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Synthesis of selenophene derivatives as novel CHK1 inhibitors

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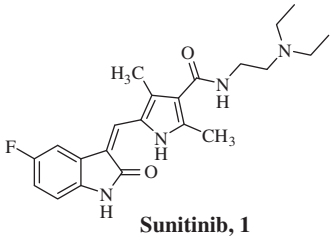
ABSTRACT

A series of selenophene derivatives **3** were synthesized as potential CHK1 inhibitors. The effects of substitution on the 4′- or 5′-position of selenophene moiety and shifting the hydroxyl group position on C6-phenolic ring of oxindole were explored. This study led to the discovery of the most potent CHK1 inhibitors **29**–**33** and **39**–**43**, which had IC_{50} values in the subnanomolar range.

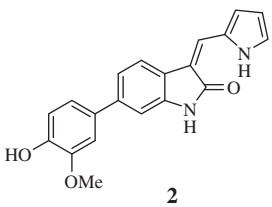
Many anticancer drugs express their biological activity through damaging DNA and have greatly contributed to the survival increases of cancer patients.[1] However, DNA-damaging anticancer agents are also very toxic to normal cells, therefore restrict to the clinic application. One of major reasons for the resistance is that the damaged tumor DNA can be repaired due to the DNA damage-induced checkpoints, thereby avoiding cell death. Checkpoint kinase 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. Consequently, CHK1 has emerged as an attractive chemosensitization target especially since approximately 50% of human cancers are p53-deficient.[4,5]

Several classes of small molecule inhibitors of CHK1 have been reported,[5] including indolocarbazoles,[6] isogranulatimides,[7] debromohymenialdisines,[8] aminopyrimidines,[9] pyrrolopyridines,[10] indolinones,[11] benzimidazole-quinolinones,[12] indazoles,[13] and diarylureas.[14]

3-Substituted indolin-2-ones have been reported as potent and selective inhibitors of different protein kinases. Among them, sunitinib **1** has been approved and marketed for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor.[15] Compound **2** showed an IC_{50} of 7 nM in the CHK1 kinase assay, however, the effects of substitution on the pyrrole moiety on



Sunitinib, 1



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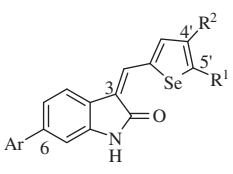

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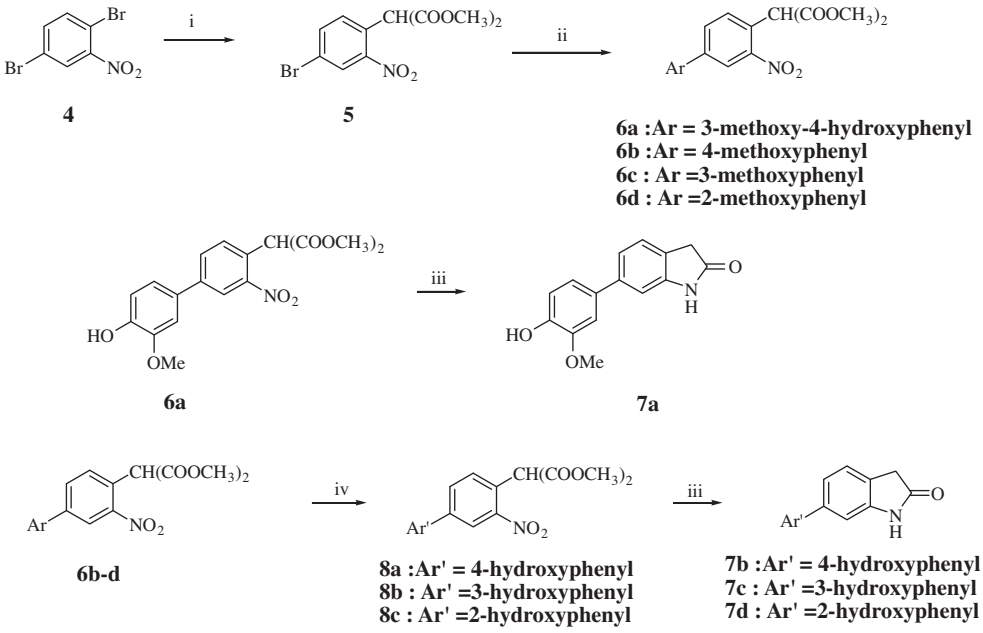
the inhibition of CHK1 kinase have not been disclosed in the literature.[11] In this report, we describe the investigational results on the synthesis of a series of selenophene derivatives **3** and their bioactivity as CHK1 kinase inhibitors.

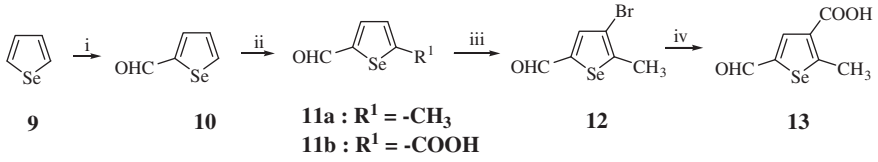
The synthesis of selenophene derivatives **3** consists of three steps: (1) preparation of the 6-aryl-indolin-2-ones (Scheme 1), (2) preparation of selenophene-2-carboxyaldehyde derivatives (Scheme 2) and (3) condensation of the 6-aryl-indolin-2-ones with the selenophene-2-carboxyaldehyde derivatives to afford the 3-substituted indolin-2-ones (Scheme 3).

As illustrated in Scheme 1 and 6-substituted oxindoles **7** were prepared via commercially available compound **4**, which undergoes regioselective substitution with dimethyl malonate under basic conditions. Pd mediated Suzuki coupling between compound **5** and commercially available aryl boronic acid gave compound **6**.[16] In one-pot reaction, 6-(4-hydroxy-3-methoxyphenyl)indolin-2-one **7a** was synthesized from intermediate **6a**.[17] Demethylation of the methoxyphenyl group of compounds **6b–d** with BBr_3 yielded the phenolic intermediates **8a–c**, which were then transformed into the 6-substituted oxindoles **7b–d**.

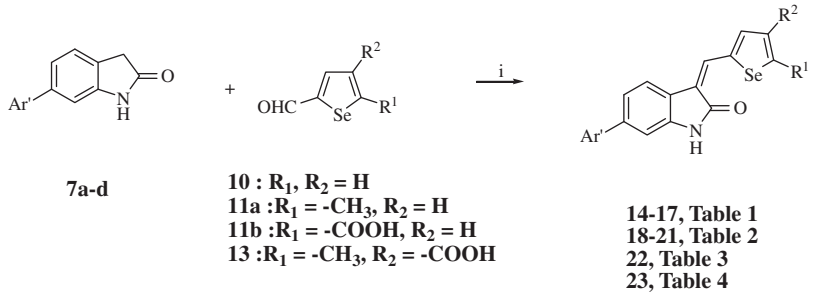
Compounds **11** and **13** were prepared from the commercially available selenophene **9** via lithiation and quenching with proper electrophile, such as DMF, CH_3I or dry ice (Scheme 2). Compound **10** was isolated after *ortho*-lithiation of selenophene **9** and quenching with DMF. Compounds **11** were synthesized from intermediate **10**, following protection, lithiation, and quenching with CH_3I or dry ice. In a regioselective bromination, compound **11a** was converted into the intermediate **12**.[18] Compound **13** was prepared from compound **12**, by protection, lithium–bromine exchange, and quenching with dry ice.



Scheme 1. Reagents: (i) $CH_2(COOCH_3)_2$/NaH/DMF (72%); (ii) $ArB(OH)_2$/$(Ph_3P)_4Pd$/$NaHCO_3$ (46–85%); (iii) Sn/HCl (55–80%); (iv) BBr_3/CH_2Cl_2 (80–86%).

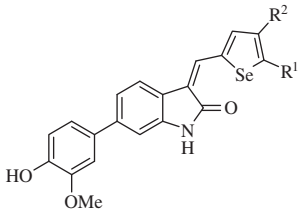


Scheme 2. Reagents: (i) (1) BuLi; (2) DMF (68%); (ii) (1) $HC(OCH_3)_3$; (2) BuLi; (3) MeI or $CO_{2(s)}$, **11a** (76%) or **11b** (55%); (iii) $Br_2/AlCl_3$ (86%); (iv) (1) $HC(OCH_3)_3$; (2) BuLi; (3) $CO_{2(s)}$ (45%).



Scheme 3. Reagents: (i) piperidine/ethanol (55–80%).

Table 1
Inhibition data for 3-methoxy-4-hydroxyphenyl analogs **14–17** and **24–33**



Compd	R^1	R^2	IC_{50}[a] (nM)
14	H	H	20.8
15	CH_3	H	13.3
16	COOH	H	71.2
17	CH_3	–COOH	12.0
24	$CONH(CH_2)_2N(CH_3)_2$	H	2.6
25	$CONH(CH_2)_2N(CH_2CH_3)_2$	H	10.0
26	$CONH(CH_2)_2N(CH_2CH_2)_2$	H	4.5
27	$CONH(CH_2)_2N(CH_2CH_2)_2O$	H	8.8
28	$CONH(CH_2)_3$-1*H*-imidazole	H	3.7
29	CH_3	$CONH(CH_2)_2N(CH_3)_2$	0.5
30	CH_3	$CONH(CH_2)_2N(CH_2CH_3)_2$	0.6
31	CH_3	$CONH(CH_2)_2N(CH_2CH_2)_2$	0.3
32	CH_3	$CONH(CH_2)_2N(CH_2CH_2)_2O$	1.0
33	CH_3	$CONH(CH_2)_3$-1*H*-imidazole	0.5

Values are means of two or more experiments.
[a] See Ref. 21 for CHK1 inhibition enzymatic assay method.

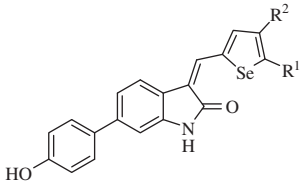
The 3-substituted indolin-2-ones **14–23** were prepared by condensing the 6-substituted oxindoles **7** with selenophene-2-carboxyaldehyde derivatives under basic conditions (Scheme 3). The 3-substituted indolin-2-ones may exist as either the *Z*- or *E*-isomer depending on the characteristics of the substituent at the C-3 position of the indolin-2-one. Oxindoles having 3-substituted thienyl group exist as *Z*-isomers and 3-substituted furanyl indolin-2-ones appear to favor the *E*-isomer form.[19] Configurations of compounds **14–23** were assigned as *Z*-isomers by comparing the chemical shift of the vinyl proton with 3-substituted thienyl compounds as described in the literature.[20]

The effect of replacement of the pyrrole ring of compound **2** with a series of selenophene derivatives is shown in Table 1. It reveals that the compound **14** shows very comparable in vitro activity with the corresponding pyrrole compound **2** (7 nM). Compounds **15** and **17** with $–CH_3$ substituent at C5′- position on the selenophene ring are marginally more potent than the compound **14**. However, compound **16** reduced the activity. Since these selenophene compounds possessed CHK1 inhibitory activity, we then turned our attention to study on the amidation of C4′- or C5′-carboxylic acid group of compound **16** and **17** with various aminoalkylamide functionalities.[22] It was hoped that the modification would enhance CHK1 enzymatic potency and provide a handle for introducing water soluble groups. The compound **24** shows a 27-fold increase in potency compared with the C5′-carboxylic acid compound **16**. Similar results were also observed in compounds **25–28**. Being encouraged by the above results, we extensively explored the C4′-carboxylic acid compound **17**. Indeed, C4′-substituted analogues **29–33** show subnanomolar IC_{50} values against CHK1 kinase. Compound **29** shows a 24-fold increase in potency compared with C4′-carboxylic acid compound **17** and a 14-fold increase in potency compared with the pyrrole compound **2**. We also found that compounds **29–33** with C4′-aminoalkylamide substituent are more potent than C5′-aminoalkylamide compounds **24–28**.

The effects of replacement the 3-methoxy-4-hydroxyphenyl moiety at C-6 position of oxindole (**14–17**) with 4-hydroxyphenyl (**18–21**) were also studied. The results are shown in Table 2. Compound **18** also shows equal activity against CHK1 by comparing to compound **14**. The C5′- methyl substituted compounds **19** and **21** retain the potency against CHK1. The compound **20** with carboxylic acid at C5′- position reduced a large activity. It is interesting to note that converting the C5′- position carboxylic acid group of compound **20** into a C5′-aminoalkylamide substituted analogues **34–38** enhance the inhibitory activity for CHK1 and have IC_{50} values in the single digital nanomolar range. The C4′-aminoalkylamide substituted analogues **39–43** are the most potent CHK1 inhibitors in this series.

We then focused our attention on the impact of shifting the hydroxyl group position on the C6 phenolic ring of oxindole. The results are shown in Table 3 and Table 4. Replacing the 4-hydroxyphenyl group in **39–43** by 3-hydroxyphenyl caused a huge reduction in potency. For example, the 3-hydroxyphenyl compound **44**

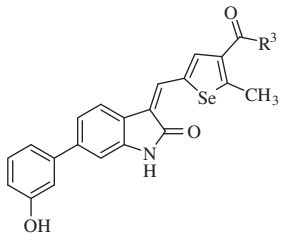
Table 2
Inhibition data for 4-hydroxyphenyl analogs **18–21** and **34–43**



Compd	R^1	R^2	IC_{50} (nM) [a]
18	H	H	12.8
19	CH_3	H	18.8
20	COOH	H	>100
21	CH_3	–COOH	15.1
34	$CONH(CH_2)_2N(CH_3)_2$	H	7.6
35	$CONH(CH_2)_2N(CH_2CH_3)_2$	H	4.6
36	$CONH(CH_2)_2N(CH_2CH_2)_2$	H	5.9
37	$CONH(CH_2)_2N(CH_2CH_2)_2O$	H	4.5
38	$CONH(CH_2)_3$-1*H*-imidazole	H	8.0
39	CH_3	$CONH(CH_2)_2N(CH_3)_2$	0.6
40	CH_3	$CONH(CH_2)_2N(CH_2CH_3)_2$	0.4
41	CH_3	$CONH(CH_2)_2N(CH_2CH_2)_2$	0.4
42	CH_3	$CONH(CH_2)_2N(CH_2CH_2)_2O$	0.8
43	CH_3	$CONH(CH_2)_3$-1*H*-imidazole	0.5

[a] Values are means of two or more experiments.

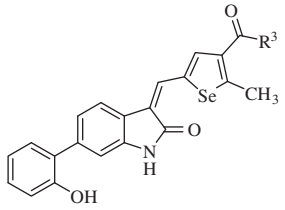
Table 3
Inhibition data for 3-hydroxyphenyl analogs **22** and **44–48**



Compd	R^3	IC_{50}[a] (nM)
22	OH	>100
44	$NH(CH_2)_2N(CH_3)_2$	33.0
45	$NH(CH_2)_2N(CH_2CH_3)_2$	78.9
46	$NH(CH_2)_2N(CH_2CH_2)_2$	74.3
47	$NH(CH_2)_2N(CH_2CH_2)_2O$	>100
48	$NH(CH_2)_3$-1*H*-imidazole	64.9

[a] Values are means of two or more experiments.

Table 4
Inhibition data for 2-hydroxyphenyl analogs **23** and **49–53**



Compd	R^3	IC_{50}[a] (nM)
23	OH	>100
49	$NH(CH_2)_2N(CH_3)_2$	>100
50	$NH(CH_2)_2N(CH_2CH_3)_2$	>100
51	$NH(CH_2)_2N(CH_2CH_2)_2$	>100
52	$NH(CH_2)_2N(CH_2CH_2)_2O$	>100
53	$NH(CH_2)_3$-1*H*-imidazole	>100

[a] Values are means of two or more experiments.

shows a 55-fold decrease in potency compared with the corresponding 4-hydroxyphenyl compound **39**. This trend was also observed on compounds **45**–**48** a more than 125-fold decrease in potency compared with corresponding 4-hydroxyphenyl compounds **40**–**43**. Table 4 also reveals that replacing the 4-hydroxyphenyl group in **39**–**43** by 2-hydroxyphenyl (**49**–**53**) greatly reduce their activity. These SAR studies clearly indicate that the 3-methoxy-4-hydroxyphenyl analogues **29**–**33** and the 4-hydroxyphenyl analogues **39**–**43** with IC_{50} values of subnanomolar range provide the most potent compounds and are far more potent than the other 3-hydroxyphenyl and 2-hydroxyphenyl analogues in this investigation.

In summary, we have demonstrated selenophene derivatives **29**–**33** and **39**–**43** are potent CHK1 inhibitors. Variation of the substituent on the C4′ or C5′-position of selenophene ring and the hydroxyl group position on C-6 phenolic ring of oxindole are critical for CHK1 inhibitory. In general, 3-methoxy-4-hydroxyphenyl analogues **29**–**33** and the 4-hydroxyphenyl analogues **39**–**43** with an IC_{50} value of subnanomolar range possess the most potent inhibitory activities against the CHK1 enzyme. Amidation of either the C4′- or C5′-carboxylic acid on the selenophene ring results in not only increase in CHK1 enzyme potency, also provides a handle for introducing water soluble groups to improve the pharmaceutical properties of the indol-2-ones. Our continued efforts to further study and improve the overall biological and pharmaceutical profile will be reported in future.

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