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Synthesis and biological evaluation of 4′-(6,7-disubstituted-2,4-dihydro-indeno[1,2-*c*]pyrazol-3-yl)-biphenyl-4-ol as potent Chk1 inhibitors

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Abstract—A new series of potent tricyclic pyrazole-based Chk1 inhibitors are described. Analogues disubstituted on the 6- and 7-positions show improved Chk1 inhibition potency compared with analogues with a single substituent on either the 6- or 7-position. Based on the lead compound 4′-(6,7-dimethoxy-2,4-dihydro-indeno[1,2-*c*]pyrazol-3-yl)-biphenyl-4-ol (**2**), detailed SAR studies on the 6- and 7-positions were performed. 3′-morpholin-4′-yl-propoxy, pyridin-4′-ylmethoxy, pyridin-3′-ylmethoxy, 2′-(5″-ethyl-pyridin-2″-yl)-ethoxy, pyridin-2′-ylethoxy, (6′-methyl-pyridin-2′-yl)-propoxyethoxy, 2′,3′-dihydroxyl-1′-yl-propoxy, and tetrahydro-furan-3′-yloxy have been identified as the best groups on the 6-position when the 7-position is substituted with methoxyl group. Pyridin-2′-ylmethoxy and pyridin-3′-ylmethoxy have been identified as the best substituents at the 7-position while the 6-position bearing methoxyl group. These compounds significantly potentiate the cytotoxicity of DNA-damaging antitumor agents in a cell-based assay and efficiently abrogate the doxorubicin-induced G2/M and the camptothecin-induced S checkpoints, suggesting that their potent biological activities are mechanism-based through Chk1 inhibition.

Many anticancer drugs express their biological activity through damaging DNA and have greatly contributed to the survival increases of cancer patients.[1] Unfortunately, DNA-damaging anticancer agents are also very toxic to normal cells and are severely resisted by tumor cells in the clinic. A major reason for the resistance is that the damaged tumor DNA can be repaired due to the DNA damage-induced checkpoints, thereby avoiding cell death.[2] Checkpoint kinase 1 (Chk 1) is a serine/threonine protein kinase which plays a critical role in DNA damage-induced checkpoints.[2,3] In response to DNA damage, ATM and ATR kinases activate Chk1 through phosphorylation in the SQ/TQ domain to arrest cells at various DNA-damaging checkpoints (G1, S, G2) to initiate the DNA repair process.[3] Since p53-deficient tumor cells lack the G1 checkpoint, they are selectively arrested at the S or G2 checkpoint after DNA damage. The inhibition of Chk1 abrogates the S and G2 checkpoints and disrupts the DNA repair process, resulting in premature chromosome condensation and leading to cell death, thereby preferentially sensitizing tumor cells, especially p53-null cells, to various DNA damaging agents. In contrast, normal cells can still arrest in the G1 phase and are less affected by S and G2 checkpoint abrogation, suggesting that a favorable therapeutic window may be achieved for G2 and/or S abrogators.[4] Consequently, Chk1 has emerged as an attractive chemosensitization target especially since approximately 50% of all human cancers are p53-deficient.[5,6]

Several classes of Chk1 inhibitors have been reported,[6] including indolocarbazoles,[7] isogranulatimides,[8] debromohymenialdisines,[9] aminopyrimidines,[10] pyrrolopyridines,[11] indolinones,[12] benzimidazole-quinolinones,[13] indazoles,[14] diarylureas[15], and macrocyclic ureas.[16] Based on a hit identified from high-through-put screening, we have discovered 4′-(2,4-dihydroindeno[1,2-*c*]pyrazol-3-yl)-biphenyl-4-ol **1** as a novel class of Chk1 inhibitors.[17] We herein report the synthesis and biological activity of

Keywords: Checkpoint kinase 1; Chk1 inhibitor; Kinase; DNA damage; DNA repair; Pyrazole; Antitumor; Cancer.
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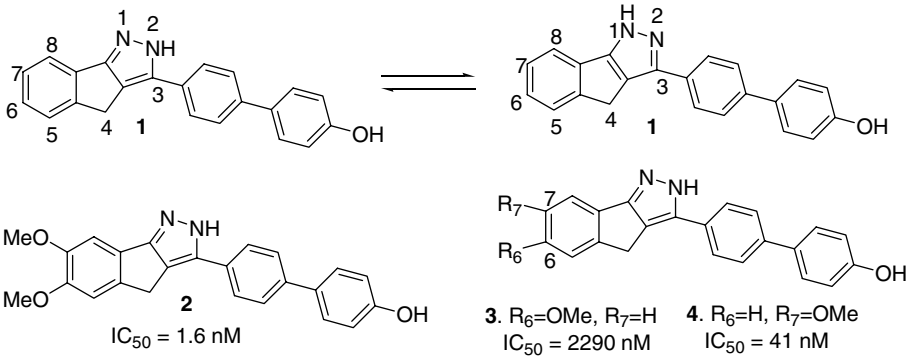
6,7-disubstituted indeno[1,2-*c*]pyrazoles as potent Chk1 inhibitors.

During the course of the optimization of **1**, we have performed detailed SAR studies on the 6- and 7- positions, and we found that analogues with substituents on both the 6- and 7-positions are more potent than the analogues with single substituent on either the 6- or 7-position. For example, 4′-(6,7-dimethoxy-2,4-dihydroindeno[1,2-*c*]pyrazol-3-yl)biphenyl-4-ol **2** is over a thousand fold more potent than the 6-position mono-substituted analogue **3** and is over 25-fold more potent than the 7-position mono-substituted analogue **4**. The lead compound **2** is not only highly potent in the inhibition of Chk1 in an enzymatic assay, but also significantly potentiates the cytotoxicity of DNA damaging agents to tumor cells (vide infra).



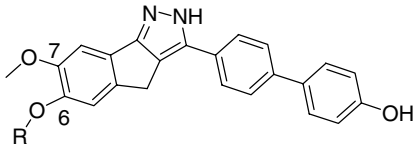
Examination of an X-ray co-crystal structure of a tricyclic pyrazole-Chk1 complex[6a,17] reveals that the 6-position is very open to a solvent accessible region, which should be able to accommodate a variety of groups for further optimization of **2**. Thus, analogues **5**–**32** were synthesized and evaluated (Table 1). Compounds **5**–**13**, which possess an aliphatic amine at the terminus of the substituent, show subnanomolar to single digital nanomolar IC_{50} values against Chk1. Compounds with an aromatic group attaching to the amine (**14** and **15**) retain the potency against Chk1. Compounds with heteroaromatic substituents on the 6-position (**16**–**24**) also show good activity against Chk1, although they are less potent than the analogues bearing aliphatic amines. The diol analogues **25**–**27** are the most potent Chk1 inhibitors identified in this series and have IC_{50} values in the picomolar range. An X-ray crystallographic analysis of the **25**-Chk1 complex indicates a hydrogen bond between a hydroxyl group of the diol and the side chain of Asp94, which may significantly contribute to the extremely high potency (data not shown). Compounds with cyclic substituents at the 6-position (**28**–**31**) exhibit subnanomolar potencies against Chk1. It is noteworthy that although analogue **31** has a hydrophobic group at the 6-position, it shows excellent Chk1 inhibition potency.

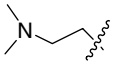
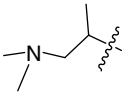
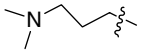
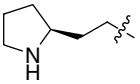
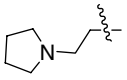
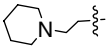
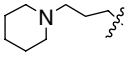
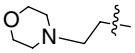
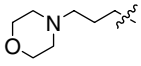
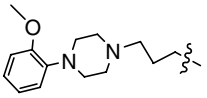
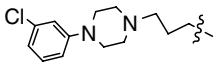
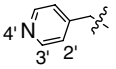
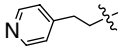
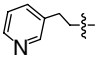
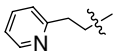
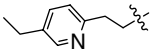
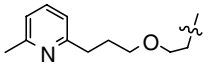
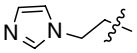
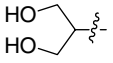
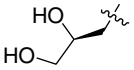
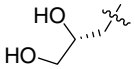
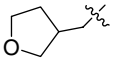
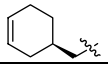
Table 2 shows the structure–activity relationship at the 7-position. X-ray co-crystal structure of a tricyclic pyrazole-Chk1 complex shows that the substituent at the 7-position is pointing into a solvent exposed region along the extended hinge,[6a,17] indicating that this position may accommodate a variety of group. Indeed, aminoalkyl substituted analogues (**34**–**42**) inhibit Chk1 with IC_{50} values of subnanomolar to single digital nanomolar. Analogues with aromatic rings (**45**–**47**) also strongly inhibit Chk1, but they are less potent compared with the aminoalkyl analogues. The insertion of an amide linker decreases potency (**48** vs **34**, **49** vs **37**, **50** vs **41**, **51** vs **45**). This may be due to the increased rigidity of amide bond that clashes with the protein. Alternatively, one could also argue that the polar amide bond might not be tolerated in this largely hydrophobic region. It is worthy of note that the trifluoromethyl analogue **52** is more than 100-fold less potent than the lead compound **2**, indicating a strong electronic effect.

The potentiation of cytotoxicity of DNA-damaging agents by Chk1 inhibitors was measured in a MTS assay using HeLa cells, a p53-null human cervical cancer cell line. The EC_{50} values for the compounds were determined either alone or in the presence of 150 nM of doxorubicin (Dox), a clinical topoisomerase II inhibitor known to arrest the G2/M checkpoint at this concentration in HeLa cells. The EC_{50} values for Chk1 inhibitors in combination with Dox were calculated from the percentage of inhibition by Chk1 compounds at various concentrations above the background inhibition by 150 nM Dox. The ability of Chk1 inhibitors to potentiate Dox is represented by the ratio of the EC_{50} values of the inhibitor alone and the inhibitor with Dox. As shown in Table 3, compounds **2**, **17**, **22**, **30**, **45**, and **46** show little or no antiproliferative activity alone but significant activity in the presence of Dox. We define these compounds as ideal Chk1 inhibitors. The substituents at the C6- and C7-position have significant impact on the cellular activity. Several other compounds such as **11**, **13**, **16**, **21**, **23**, and **26** significantly potentiate the cytotoxicity of Dox, but they also exhibit single agent antiproliferative activity. Physicochemical properties such as variation in cellular penetration and potential off-target activity[18,19] may contribute to the lack of a good correlation between Chk1 enzymatic inhibition potency and cellular antiproliferative activity.

Fluorescence-activated cell sorting (FACS) analysis of cell cycle profiles was performed to confirm that the

Table 1. Structure–activity relationship at the 6-position

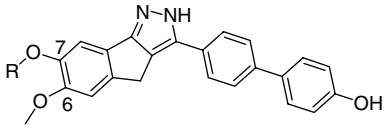


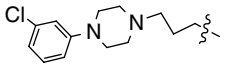
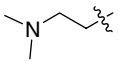
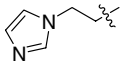
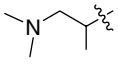
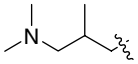
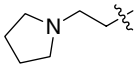
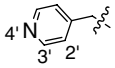
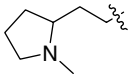
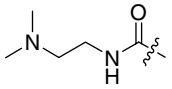
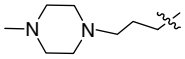
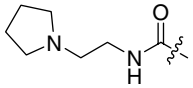
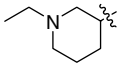
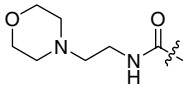
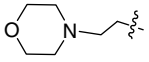
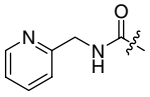
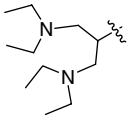
Compound	R=	Chk1 inhibition (IC_{50}, nM)[a]	Compound	R=	Chk1 inhibition (IC_{50}, nM)[a]
5		2	**6**		2
7		0.7	**8**		2
9		0.8	**10**		1
11		4	**12**		2
13		6	**14**		25
15		8	**16**		8
17		18	**18**		20
19		5	**20**		13
21		30	**22**		23
23		62	**24**		5
25		<0.1	**26**		0.1
27		0.1	**28**		0.8
29		0.2	**30**		0.4
31		0.7	**32**	H	1

[a] For Chk1 inhibition enzymatic assay method, see Ref. 15a.

biological activity of the Chk1 inhibitors is expressed through the abrogation of DNA damage-induced checkpoints. Thus, H1299 cells were treated with Chk1 inhibitors in the presence and absence of Dox and their detailed cell cycle kinetics were analyzed by using FACS. As expected, Dox itself induced a remarkable G2/M-phase arrest at 500 nM concentration. Table 4 shows the EC_{50} values for abrogation of the G2/M checkpoint caused by Dox in the presence of various concentrations of Chk1 inhibitors. Chk1 inhibitors did not affect the regular cell cycle profile at high concentration (up to 50 μM), but efficiently abrogated the Dox-induced-G2/M checkpoint with nanomolar EC_{50} values. Furthermore, we confirmed that the

Table 2. Structure–activity relationship at 7-position



Compound	R=	Chk1 inhibition (IC_{50}, nM)[a]	Compounds	R=	Chk1 inhibition (IC_{50}, nM)[a]
33	H	5	**43**		10
34		0.8	**44**		3
35		2	**45**		24
36		0.6	**46**		23
37		2	**47**		36
38		0.8	**48**		40
39		0.2	**49**		21
40		0.6	**50**		74
41		5	**51**		48
42		2	**52**		290

[a] For Chk1 inhibition enzymatic assay method, see Ref. 15a.

Table 3. Cellular activities[a]

Compound	MTS EC_{50} (μM) compound + Dox/(compound alone)	Potentiation ratio	Compound	MTS EC_{50} (μM) compound + Dox/(compound alone)	Potentiation ratio
2	1.02/>59.3	>59	**23**	0.3/4.1	14
7	0.1/0.8	8	**26**	0.4/7.7	19
11	0.1/2.3	23	**27**	0.5/3.5	7
13	0.08/4.3	54	**30**	0.3/49	163
16	0.2/3.2	16	**36**	0.2/1.6	8
17	1.3/>59.3	>46	**44**	0.2/1.9	10
21	0.25/3.4	14	**45**	0.38/>59.3	>156
22	0.8/29.4	37	**46**	0.7/35.2	50

[a] For detailed experimental procedure, see Ref. 15a.

Chk1 inhibitors efficiently abrogated the camptothecin (CPT)-induced S arrest. CPT damages DNA through the inhibition of topoisomerase I and is known to induce S phase arrest. As shown in Figure 1, compound **2** alone did not alter the regular cell cycle profile, but it efficiently abrogated CPT-induced S arrest and forced the cells further into the G2/M phase even at 30 nM concentration. The subG0/G1 population represents the resulting apoptosis.

The synthesis of **2** is shown in Scheme 1. Acid **53** was activated by DCI and then coupled with indanone **55**

Table 4. FACS Analysis data[a]

Compound	FACS analysis EC_{50}[a] (μM) compound + Dox/(compound alone)
2	0.2/>50
11	0.4/>10
21	0.6/>10
22	0.5/>10
23	0.4/>10
26	0.2/>50
45	0.8/>50
46	0.3/>50

[a] For detailed experimental procedure, see Ref. 15a.

in the presence of NaH to provide the diketone **56**. The diketone was treated with hydrazine to produce **2** in 15% total yield for three steps. Alternatively, **2** was also prepared by a improved four-step sequence. Acid **57** was activated by DCI and then was coupled to indanone **55** to yield the diketone **59**. The tricyclic pyrazolyl bromide **60**, obtained by the cyclization of **59**, was treated with 4-hydroxyphenyl boronic acid under Suzuki conditions to produce **2** in 66% total yield for 4 steps. Compounds **3** and **4** were prepared by using a similar synthetic procedure described for **2**.

Scheme 2 outlines the synthesis of compounds **5**–**32**. The 5-methoxyl group of **55** was selectively demethylated and the released hydroxyl group was protected to provide benzyl ether **62**. Diketone **63**, obtained through the coupling of **62** and **58**, was treated with hydrazine to give **64**. The treatment of **64** with SEMCl produced the protected pyrazole **65** as a mixture of two regioisomers with a SEM group on either of the nitrogen atoms (for clarity, only one isomer is shown). Compound **66** was prepared by the Suzuki coupling of **65** and 4-hydroxyphenyl boronic acid, and the phenol was protected to give **67**. The key intermediate **68** was obtained by the debenzylation of **67**. Compound **69** was prepared by coupling of **68** with an alcohol under Mitsunobu conditions or with organohalides in the presence of base. Removal of the SEM groups under acidic conditions provided Chk1 inhibitors **5**–**32**.

The synthesis of **34**–**47** is shown in Scheme 3. Demethylation of **55** gave diol **70** in quantitative yield. The 6-hydroxyl group was selectively methylated to provide **71** in good yield and the 7-hydroxyl group of **71** was protected to afford benzyl ether **72**. With **72** in hand, the key intermediate **78** was prepared by following a synthetic sequence similar to that described for **68**. Alkylation of the hydroxyl group of **78** by Mitsunobu reaction under various conditions gave only poor yield. Fortunately, direct alkylation of the phenol with organic halides was achieved in the presence of Cs_2CO_3 in DMF. This simple

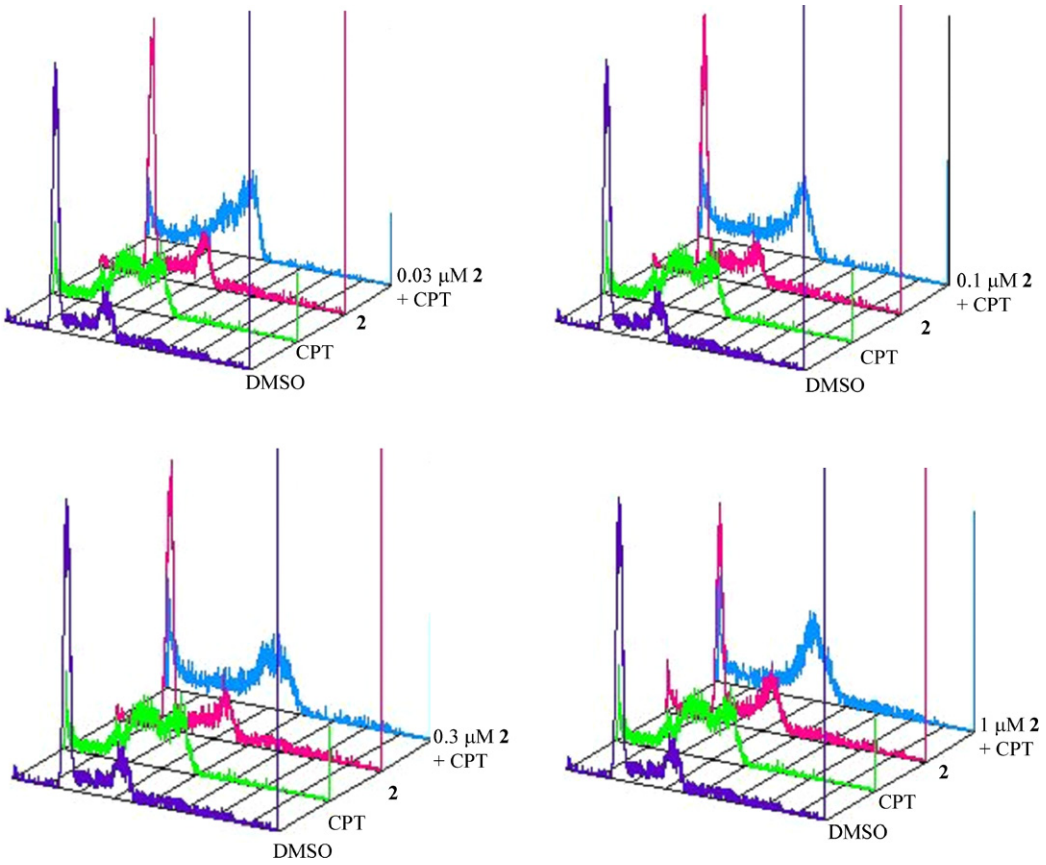
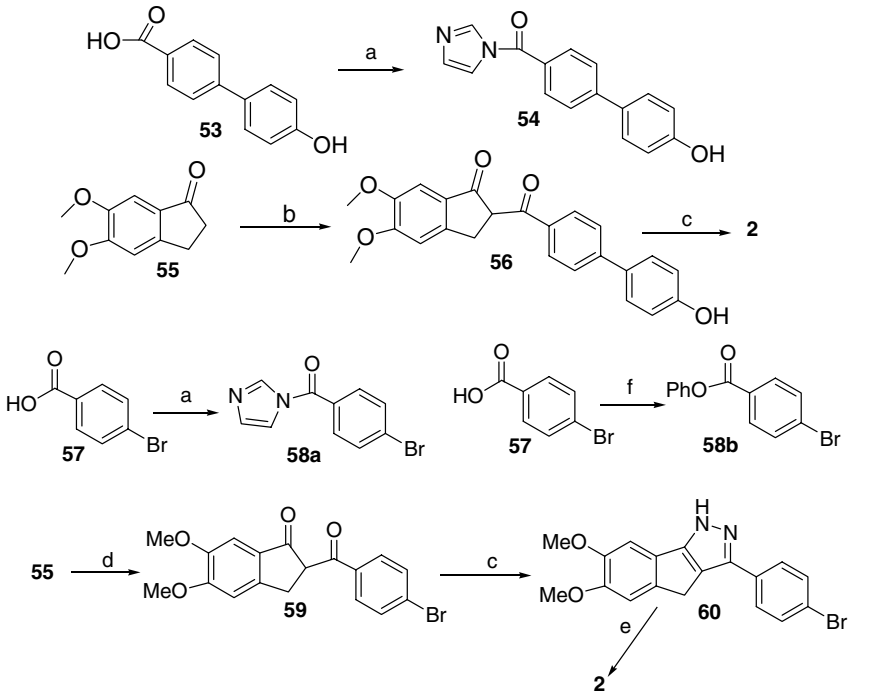
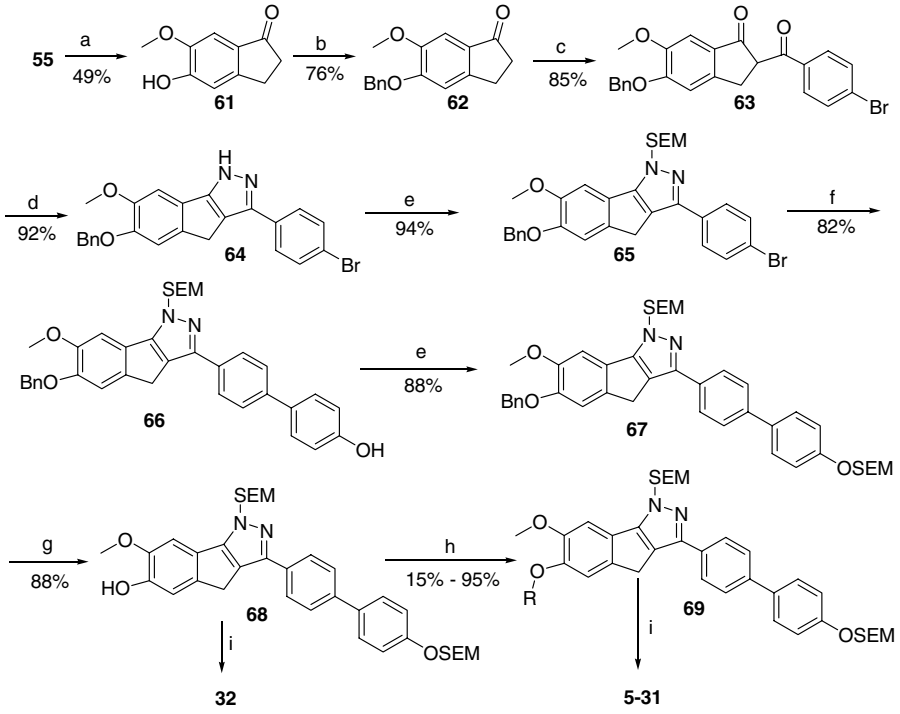


Figure 1. FACS profiles of SW620 cells treated with CPT (75 nM) in the presence and absence of various concentrations of Chk1 inhibitors **2** for 48 h. The cells were stained with propidium iodide for DNA contents. G0/G1 cells contain 2 N DNA, while cells in G2/M phase have 4 N DNA. S phase cells have DNA content between 2 and 4 N. Apoptotic cells contain less than 2 N DNA. The figures show cell numbers on the *Y*-axis and DNA content on the *X*-axis.



Scheme 1. Reagents: (a) DCI, DMF; (b) **54**, NaH, THF; (c) NH_2NH_2, HOAc, ethanol; (d) **58a** (or **58b**), NaH, THF; (e) 4-hydroxyphenyl boronic acid, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME–EtOH–H_2O; (f) phenol, DCC, DMAP, ether.

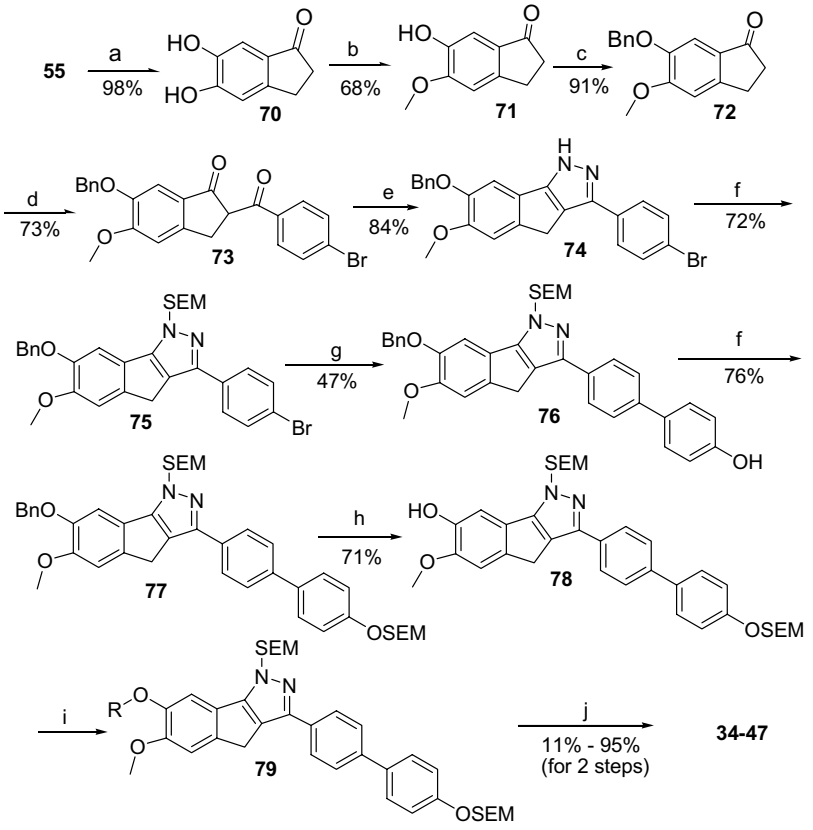


Scheme 2. Reagents and conditions: (a) NaCN, DMSO, 100 °C; (b) BnBr, K_2CO_3, NaI, acetone; (c) **58**, NaH, THF; (d) NH_2NH_2, HOAc, ethanol; (e) NaH, SEMCl, DMF; (f) 4-hydroxyphenyl boronic acid, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME–EtOH–H_2O, microwave, 160 °C; (g) Pd/C (10%), THF; (h) RCl (or RBr), Cs_2CO_3, DMF, or ROH, DBAD, PS–Ph_3P, THF; (i) HCl, MeOH.

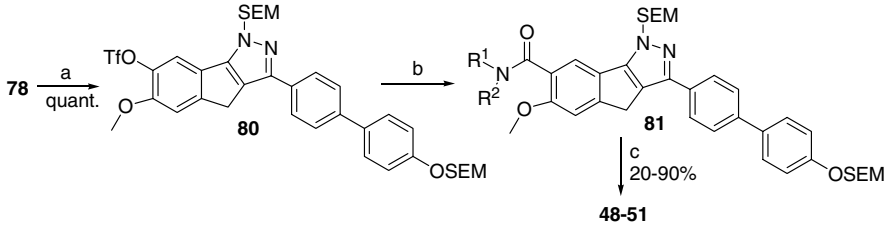
alkylation expedited the synthesis of ether analogues **79**. Complete deprotection of **79** in a HCl–ethanol system provided **34**–**47**.

Scheme 4 outlines the synthesis of compounds **48**–**51**. Compound **78** was converted to the triflate **80** in quantitative yield. Amidation of **80** gave amides **81**. Removal of SEM group in an acidic condition provided final product **48**–**51**.

The synthesis of **52** is shown in Scheme 5. Compound **71** was converted to dithionocarbamate **82** in moderate

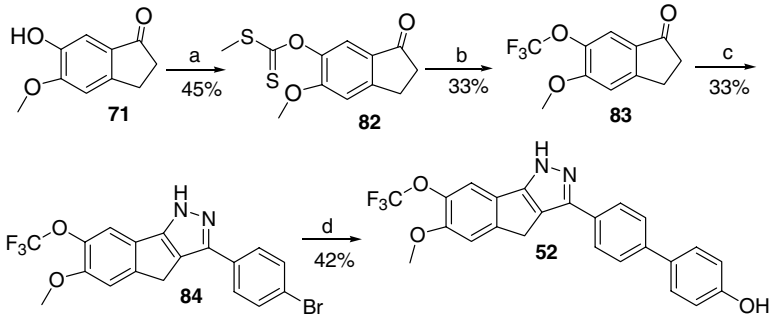


Scheme 3. Reagents and conditions: (a) BBr_3, CH_2Cl_2; (b) MeI, Li_2CO_3, DMF; (c) BnBr, K_2CO_3, acetone; (d) **58a** (or **58b**), NaH, THF; (e) NH_2NH_2, HOAc, ethanol; (f) NaH, SEMCl, DMF; (g) 4-hydroxylphenyl boronic acid, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME–EtOH–H_2O, microwave, 160 °C; (h) Pd/C (10%), THF; (i) RCl (or RBr), Cs_2CO_3, DMF; (j) HCl, EtOH.



Scheme 4. Reagents: (a) NaH, *N*-phenyltrifluoromethane sulfonamide, THF; (b) R_1R_2NH, $PdCl_2$ (dppf), CO (100 psi), triethyl amine, CH_2Cl_2; (c) HCl, EtOH.

yield. The oxidative desulfurization-fluorination of **82** provided trifluoromethyl ether **83**. Compound **83** was coupled to **38b** and the resulting diketone was cyclized in one pot to afford **84**. The Suzuki reaction of **84** with hydroxyphenyl boronic acid in a microwave synthesizer smoothly produced **52**.



Scheme 5. Reagents and conditions: (a) NaH, CS_2, DMF; then MeI; (b) 1,3-dibromo-5,5-dimethylhydantoin, HF/pyridine (70%), CH_2Cl_2; (c) **38b**, NaH, benzene; then, NH_2NH_2, HOAc, ethanol; (d) 4-hydroxylphenyl boronic acid, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME–EtOH–H_2O, microwave, 160 °C.

In summary, a new series of potent tricyclic pyrazole-based Chk1 inhibitors are described. Analogues disubstituted on the 6- and 7-positions show improved Chk1 inhibition potency compared with analogues bearing a single substituent on either the 6- or 7-position. Based on the lead compound **2**, a detailed SAR study on the 6- and 7-positions led to the identification of the potent Chk1 inhibitors **11**, **13**, **16**, **17**, **22**, **21**, **23**, **26**, **30**, **45**, and **46**. These compounds significantly potentiate the cytotoxicity of DNA-damaging antitumor agents in a cell-based assay and efficiently abrogate the Dox-induced G2/M and CPT-induced S checkpoints, supporting that their potent biological activities are mechanism-based through Chk1 inhibition. The introduction of polar groups at the 6- and 7-positions would improve the physicochemical properties such as solubility.

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