine equipped with a C18-coated column (Phenomenex, Luna, 10 μ, 250 × 21.2 mm), eluting with gradient 0−70% acetonitrile in 0.1% TFA water.

General Procedure for Preparation of Compound 5−14 and 25. 3-Bromo-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (4b). A mixture of 4-bromo-2-chlorobenzoic acid (2.35 g, 10 mmol), 1,2-benzenediamine (1.08 g, 10 mmol), and copper (0.63 g, 10 mmol) in chlorobenzene (150 mL) was heated to reflux for 48 h

and filtered. The filter cake was washed with ethyl acetate several times. The combined filtrates were concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel with eluting 4:1 hexanes/ethyl acetate to provide 1.20 g (22%) of the title compound. MS (DCI) *m*/*e* 289 $(M + H)^+$, 307 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.02 (s, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.24 (d, $J = 1.8$ Hz, 1H), 7.06 (dd, $J = 8.4$, 1.8 Hz, 1H), 6.92−6.95 (m, 4H).

3-(4-Hydroxy-3-methoxyphenyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (14). A mixture of compound **4b** (116 mg, 0.4 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (150 mg, 0.6 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and CsF (121 mg, 0.8 mmol) in DME (20 mL) and methanol (10 mL) was heated to reflux for 16 h. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with additional ethyl acetate. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 1:1 hexanes/ethyl acetate to provide 0.108 g (81%) of the desired product. MS (DCI) *m*/*e* 333 $(M + H)^+$, 350 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.02 (s, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.24 (d, $J = 1.8$ Hz, 1H), 7.15−7.18 (m, 2H), 7.08 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.97−7.02 (m, 5H), 3.86 (s, 3H). Anal. ($C_{20}H_{16}N_2O_3$·0.4MeOH) C, H, N.

3-Phenyl-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (5). Compound **5** was prepared in a similar manner to the synthesis of compound **14** by substituting benzeneboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol in 67% yield. MS (DCI) *m*/*e* 287 $(M + H)^+$, 304 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.93 (s, 1H), 7.77 (d, $J = 8.11$ Hz, 1H), 7.63 (d, $J = 7.18$ Hz, 2H), 7.48−7.51 (m, 2H), 7.40−7.43 (m, 1H), 7.30 (d, $J = 1.56$ Hz, 1H), 7.19 (dd, $J = 8.11$, 1.56, 1H), 6.89−7.02 (m, 4H). Anal. ($C_{19}H_{14}N_2O$·0.1MeOH) C, H, N.

3-(2-Methoxy-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (6). Compound **6** was prepared in a similar manner to the synthesis of compound **14** by substituting 2-methoxyphenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol in 90% yield. MS (DCI) *m*/*e* 317 $(M + H)^+$, 334 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.85 (s, 1H), 7.70 (d, $J = 8.11$ Hz, 1H), 7.36−7.39 (m, 1H), 7.28 (dd, $J = 7.49$, 1.56 Hz, 1H), 7.12−7.13 (m, 2H), 6.88−7.05 (m, 6H), 3.78 (s, 3H). Anal. ($C_{20}H_{16}N_2O_2$) C, H, N.

3-(3-Methoxy-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (7). Compound **7** was prepared in a similar manner to the synthesis of compound **14** by substituting 3-methoxyphenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol in 84% yield. MS (DCI) *m*/*e* 317 $(M + H)^+$, 334 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.91 (s, 1H), 7.77 (d, $J = 8.11$ Hz, 1H), 7.39−7.42 (m, 1H), 7.30 (d, $J = 1.56$ Hz, 1H), 7.19−7.21 (m, 2H), 7.16 (d, $J = 2.18$ Hz, 1H), 6.89−7.02 (m, 5H), 3.83 (s, 3H). Anal. ($C_{20}H_{16}N_2O_2$) C, H, N.

3-(3-Ethoxy-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (8). Compound **8** was prepared in a similar manner to the synthesis of compound **14** by substituting 3-ethoxyphenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 89% yield. MS (DCI) *m*/*e* 331 $(M + H)^+$, 348 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.89 (s, 1H), 7.76 (d, $J = 8.11$ Hz, 1H), 7.37−7.40 (m, 1H), 7.31 (d, $J = 1.56$ Hz, 1H), 7.19−7.20 (m, 2H), 7.15 (d, $J = 2.18$ Hz, 1H), 6.89−7.02 (m, 5H), 4.01 (q, $J = 6.97$ Hz, 2H), 1.36 (t, $J = 7.02$ Hz, 3H). Anal. ($C_{21}H_{18}N_2O_2$) C, H, N.

3-(3-Cyano-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (9). Compound **9** was prepared in a similar manner to the synthesis of compound **14** by substituting 3-cyanophenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 72% yield. MS (DCI) *m*/*e* 312 $(M + H)^+$, 329 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.10 (s, 1H), 7.98 (d, $J = 8.42$ Hz, 1H), 7.94 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 8.11$ Hz, 1H), 7.69−7.72 (m, 1H), 7.35 (d, $J = 1.56$ Hz, 1H), 7.27 (dd, $J = 8.27$, 1.72 Hz, 1H), 6.90−7.02 (m, 4H). Anal. ($C_{20}H_{13}N_3O$·0.3MeOH) C, H, N.

3-(4-Cyano-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (10). Compound **10** was prepared in a similar manner to the synthesis of compound **14** by substituting 4-cyanohenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 80% yield. MS (DCI) *m*/*e* 312 $(M + H)^+$, 329 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.10 (s, 1H), 7.98 (d, $J = 8.42$ Hz, 1H), 7.94 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 8.11$ Hz, 1H), 7.69−7.72 (m, 1H), 7.35 (d, $J = 1.56$ Hz, 1H), 7.27 (dd, $J = 8.27$, 1.72 Hz, 1H), 6.90−7.02 (m, 4H). Anal. ($C_{20}H_{13}N_3O$ ·0.3MeOH) C, H, N.

3-(2-Acetyl-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (11). Compound **11** was prepared in a similar manner to the synthesis of compound **14** by substituting 2-acetylphenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 73% yield. MS (DCI) *m*/*e* 329 $(M + H)^+$, 346 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.95 (s, 1H), 7.72 (d, $J = 8.11$ Hz, 1H), 7.64−7.66 (m, 1H), 7.58−7.61 (m, 1H), 7.49−7.53 (m, 1H), 7.40 (d, $J = 6.55$ Hz, 1H), 6.90−7.00 (m, 5H), 6.81 (dd, $J = 8.11$, 1.56 Hz, 1H), 2.25 (s, 3H). Anal. ($C_{21}H_{16}N_2O_2$ ·0.4MeOH) C, H, N.

3-(3-Acetyl-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (12). Compound **12** was prepared in a similar manner to the synthesis of compound **14** by substituting 3-acetylphenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 78% yield. MS (DCI) *m*/*e* 329 $(M + H)^+$, 346 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.19 (s, 1H), 7.99−8.03 (m, 2H), 7.92 (d, $J = 8.59$ Hz, 1H), 7.81 (d, $J = 8.29$ Hz, 1H), 7.67−7.68 (m, 1H), 7.39 (d, $J = 1.84$ Hz, 1H), 7.27 (dd, $J = 8.13$, 1.69 Hz, 1H), 6.90−7.04 (m, 4H), 2.66 (s, 3H). Anal. ($C_{21}H_{16}N_2O_2$·0.35MeOH) C, H, N.

3-(4-Acetyl-phenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (13). Compound **13** was prepared in a similar manner to the synthesis of compound **14** by substituting 4-acetylphenylboronic acid for 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 61% yield. MS (DCI) *m*/*e* 329 $(M + H)^+$, 346 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.07 (d, $J = 8.42$ Hz, 2H), 7.99 (s, 1H), 7.78−7.81 (m, 3H), 7.38 (d, $J = 1.87$ Hz, 1H), 7.26 (dd, $J = 8.27$, 1.72 Hz, 1H), 6.90−7.03 (m, 4H), 2.62 (s, 3H). Anal. ($C_{21}H_{16}N_2O_2$·0.3MeOH) C, H, N.

2-Bromo-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (4a). Compound **4a** was prepared in a similar manner to the synthesis of compound **4b** by substituting 5-bromo-2-chloro-benzoic acid for 4-bromo-2-chlorobenzoic acid in 22% yield. MS (DCI) *m*/*e* 333 $(M + H)^+$, 350 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.03 (s, 1H), 7.74 (d, $J = 2.37$ Hz, 1H), 7.49 (dd, $J = 8.65$, 2.54 Hz, 1H), 6.91−6.98 (m, 4H).

2-(4-Hydroxy-3-methoxy-phenyl)-5,10-dihydro-dibenzo[*b*,*e*]-[1,4]diazepin-11-one (25). Compound **25** was prepared in a similar manner described for the synthesis of compound **14** by substituting compound **4a** for compound **4b** in 73% yield. MS (DCI) *m*/*e* 333 $(M + H)^+$, 350 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 1H), 9.00 (s, 1H), 7.88 (s, 1H), 7.87 (d, $J = 2.5$ Hz, 1H), 7.61 (dd, $J = 8.42$, 2.5 Hz, 1H), 7.10 (d, $J = 2.18$ Hz, 1H), 7.05 (d, $J = 8.42$ Hz, 1H), 6.89−7.02 (m, 5H), 6.83 (d, $J = 8.42$ Hz, 1H), 3.84 (s, 3H). Anal. ($C_{20}H_{16}N_2O_3$) C, H, N.

2-(3-Methoxy-4-nitro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (16). A mixture of PCy_3 (33.6 mg, 0.12 mmol) and $Pd_2(dba)_3$ (23 mg, 0.025 mmol) in dioxane (6.0 mL) purged with nitrogen was stirred at room temperature under nitrogen for 30 min. To this red solution, 4-chloro-2-methoxy-1-nitro-benzene (188 mg, 1.0 mmol), bis(pinacolato)diboron (279 mg, 1.1 mmol), and potassium acetate (147 mg, 1.5 mmol) were added. The reaction mixture was subjected to a vacuum/nitrogen cycle several times and stirred at 85 °C for 20 h. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with additional ethyl acetate. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The

residue was purified by flash chromatography on silica gel eluting with 1:4 ethyl acetate/hexane to give 170 mg of the desired product (61%). Alternatively, the residue was dissolved in 1 mL of CH_2Cl_2 and treated with 10 mL of hexanes. The suspension was stirred overnight, and the solid was collected to give analytically pure product. MS (DCI/NH_3) *m/e* 409 $(M + H)^+$; MS (DCI) *m/e* 279 $(M)^+$, 297 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J = 7.8$ Hz, 1H), 7.46 (s, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 3.95 (s, 3H), 1.33 (s, 12H).

3-(3-Methoxy-4-nitro-phenyl)-5,10-dihydro-dibenzo[*b,e*][1,4]-diazepin-11-one (17). Compound **17** was prepared in a similar manner to the synthesis of compound **14** by substituting compound **16** with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol in 76% yield. MS (DCI) *m/e* 362 $(M + H)^+$, 379 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.00−8.02 (m, 2H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 1.8$ Hz, 1H), 7.33−7.36 (m, 2H), 7.30 (dd, $J = 8.1$, 1.7 Hz, 1H), 6.90−7.03 (m, 4H), 4.03 (s, 3H). Anal. ($C_{20}H_{15}N_3O_4$·0.4MeOH) C, H, N.

3-(4-Amino-3-methoxy-phenyl)-5,10-dihydro-dibenzo[*b,e*][1,4]-diazepin-11-one (18). A mixture of compound **17** (50 mg) and 5% palladium on carbon (20 mg) in MeOH (15 mL) was equipped with a balloon of hydrogen gas and stirred at room temperature. After the reaction was over, the solution was filtered through a pack of Celite. The solvent was removed and the residue was purified by reverse-phase prep HPLC to give the desired product as a TFA salt (27%). MS (DCI) *m/e* 332 $(M + H)^+$, 349 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.92 (s, 1H), 7.77 (d, $J = 8.29$ Hz, 1H), 7.31 (s, 1H), 7.20−7.24 (m, 2H), 7.16 (d, $J = 1.84$ Hz, 1H), 6.94−7.10 (m, 3H), 6.72 (d, $J = 8.29$ Hz, 1H), 4.70 (s, 1H), 3.72 (s, 1H). Anal. ($C_{20}H_{17}N_3O_2$·TFA) C, H, N.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5*H*-dibenzo-[b,e][1,4]diazepin-11(10H)-one (19). Compound **19** was prepared in a similar manner to the synthesis of compound **16** by substituting 4-chloro-2-methoxy-1-nitro-benzene with compound **4b** in 92% yield. MS (DCI) *m/e* 337 $(M + H)^+$, 354 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.82 (s, 1H), 7.69 (d, $J = 7.8$ Hz, 1H), 7.42 (s, 1H), 7.16 (d, $J = 7.8$ Hz, 1H), 7.01−7.03 (m, 1H), 6.88−6.97 (m, 3H), 1.30 (s, 12H).

2-Methoxy-4-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]-diazepin-3-yl)-benzonitrile (20). Compound **20** was prepared in a similar manner to the synthesis of compound **14** by using compound **19** and 4-chloro-2-methoxy-benzonitrile in 41% yield. MS (DCI) *m/e* 342 $(M + H)^+$, 359 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.98 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.42 (s, 1H), 7.33−7.35 (m, 2H), 7.29 (dd, $J = 8.1$, 1.6 Hz, 1H), 6.90−7.02 (m, 4H), 4.02 (s, 3H). Anal. ($C_{21}H_{15}N_3O_2$·0.46EtOAc) C, H, N.

3-(4-Chloro-3-methoxy-phenyl)-5,10-dihydro-dibenzo[*b,e*][1,4]-diazepin-11-one (21). Compound **21** was prepared in a similar manner to the synthesis of compound **14** by using compound **19** and 1-chloro-4-iodo-2-methoxy-benzene in 74% yield. MS (DCI) *m/e* 362 $(M + H)^+$, 379 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.95 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 1.8$ Hz, 1H), 7.31 (m, 1H), 7.20−7.25 (m, 2H), 6.89−7.03 (m, 2H), 3.96 (s, 3H). Anal. ($C_{20}H_{15}ClN_2O_2$) C, H, N.

3-(4-Acetyl-3-methoxy-phenyl)-5,10-dihydro-dibenzo[*b,e*][1,4]-diazepin-11-one (22). Compound **22** was prepared in a similar manner to the synthesis of compound **14** by using compound **19** and 1-(4-chloro-2-methoxy-phenyl)-ethanone in 51% yield. MS (ESI) *m/e* 359 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.99 (s, 1H), 7.79 (d, $J = 8.14$ Hz, 1H), 7.70 (d, $J = 8.14$ Hz, 1H), 7.27−7.36 (m, 3H), 6.91−7.01 (m, 5H), 4.00 (s, 3H), 2.56 (s, 3H). Anal. ($C_{22}H_{18}N_2O_3$·0.4MeOH) C, H, N.

Methyl 2-Methoxy-4-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*]-[1,4]diazepin-3-yl)benzoate (23). Compound **23** was prepared in a similar manner to the synthesis of compound **14** by using compound **19** and methyl 4-chloro-2-methoxybenzoate in 52% yield. MS (DCI) *m/e* 375 $(M + H)^+$, 392 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.97 (s, 1H), 7.76−7.80 (m, 2H), 7.34−7.36 (m, 2H), 7.28 (d, $J = 1.6$ Hz, 1H), 7.27 (d, $J = 1.6$ Hz, 1H), 6.91−7.03 (m, 4H), 3.93 (s, 3H), 3.81 (s, 3H). Anal. ($C_{22}H_{18}N_2O_4$) C, H, N.

2-Methoxy-4-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]-diazepin-3-yl)benzamide (24). Compound **24** was prepared in a similar manner to the synthesis of compound **14** by using compound **19** and 4-chloro-2-methoxybenzamide in 49% yield. MS (DCI) *m/e* 360 $(M + H)^+$, 377 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.00 (s, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.70 (s, 1H), 7.60 (d, $J = 1.2$ Hz, 1H), 7.36 (d, $J = 1.8$ Hz, 1H), 7.33 (s, 1H), 6.89−7.04 (m, 4H), 4.00 (s, 3H). Anal. ($C_{21}H_{17}N_3O_3$·0.15CH_2Cl_2) C, H, N.

Representative Procedure for the Formation of Diaryl Amine from Methyl 2-Chloro-4-iodobenzoate and Substituted 2-Nitroanilines (General Method A). Methyl 4-Chloro-2-(5-morpholino-2-nitrophenylamino)benzoate (28g). A mixture of methyl-2-chloro-4-iodobenzoate (0.81 g, 2.73 mmol), 5-morpholino-2-nitroaniline (0.61 g, 2.73 mmol), K_2CO_3 (0.395 g, 2.86 mmol), and copper (0.180 g, 2.86 mmol) in chlorobenzene (50 mL) was heated to reflux for 48 h and filtered. The filter cake was washed with ethyl acetate several times. The combined filtrates were concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel eluting with 4:1 hexanes/ethyl acetate to provide 0.80 g (75%) of the title compound. The yield for this transformation varied from 40% to 80%, depending on the substrates. MS (DCI) *m/e* 392 $(M + H)^+$, 409 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.06 (d, $J = 9.51$ Hz, 1H), 7.95 (d, $J = 8.59$ Hz, 1H), 7.66 (d, $J = 2.15$ Hz, 1H), 7.12 (dd, $J = 8.59$, 2.15 Hz, 1H), 6.87 (d, $J = 2.45$ Hz, 1H), 6.74 (dd, $J = 6.67$, 2.61 Hz, 1H), 3.87 (s, 3H), 3.69−3.71 (m, 4H), 3.34−3.36 (m, 4H).

Representative Procedure for the Formation of 5*H*-Dibenzo-[*b,e*][1,4]diazepin-11(10*H*)-one (General Method B). 3-Chloro-7-morpholino-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one (30f). A mixture of compound **28g** (0.60 g, 1.53 mmol) and platinum on carbon (0.1 g) in MeOH (20 mL) was equipped with a balloon of hydrogen gas and stirred at room temperature. After uptake of H_2 was complete, the solution was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was treated with LiOH·H_2O (0.32 g, 7.67 mmol), MeOH (10 mL), and H_2O (10 mL). The reaction mixture was heated under reflux for 6 h. After cooling, the reaction mixture was neutralized to pH = 4 with 10% HCl. The mixture was extracted with ethyl acetate several times. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (10 mL), and the solution was treated with HATU (0.70 g, 1.83 mmol) and Et_3N (0.62 g, 6.12 mmol). The reaction mixture was stirred for 1 h at room temperature. It was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was triturated with 1:4 ethyl acetate/hexanes (10 mL) overnight to give 0.302 g of the desired product (60%). The yield for this transformation varied from 60% to 81%, depending on the substrates. MS (DCI) *m/e* 330 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.89 (s, 1H), 7.67 (d, $J = 8.42$ Hz, 1H), 7.04 (d, $J = 1.87$ Hz, 1H), 6.92 (dd, $J = 8.58$, 2.03 Hz, 1H), 6.83 (d, $J = 8.42$ Hz, 1H), 6.55−6.58 (m, 2H), 3.71−3.73 (m, 4H), 2.99−3.01 (m, 4H).

Representative Procedure for the Formation of 5*H*-Dibenzo-[*b,e*][1,4]diazepin-11(10*H*)-one (General Method C). A mixture of methyl 2-(2-amino-4-(benzyloxy)phenylamino)-4-chlorobenzoate **29b** (0.72 g, 1.88 mmol), prepared from **28b** by hydrogenation as described in the synthesis of compound **30f**, and TsOH·H_2O (0.72 g, 3.76 mmol) in toluene (100 mL) was equipped with a Dean−Stark trap. The reaction mixture was heated under reflux for 2 days. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 1:1 hexanes/ethyl acetate to provide

0.32 g (65%) of the title compound along with corresponding benzyl ether (35%). The yield for this transformation varied from 40% to 77%, depending on the substrates. MS (DCI) *m/e* 260 $(M)^+$, 278 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.15 (s, 1H), 7.56 (s, 1H), 7.71 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.87 (dd, J = 8.4, 2.2 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 6.44 (d, J = 2.5 Hz, 1H), 6.38 (dd, J = 8.4, 2.5 Hz, 1H).

Representative Procedure for the Suzuki Coupling between Aryl Chlorides and Pinacol Arylboronates (General Method D). 3-(3-Methoxy-4-nitrophenyl)-7-morpholino-5*H*-dibenzo[*b,e*][1,4]-diazepin-11(10*H*)-one (31e). A mixture of compound **30f** (50 mg, 0.15mmol), compound **16** (84 mg, 0.30 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Cy-Map (19.7 mg, 0.05 mmol), and CsF (68 mg, 0.45 mmol) in DME (4 mL) and MeOH (2 mL) was heated under reflux for 12 h. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 2:3 hexanes/ethyl acetate to provide 35 mg (52%) of the title compound. The yield for this transformation varied from 20% to 70%, depending on the substrates. MS (ESI) *m/e* 447 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.01 (d, J = 8.42 Hz, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.42 Hz, 1H), 7.53 (d, J = 1.56 Hz, 1H), 7.33−7.36 (m, 2H), 7.30 (dd, J = 8.27, 1.72 Hz, 1H), 6.85 (d, J = 8.73 Hz, 1H), 6.62 (d, J = 2.49 Hz, 1H), 6.56 (dd, J = 8.73, 2.81 Hz, 1H), 4.03 (s, 3H), 3.71−3.73 (m, 4H), 3.00−3.02 (m, 4H). Anal. ($C_{24}H_{22}N_4O_5$·0.45 TFA) C, H, N.

9-Hydroxy-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[b,e][1,4]-diazepin-11(10*H*)-one (31a). 3-(3-Methoxy-4-nitrophenyl)-9-(methoxymethoxy)-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one (15 mg), which was prepared from **26a** using the general methods A, C, and D, was dissolved in THF/MeOH 1:1 (0.5 mL), then 2 drops of concentrated HCl was added and the reaction was heated at 70 °C for 30 min. The reaction was then cooled, concentrated, and purified by reverse-phase prep HPLC to give the product (3 mg, 23%) as a white solid. MS (DCI/NH_3) *m/e* 378 $(M + H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.36 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.37 (s, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 6.80 (dd, J = 8.0, 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 2H), 4.03 (s, 3H).

8-Hydroxy-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[*b,e*][1,4]-diazepin-11(10*H*)-one (31b). The title compound was prepared using general methods A, C, and D from **26b**. MS (DCI) *m/e* 378 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.12 (s, 1H), 8.00 (d, J = 8.42 Hz, 1H), 7.78 (d, J = 8.11 Hz, 1H), 7.66 (s, 1H), 7.52 (d, J = 1.52 Hz, 1H), 7.32−7.35 (m, 2H), 7.26 (dd, J = 8.27, 1.72 Hz, 1H), 6.82 (d, J = 8.73 Hz, 1H), 6.46 (d, J = 2.5 Hz, 1H), 6.38 (dd, J = 8.58, 2.65 Hz, 1H), 4.03 (s, 3H). Anal. ($C_{20}H_{15}N_3O_5$·0.5CH_3OH) C, H, N.

8-Methoxy-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[*b,e*][1,4]-diazepin-11(10*H*)-one (31c). The title compound was prepared using general methods A, C, and D from **26c**. MS (DCI) *m/e* 392 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.01 (d, J = 8.29 Hz, 1H), 7.78−7.81 (m, 2H), 7.52 (d, J = 1.53 Hz, 1H), 7.32−7.35 (m, 2H), 7.28 (dd, J = 8.29, 1.53 Hz, 1H), 6.94 (d, J = 8.29 Hz, 1H), 6.57−6.61 (m, 2H), 4.03 (s, 3H), 3.67 (s, 3H). Anal. ($C_{21}H_{17}N_3O_5$·2H_2O·TFA) C, H, N.

7-Amino-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[*b,e*][1,4]-diazepin-11(10*H*)-one (31d). The title compound was prepared using general methods A, B, and D from **26f**. MS (DCI) *m/e* 377 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.01 (d, J = 8.42 Hz, 1H), 7.77 (d, J = 8.11 Hz, 1H), 7.69 (s, 1H), 7.51 (d, J = 1.87 Hz, 1H), 7.36 (d, J = 1.87 Hz, 1H), 7.33 (dd, J = 8.42, 1.87 Hz, 1H), 7.29 (dd, J = 8.11, 1.87 Hz, 1H), 6.66 (d, J = 8.42 Hz, 1H), 6.25 (d, J = 2.18 Hz, 1H), 6.16 (dd, J = 8.42, 2.50 Hz, 1H), 4.90 (s, 2H), 4.03 (s, 3H). Anal. ($C_{20}H_{16}N_4O_4$·0.6EtOAc) C, H, N.

3-Chloro-6-methoxy-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one (32). A mixture of **30d** (54 mg, 0.2 mmol), prepared using general methods A and C from **26d**, iodomethane (14 μL, 0.22 mmol), and K_2CO_3 (34.5 mg, 0.25 mmol) in acetone (4 mL) was stirred overnight at room temperature, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel to give 33 mg (58%) of compound **32**. MS (ESI) *m/e* 275 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.66 (d, J = 8.48 Hz, 1H), 7.34 (s, 1H), 7.24 (d, J = 2.03 Hz, 1H), 6.87−6.96 (m, 2H), 6.74 (dd, J = 8.14, 1.36 Hz, 1H), 6.61 (dd, J = 8.14, 1.36 Hz, 1H), 3.83 (s, 3H).

6-Methoxy-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[*b,e*][1,4]-diazepin-11(10*H*)-one (33). The title compound was prepared using general method D from **32** in 50% yield. MS (ESI) *m/e* 392 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.01 (d, J = 8.48 Hz, 1H), 7.80 (d, J = 8.48 Hz, 1H), 7.54 (d, J = 1.70 Hz, 2H), 7.38 (dd, J = 8.48, 1.70 Hz, 1H), 7.34 (dd, J = 8.31, 1.86 Hz, 1H), 7.20 (s, 1H), 6.89 (t, J = 8.14 Hz, 1H), 6.73−6.78 (m, 1H), 6.63 (dd, J = 7.97, 1.19 Hz, 1H). Anal. ($C_{21}H_{17}N_3O_5$·0.02CCl_4) C, H, N.

3-(3-Methoxy-4-nitrophenyl)-6-((2-(trimethylsilyl)ethoxy)-methoxy)-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one (34). A mixture of **30d** (1.3 g, 5.03 mmol), SEMCl (1.07 mL, 6.04 mmol) and diisopropylethylamine (DIPEA; 1.3 mL, 7.55 mmol) in CH_2Cl_2 (10 mL) and CH_3CN (20 mL) was stirred overnight at room temperature. Additional SEMCl (360 μL) and DIPEA (450 μL) were added and stirring was continued for about 8 h. The reaction mixture was concentrated, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography on silica gel using a mixture of hexanes and ethyl acetate to give 623 mg (32%) of 3-chloro-6-((2-(trimethylsilyl)-ethoxy)methoxy)-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one. MS (ESI) *m/e* 391 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.67 (d, J = 8.48 Hz, 1H), 7.38 (s, 1H), 7.26 (d, J = 2.03 Hz, 1H), 6.95 (dd, J = 8.48, 2.03 Hz, 1H), 6.83−6.88 (m, 2H), 6.65 (dd, J = 7.12, 2.37 Hz, 1H), 5.29 (s, 2H), 3.69−3.75 (m, 2H), 0.84−0.90 (m, 2H), −0.07− −0.05 (m, 9H).

Compound **34** was prepared using the general method D from 3-chloro-6-((2-(trimethylsilyl)ethoxy)methoxy)-5*H*-dibenzo[*b,e*]-[1,4]diazepin-11(10*H*)-one. MS (ESI) *m/e* 508 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.00 (d, J = 8.48 Hz, 1H), 7.80 (d, J = 8.14 Hz, 1H), 7.51−7.57 (m, 2H), 7.29−7.44 (m, 2H), 7.24 (s, 1H), 6.80−6.94 (m, 2H), 6.67 (dd, J = 6.44, 3.05 Hz, 1H), 5.30 (s, 2H), 4.03 (s, 3H), 3.66−3.76 (m, 2H), 0.78−0.86 (m, 2H), −0.17 (s, 9H).

3-(3-Methoxy-4-nitrophenyl)-6-(pyridin-4-ylmethoxy)-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one (35). A mixture of **34** (275 mg, 0.54 mmol) in THF (6 mL), MeOH (4 mL), and 5 drops of concentrated HCl was stirred at room temperature overnight. The solvents were removed under reduced pressure, and the residue was purified with reverse-phase prep HPLC to give 65 mg of 6-hydroxy-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one. MS (ESI) *m/e* 378 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.00 (d, J = 8.48 Hz, 1H), 7.79 (d, J = 8.14 Hz, 1H), 7.56 (d, J = 1.70 Hz, 2H), 7.30−7.43 (m, 3H), 7.05 (s, 1H), 6.73 (t, J = 7.97 Hz, 1H), 6.58 (dd, J = 8.14, 1.36 Hz, 1H), 6.48 (dd, J = 7.97, 1.19 Hz, 1H), 4.04 (s, 3H).

A mixture of 6-hydroxy-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo-[*b,e*][1,4]diazepin-11(10*H*)-one (20 mg, 0.053 mmol), 4-(chloromethyl)pyridine hydrochloride (13 mg, 0.080 mmol) and K_2CO_3 (22 mg, 0.159 mmol) in DMF (1 mL) was heated at 50 °C overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was triturated with MeOH. The solid was collected by filtration, washed with MeOH, and redissolved in a mixture of MeOH and 4 N HCl in dioxane. After several minutes, a precipitate formed and was collected to give 14.5 mg of **35** as an HCl salt (54%). MS (ESI) *m/e* 469 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.79 (d, J = 6.44 Hz, 2H), 8.03 (d, J = 8.48 Hz, 1H), 7.96 (d, J = 5.76 Hz, 2H),

7.82 (d, $J = 8.14$ Hz, 1H), 7.54 (dd, $J = 5.09$, 1.70 Hz, 2H), 7.35−7.42 (m, 3H), 6.89 (t, $J = 8.14$ Hz, 1H), 6.76−6.82 (m, 1H), 6.67−6.71 (m, 1H), 5.46 (s, 2H), 4.03 (s, 3H). Anal. ($C_{26}H_{20}N_4O_5 \cdot HCl \cdot 0.8CH_2Cl_2$) C, H, N.

8-Amino-3-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (37). The title compound was prepared using general methods A and C from compound **36**. MS (DCI) *m*/*e* 259 $(M)^+$, 277 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.56 (s, 1H), 7.00 (d, $J = 1.9$ Hz, 1H), 6.85 (dd, $J = 8.4$, 1.9 Hz, 1H), 6.65 (d, $J = 8.1$ Hz, 1H), 6.20−6.21 (m, 2H), 4.81 (s, 2H).

8-Amino-3-(3-methoxy-4-nitrophenyl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (38). The title compound was prepared using general method D from compound **37** in 60% yield. MS (DSI) *m*/*e* 377 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6, TFA salt) δ 9.91 (s, 1H), 7.94 (d, $J = 8.3$ Hz, 1H), 7.87 (s, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.45 (s, 1H), 7.27−7.28 (m, 2H), 7.23 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.58−6.61 (m, 2H), 3.96 (s, 3H). Anal. ($C_{20}H_{16}N_4O_4 \cdot 0.5$EtOAc) C, H, N.

8-(1,1-Dioxo-1l6-isothiazolidin-2-yl)-3-(3-methoxy-4-nitrophenyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (39). A mixture of **38** (60 mg, 0.159 mmol) and 3-chloropropane-1-sulfonyl chloride (34 mg, 0.191 mmol) in pyridine (2 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with aqueous 4 N HCl and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified with reverse-phase prep HPLC to give 65 mg of 3-chloro-*N*-(3-(3-methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-8-yl)propane-1-sulfonamide (68%). MS (DCI) *m*/*e* 517 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.70 (s, 1H), 8.01−8.02 (m, 2H), 7.80 (d, $J = 8.24$ Hz, 1H), 7.52 (s, 1H), 7.30−7.35 (m, 3H), 6.98 (d, $J = 8.24$ Hz, 1H), 6.94 (d, $J = 2.14$ Hz, 1H), 6.83 (dd, $J = 8.54$, 2.44 Hz, 1H), 4.03 (s, 3H), 3.71 (t, $J = 3.71$ Hz, 2H), 3.13−3.15 (m, 2H), 2.06−2.13 (m, 2H).

Sodium ethoxide solution was prepared by adding sodium metal (24 mg, 1.0 mmol) to EtOH (10 mL) at room temperature. To this solution was added 3-chloro-*N*-(3-(3-methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)propane-1-sulfonamide (51 mg, 0.1 mmol). The reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture yielded a yellow precipitate that was collected by filtration to give 34 mg of compound **39** (72%). MS (DCI) *m*/*e* 481 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.00−8.02 (m, 2H), 7.81 (d, $J = 8.42$ Hz, 1H), 7.53 (d, $J = 1.56$ Hz, 1H), 7.34−7.35 (m, 2H), 7.30 (dd, $J = 8.26$, 1.72 Hz, 1H), 7.02 (d, $J = 8.42$, Hz, 1H), 6.92 (d, $J = 2.18$ Hz, 1H), 6.88 (dd, $J = 8.42$, 2.50 Hz, 1H), 4.03 (s, 3H), 3.63 (t, $J = 6.39$ Hz, 2H), 3.46 (t, $J = 7.49$ Hz, 2H), 2.34−2.41 (m, 2H). Anal. ($C_{23}H_{20}N_4O_6 \cdot 0.1CH_2Cl_2$) C, H, N.

3-Chloro-8-(2-oxopyrrolidin-1-yl)-5,10-dihydro-11*H*-dibenzo-[*b*,*e*][1,4]diazepin-11-one (40). Compound **37** (0.41 g, 1.58 mmol) in pyridine (3 mL) was treated with 4-chlorobutanoyl chloride (0.267 g, 1.90 mmol) in CH_2Cl_2 (3 mL) dropwise at room temperature. The reaction was stirred overnight. It was partitioned between ethyl acetate and water. The organic layer was washed with aqueous 4 N HCl and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 2:3 hexanes/ethyl acetate to provide 0.345 g of 4-chloro-*N*-(3-chloro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)butanamide (60%). MS (DCI) *m*/*e* 365 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.88 (s, 1H), 7.95 (s, 1H), 7.67 (d, $J = 8.48$ Hz, 1H), 7.27 (d, $J = 2.03$ Hz, 1H), 7.18 (dd, $J = 8.48$, 2.37 Hz, 1H), 7.05 (d, $J = 2.03$ Hz, 1H), 6.87−6.93 (m, 2H), 3.68 (t, $J = 6.61$ Hz, 2H), 2.43 (t, $J = 7.29$ Hz, 2 H), 1.97−2.05 (m, 2H).

Sodium ethoxide solution was prepared by adding sodium metal (138 mg, 0.6 mmol) to EtOH (15 mL) at room temperature. To this solution was added 4-chloro-*N*-(3-chloro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)butanamide (182 mg, 0.5 mmol). A precipitate started to form several minutes later. The reaction mixture was stirred overnight at room temperature, and the solid was collected by filtration to give 154 mg of compound **40** (94%). MS (DCI) *m*/*e* 328 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.06 (s, 1H), 7.72 (d, $J = 8.48$ Hz, 1H), 7.37 (d, $J = 2.50$ Hz, 1H), 7.28 (dd, $J = 8.73$, 2.50 Hz, 1H), 7.09 (d, $J = 1.87$ Hz, 1H), 6.98 (d, $J = 8.73$ Hz, 1H), 6.95 (dd, $J = 8.42$, 1.87 Hz, 1H), 3.77 (t, $J = 7.02$ Hz, 2H), 2.49 (t, $J = 7.95$ Hz, 2 H), 2.04−2.10 (m, 2H).

3-(3-Methoxy-4-nitrophenyl)-8-(2-oxopyrrolidin-1-yl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (41). The title compound was prepared using general method D from compound **40** in 28% yield. MS (DCI) *m*/*e* 445 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.00−8.02 (m, 2H), 7.81 (d, $J = 8.29$ Hz, 1H), 7.63 (d, $J = 1.53$ Hz, 1H), 7.32−7.35 (m, 3H), 7.28−7.31 (m, 1H), 7.25 (dd, $J = 8.75$, 2.30 Hz, 1H), 7.00 (d, $J = 8.90$ Hz, 1H), 4.03 (s, 3H), 3.74 (t, $J = 6.90$ Hz, 2H), 2.46 (t, $J = 8.13$ Hz, 2 H), 2.01−2.08 (m, 2H). Anal. ($C_{24}H_{20}N_4O_5 \cdot 0.62CH_2Cl_2$) C, H, N.

Representative Procedure for the Formation of Diaryl Amine from Methyl 2-Chloro-4-iodobenzoate and Substituted 2-Nitroanilines Mediated by Palladium (General Method E). Methyl 4-Chloro-2-{[4-(2-methoxy-2-oxoethyl)-2-nitrophenyl]amino}-benzoate (43a). A mixture of compound **42a** (4.21 g, 20 mmol), compound **27** (5.93 g, 20 mmol), $Pd(OAc)_2$ (0.224 g, 1 mmol), dppf (1.11 g, 2 mmol), and Cs_2CO_3 in toluene (80 mL) was degassed via vacuum/nitrogen cycle several times. The reaction mixture was heated at 95 °C for 16 h. After cooling to ∼80 °C, the reaction mixture was filtered through a pack of silica gel and washed with additional 3:7 ethyl acetate/hexanes until all the desired product was washed off. The solvents were removed under reduced pressure, and the residue was recrystallized in EtOH (100 mL) to give 5.4 g of compound **43a**. The mother liquid was concentrated and purified by column chromatography on silica gel eluting with 85:15 hexanes/ethyl acetate to provide additional 1.2 g of **43a** (total yield: 87%). MS (DCI) *m*/*e* 379 $(M + H)^+$, 396 $(M + NH_4)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.10 (d, $J = 2.1$ Hz, 1H), 7.96 (d, $J = 8.5$, Hz, 1H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.60 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.11 (dd, $J = 8.5$, 2 Hz, 1H), 3.69 (s, 3H), 3.81 (s, 2H), 3.65 (s, 3H).

Methyl (3-Chloro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-8-yl)acetate (44a). The title compound was prepared using general method C from compound **43a** in 78% yield. MS (DCI) *m*/*e* 317 $(M + H)^+$, 334 $(M + NH_4)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.03 (s, 1H), 7.68 (d, $J = 8.7$ Hz, 1H), 7.06 (d, $J = 2.2$ Hz, 1H), 6.91−6.93 (m, 2H), 6.86−6.87 (m, 2H), 3.60 (s, 3H), 3.54 (s, 2H). Anal. ($C_{23}H_{19}N_3O_6 \cdot 0.1CH_2Cl_2$) C, H, N.

Methyl [3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]acetate (45a). The title compound was prepared using general method D from compound **44a** in a 78% yield. MS (ESI) *m*/*e* 432 $(M - H)^-$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.98−8.01 (m, 2H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.51 (d, $J = 1.6$ Hz, 1H), 7.30−7.34 (m, 2H), 7.29 (dd, $J = 8.3$, 1.7 Hz, 1H), 6.96 (d, $J = 7.8$ Hz, 1H), 6.85−6.87 (m, 2H), 4.02 (s, 3H), 3.59 (s, 3H), 3.53 (s, 2H).

2-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]-*N*,*N*-dimethylacetamide (46b). A mixture of **45a** (0.864 g, 2 mmol) and $LiOH \cdot H_2O$ (0.335 g, 8 mmol) in MeOH (20 mL) and water (20 mL) was heated under reflux overnight. The reaction mixture was neutralized to pH = 4 and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.75 g of [3-(3-methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]acetic acid that was used for the next reaction without further purification (89%).

A mixture of [3-(3-methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]acetic acid (83 mg, 0.2 mmol), HATU (92 mg, 0.24 mmol), dimethyl amine hydrochloride (32 mg, 0.4 mmol), and Et_3N (81 mg, 0.8 mmol) in DMF (3 mL) was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The

residue was purified by reverse phase prep HPLC to give 62 mg of the title compound (71%). MS (ESI) *m/e* 445 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.01 (d, $J = 8.48$ Hz, 1H), 7.97 (s, 1H), 7.79 (d, $J = 8.14$ Hz, 1H), 7.52 (d, $J = 1.70$ Hz, 1H), 7.32−7.36 (m, 2H), 7.28−7.32 (dd, $J = 8.14$, 1.70 Hz, 1H) 6.95 (d, $J = 7.80$ Hz, 1H), 6.80−6.85 (m, 2H), 4.03 (s, 3H), 3.55 (s, 2H), 2.97 (s, 3H), 2.81 (s, 3H). Anal. ($C_{24}H_{22}N_4O_5 \cdot 0.3H_2O$) C, H, N.

2-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]-*N*-[4-(4-morpholinyl)phenyl]acetamide (46c). The title compound was prepared in a similar manner as described in the preparation of **46b** in 80% yield. MS (ESI) 580 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 9.90 (s, 1H), 9.87 (s, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.96 (s, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 1.2$ Hz, 1H), 7.44 (d, $J = 9.0$ Hz, 2H), 7.35 (m, 2H), 7.30 (dd, $J = 8.3$, 1.7 Hz, 1H), 6.95 (m, 3H), 6.88 (d, $J = 9.0$ Hz, 2H), 4.03 (s, 3H), 3.72 (m, 4H), 3.48 (s, 2H), 3.03 (m, 4H). Anal. ($C_{32}H_{29}N_5O_6 \cdot 1.4$ HCl$\cdot 2.75H_2O$) C, H, N.

2-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]-2-methyl-*N*-(4-morpholin-4-ylphenyl)propanamide (46d). The title compound was prepared in a similar manner as described in the preparation of **46b** from compound **42c**. MS (DCI) *m/e* 608 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.79 (s, 1H), 8.01 (m, 2H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.52 (s, 1H), 7.42 (d, $J = 8.7$ Hz, 2H), 7.30−7.35 (m, 3H), 7.06 (s, 1H), 7.00 (m, 1H), 6.95 (m, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 4.03 (s, 3H), 3.71 (m, 4H), 3.00 (m, 4H), 1.49 (s, 6H). Anal. ($C_{34}H_{33}N_5O_6 \cdot 0.9H_2O$) C, H, N.

3-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]-*N*,*N*-dimethylpropanamide (46e). The title compound was prepared in a similar manner as described in the preparation of **46b** from compound **42b**. MS (ESI) *m/e* 461 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.01 (d, $J = 8.14$ Hz, 1H)), 7.93 (s, 1H), 7.79 (d, $J = 8.14$ Hz, 1H), 7.5 (d, $J = 1.7$ Hz, 1H), 7.3 (m, 3H), 6.9 (m, 1H), 6.83 (d, $J = 5.43$ Hz, 2H), 4.03 (s, 3H), 2.92 (s, 3H), 2.80 (s, 3H), 2.67 (t, $J = 7.46$, 2H), 2.50−2.52 (m, 2H). Anal. ($C_{25}H_{24}N_4O_5 \cdot 0.42TFA\cdot 0.4CH_3OH$) C, H, N.

3-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl]-*N*-(4-morpholin-4-ylphenyl)propanamide (46f). The title compound was prepared in a similar manner as described in the preparation of **46b** from compound **42b**. MS (ESI) *m/e* 594 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.78 (s, 1H), 9.7 (s, 1H), 7.93 (d, $J = 8.42$ Hz, 1H), 7.85 (s, 1H), 7.72 (d, $J = 8.11$ Hz, 1H), 7.45 (d, $J = 1.56$ Hz, 1H), 7.34 (d, $J = 9.04$ Hz, 2H), 7.27 (m, 2H), 7.22 (dd, $J = 8.26$, 1.72 Hz, 1H), 6.86 (d, $J = 8.11$ Hz, 1H), 6.75−6.79 (m, 4H), 3.96 (s, 3H), 3.64 (br, m, 4H), 2.95 (br, m, 4H), 2.65−2.68 (m, 2H), 2.43−2.45 (m, 2H). Anal. ($C_{33}H_{31}N_5O_6 \cdot 0.7$TFA) C, H, N.

2-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-7-yl]-*N*,*N*-dimethylacetamide (46g). The title compound was prepared in a similar manner as described in the preparation of **46b** from compound **42d**. MS (DCI) *m/e* 447 $(M + H)^+$, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.00 (m, 2H), 7.80 (d, $J = 8.11$ Hz, 1H), 7.52 (d, $J = 1.56$ Hz, 1H), 7.37 (d, $J = 1.56$ Hz, 1H), 7.34 (dd, $J = 8.42$, 1.56 Hz, 1H), 7.30 (dd, $J = 8.11$ Hz, 8.42, 1.56 Hz, 1H), 6.89−6.91 (m, 2H), 6.78 (dd, $J = 7.95$, 1.72 Hz, 1H), 4.03 (s, 3H), 3.56 (s, 2H), 2.98 (s, 3H), 2.82 (s, 3H). Anal. ($C_{24}H_{22}N_4O_5 \cdot 0.9H_2O$) C, H, N.

2-[3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-7-yl]-2-methyl-*N*-(4-morpholin-4-ylphenyl)propanamide (46h). The title compound was prepared in a similar manner as described in the preparation of **46b** from compound **42e**. MS (ESI) *m/e* 608 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.85 (s, 1H), 8.06 (s, 1H), 8.01 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 1.7$ Hz, 1H), 7.42 (d, $J = 9.2$ Hz, 2H), 7.29−7.38 (m, 3H), 7.04 (d, $J = 1.7$ Hz, 1H), 6.91 (m, 2H), 6.83 (d, $J = 9.2$ Hz, 2H), 4.03 (s, 3H), 3.71 (m, 4H), 3.00 (m, 4H), 1.49 (s, 6H). Anal. ($C_{34}H_{33}N_5O_6 \cdot 0.1CH_2Cl_2$) C, H, N.

Methyl 4-Chloro-2-(methyl(2-nitrophenyl)amino)benzoate (47). Compound **28e** (0.26 g, 0.85 mmol) in DMF (8.0 mL) was treated with 95% NaH (35 mg, 1.38 mmol), followed by iodomethane (0.25 g, 1.67 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The product (0.27 g, 100%) was recovered as a yellow solid. MS (DCI/NH_3) *m/e* 323, 321 $(M + H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (dd, $J = 7.78$, 1.36 Hz, 1H), 7.63−7.69 (m, 1H), 7.45 (d, $J = 8.14$ Hz, 1H), 7.35 (d, $J = 7.46$ Hz, 1H), 7.29 (d, $J = 2.03$ Hz, 1H), 7.22 (t, $J = 7.63$ Hz, 1H), 7.15 (dd, $J = 8.14$, 2.03 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H).

3-Chloro-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (48). The title compound was prepared using general methods C and D from compound **47**. MS (DCI/NH_3) *m/e* 259, 261 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.63 (d, $J = 8.5$ Hz, 1H), 7.23−7.04 (m, 6H), 3.28 (s, 3H).

3-(3-Methoxy-4-nitrophenyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (49). The title compound was prepared using general method D from compound **48** in 46% yield. MS (DCI/NH_3) *m/e* 376 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.00 (d, $J = 8.2$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.58 (s, 1H), 7.46 (m, 3H), 7.22 (d, $J = 7.9$ Hz, 1H), 7.13 (m, 1H), 7.07 (m, 2H), 4.04 (s, 3H), 3.40 (s, 3H).

Methyl 2-(4-Fluoro-3-nitrophenyl)acetate (51). 4-Fluoro-3-nitrobenzoic acid (**50**; 35.0 g, 189 mmol) was dissolved in $SOCl_2$ (300 mL) and heated under reflux for 2 h. The reaction was cooled and concentrated, then the last of the $SOCl_2$ was removed using a toluene azeotrope. The resultant brown oil (40.4 g) was dissolved in Et_2O (100 mL) and that solution was added dropwise to 2.0 M $(TMS)CHN_2$ in hexanes. After stirring the reaction at room temperature for 45 min, it was concentrated and the crude was purified by flash chromatography using 7:3 hexanes/ethyl acetate. The diazoketone intermediate (24.5 g, 62%) was recovered as orange solids. The diazoketone (20.0 g, 96 mmol) was dissolved in MeOH (100 mL) and heated to 70 °C, and to that was added in portions over 1 h a solution of silver benzoate (0.4 g, 1.7 mmol) in triethylamine (4.0 mL). After heating for an additional 1 h, the reaction was cooled, filtered, and concentrated, and the crude was purified by flash chromatography using 78:22 hexanes/ethyl acetate. The homologated ester (8.8 g, 43%) was recovered as a yellow oil. MS (DCI/NH_3) *m/e* 231 $(M + H + NH_3)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, $J = 6.8$, 2.4 Hz, 1H), 7.57 (m, 1H), 7.26 (m, 1H), 3.73 (s, 3H), 3.69 (s, 2H).

Methyl 4-Chloro-2-(4-(2-methoxy-2-oxoethyl)-2-nitrophenoxy)-benzoate (52). Compound **51** (1.0 g, 4.7 mmol) and methyl 4-chloro-2-hydroxybenzoate (1.0 g, 5.4 mmol) were dissolved in DMA (2.0 mL), K_2CO_3 (0.73 g, 5.3 mmol) was added, and the reaction was heated at 80 °C under nitrogen overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The crude was purified by flash chromatography using 4:1 hexanes/ethyl acetate. The above diaryl ether (0.89 g, 50%) was recovered as an oil that slowly crystallized. MS (DCI/NH_3) *m/e* 399, 397 $(M + H + NH_3)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04 (d, $J = 2.2$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.57 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.49 (dd, $J = 8.8$, 1.8 Hz, 1H), 7.37 (d, $J = 1.8$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 1H), 3.83 (s, 2H), 3.70 (s, 3H), 3.65 (s, 3H).

Methyl 2-(3-Chloro-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]-oxazepin-8-yl)acetate (53). The title compound was prepared using general method C from compound **52** in 70% yield. MS (DCI/NH_3) *m/e* 320, 318 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.53 (d, $J = 2.0$ Hz, 1H), 7.40 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.49 (d, $J = 7.8$ Hz, 1H), 7.04 (m, 2H), 3.65 (s, 2H), 3.59 (s, 3H).

Methyl 2-(3-(3-Methoxy-4-nitrophenyl)-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepin-8-yl)acetate (54). The title compound was prepared using general method D from compound **53** in 70% yield. MS (DCI/NH_3) *m/e* 435 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.00 (d, $J = 8.5$ Hz, 1H), 7.89 (d, $J = 8.1$ Hz, 1H), 7.82 (d, $J = 1.7$ Hz, 1H), 7.75 (dd, $J = 8.1$,

2.0 Hz, 1H), 7.64 (d, $J = 1.4$ Hz, 1H), 7.48 (dd, $J = 8.5$, 1.4 Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.08 (d, $J = 1.7$ Hz, 1H), 7.05 (dd, $J = 8.1$, 2.0 Hz, 1H), 4.06 (s, 3H), 3.65 (s, 2H), 3.60 (s, 3H). Anal. ($C_{23}H_{18}N_2O_7 \cdot 0.55\ H_2O$) C, H, N.

Chk1 Assay. The Chk1 enzymatic assay was carried out using a recombinant Chk1 kinase domain. A human Cdc25C peptide was used as the substrate in the assay. The reaction mixture contained 25 mM of HEPES at pH 7.4, 10 mM $MgCl_2$, 0.08 mM Triton X-100, 0.5 mM DTT, 5 μM ATP, 4nM ^{33}P ATP, 5 μM Cdc25C peptide substrate, and 5 nM of the recombinant Chk1 protein. For potent compounds with K_i below 1 nM, 0.5 nM of the recombinant Chk1 protein and 8 nM of ^{33}P were used in the assays. The compound vehicle DMSO was maintained at 2% in the final reaction. After 30 min at room temperature, the reaction was stopped by the addition of equal volumes of 4 M NaCl and 0.1 M EDTA, pH 8. A 40 μL aliquot of the reaction mixture was added to a well in a FlashPlate (NEN Life Science Products, Boston, MA) containing 160 μL of phosphate-buffered saline (PBS) without calcium chloride and magnesium chloride and incubated at room temperature for 10 min. The plate was then washed 3 times in PBS with 0.05% of Tween-20 and counted in a Packard TopCount counter (Packard BioScience Company, Meriden, CT).

In Vitro Kinase Assay for Selectivity. Recombinant Cdc2, PKC$_\gamma$, and PKC$_\delta$ (Calbiochem, San Diego, California); PKA (Panvera, Madison, Wisconsin); Src, SGK and full-length cTak1 (Upstate Biotechnology, Charlottesville, Virginia); ERK2 (New England Biolabs, Beverly, Massachusetts); and cKit(544-976; ProQinase, Freiburg, Germany) were commercially obtained. His-tagged AKT1[S378A, S381A, T450D, S473D](139-480), Chk1(1-269), KDR(789-1354), Flt-1(786-1338), and PDK1(1-396), Lck(62-509), Lyn, Fyn-catalytic domain, HCK, Tie2, FGR(60-529), and Flt4 were expressed using the FastBac bacculovirus expression system (GIBCO BRL, Gaithersburg, MD) and purified using either nickel (his-tag) or glutathione (GST) affinity S5 chromatography. His-tagged Flt3 (569-993) was expressed in *E. coli*. Peptide substrates had the general structure biotin−Ahx−peptide with sequences: Chk1 and Chk2, AKVSRSGLYRSPSMPENLNRPR; AKT, EELSPFRGRSRSAPPNLWAAQR; Cdc2, PKTPKKAKKL; ERK2, KRELVEPLTPSGEAPNQALLR; SGK, RPRAATF; PKA, LRRASLG; PKC$_\gamma$ and PKC$_\delta$, ERMRPRKRQGSVRRRV; cTak1, AKVSRSGLYRSPSMPENLNRPR; KDR, Flt-1, Flt-3, Flt-4, and cKit, AEEEYFFLFA-amide; Tie2, biotin-poly(Glu-Tyr); FGR, Lck, Lyn, Fyn, and HCK, GAEEEIYAAFFA. For Src assays, the biotinylated substrate PTK-2 (Promega, Madison, Wisconsin) was used.

For S/T kinases and Src, a radioactivity-based assay was utilized. In this format, compounds were incubated with gamma-[33P]-ATP (5 μM), enzyme, and biotinylated peptide substrates (2 μM) in kinase assay buffer for 30 min at room temperature and then the reaction was stopped by the addition of 100 mM EDTA. The quenched reactions were transferred to streptavidin-coated FlashPlates (Perkin-Elmer), the plates were washed, and peptide phosphorylation was quantified on a TopCount scintillation plate reader. For all TKs (except Src and Tie2), an HTRF assay format was employed. In this format, compounds were incubated with enzymes, biotinylated-peptide substrates (0.5 μM), and ATP (1 mM) for 1 h at room temperature before stopping with 100 mM EDTA. To the stopped reaction, revelation buffer containing Eu-labled anti-pY-Ab (Cis Bio HTRF) and streptavidin-APC (Prozyme) were added, and the mixture was allowed to incubate for 1 h. Plates were subsequently read on a Discovery HTRF plate reader monitoring the time-resolved fluorescence ratio (665 nm/615 nm). Tie-2 activity was measured using an Elisa-type assay.

Cell Culture. SW620 cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum (FBS) at 37 °C in a 5% CO_2 incubator, H1299 cells were grown in RPMI 1640 S6 supplemented with 10% FBS, 1 mM sodium pyruvate, and 0.45% glucose, and Hela cells were grown in MEM supplemented with 10% FBS.

MTS Assay. Exponential growing cells were seeded in 96-well plates and allowed to attach an incubator. After 24 h, the cells received various amounts of the compounds and continued to incubate for 48 h. Doxorubicin (DOX) and CPT were purchased from Sigma (St. Louis, MO). After the treatment, MTS reagents that measured the amount of live cells (Promega, Madison, WI) were added to the incubated cells and allowed to develop for 20 min to 2 h. Colorimetric measurements were taken at 490 nm on a Spectra MAX 190 plate reader from Molecular Device (Sunnyvale, CA).

FACS Analysis. Cells were treated with compounds at the indicated concentrations for the indicated time. The medium and the washing solution, phosphate-buffered saline (PBS), were collected to include the floating cells. The cells were then trypsinized and added to the tubes with the medium and PBS. After spinning at 1000 × *g* for 5 min, the cells were washed in PBS and fixed in 70% ethanol. The washed cells were treated with RNase A at 37 °C for 30 min. Finally, the cells were stained with propidium iodide (PI) and analyzed by fluorescence-activated cell sorting (FACS) on a FACSCalibur (Becton Dickinson, San Jose, CA). Cells were counted and analyzed using the CellQuest Pro program provided by the vendor. Thymidine and paclitaxel were used as controls for positioning the S and G2/M phases, respectively.

Soft Agar Assay. The soft agar experiments were performed in 12-well plates. The bottom layer contained 0.5 mL of 0.7% agar with the growth medium. The top layer contained 0.5 mL of 0.35% agar with the medium mixed with 5000 cells/well of SW620 cells. Chk1 compounds were diluted in 0.5 mL of the medium and added to each well. After 14 days, colonies were stained with iodonitrotetrazolium at 0.5 μg/mL overnight and counted using a Sony CCD camera linked to the Image-Pro Plus software (MediaCybernetics, Silver Spring, MD).

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Supporting Information Available: FACS analysis of **46d** with doxorubicin and camptothecin, soft agar assay of **46d** with doxorubicin, and elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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