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Design and synthesis of novel bis-thiazolone derivatives as micromolar CDC25 phosphatase inhibitors: Effect of dimerisation on phosphatase inhibition

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ABSTRACT

CDC25 phosphatases are involved in deregulated cell cycle progression and tumor development with poor prognosis. Among the most potent CDC25 inhibitors, quinonoid-based derivatives have been extensively studied. Dimerisation of heterocyclic quinones has led to IRC-083864, a bis-quinone compound with increased CDC25B inhibitory activity. Thirty-one bis-thiazolone derivatives were synthesized and assayed for CDC25 inhibitory activity. Most of the dimers displayed enhanced inhibitory activities with micromolar IC_{50} values lower than that observed for each thiazolone scaffold separately. Moreover, most of these compounds were selective CDC25 inhibitors. Dimer **40** showed an IC_{50} value of 2.9 μM and could inhibit CDC25 activity without generating reactive oxygen species which is likely to occur with quinone-based inhibitors. Molecular docking studies suggested that the dimers could bind simultaneously to the active site and the inhibitor binding pocket.

Cell signaling is regulated by covalent and reversible phosphorylation and dephosphorylation reactions which are controlled by protein tyrosine kinases and phosphatases.[1,2] These signaling pathways are responsible for essential cell events including growth, differentiation, division or death. Thus, abnormal regulation of this fine-tuned mechanism can lead to the development of human diseases such as cancers.

Protein tyrosine phosphatases (PTPs), as their counterparts the protein tyrosine kinases, are now considered as promising therapeutic targets.[3,4] Their implication in numerous human diseases has led to an intensive search for potent inhibitors.[5] Among the super family of PTPs, CDC25 phosphatases are dual-specificity phosphatases which play a central role in cell cycle progression and in the checkpoint response to DNA damage in normal cells.[6,7] Three isoforms have been identified in human, namely CDC25A, B and C.[8–10] Up-regulation of CDC25A and B has been observed in a wide variety of human cancers[11,12] and CDC25 are also involved in oncogenic transformation.[13] Thus, isoforms A and B have been identified as potential targets for cancer therapy. Consequently, many efforts have been devoted to search for CDC25 inhibitors. The most potent are quinonoid-based structures which have been extensively studied.[14] Dimerisation of heterocyclic quinones has led to the bis-quinone IRC-083864 with increased potency which is currently the most potent CDC25 inhibitor with IC_{50} values in the nanomolar range (Fig. 1).[15] In addition, it was demonstrated to reduce the growth of prostatic and pancreatic human tumors in mice with tumor xenografts. However, quinonoid-based inhibitors are likely to induce toxicity, mostly by generating reactive oxygen species during the redox cycling of quinone moieties.

Starting from in silico/in vitro screening experiments to identify non quinonoid-based CDC25 inhibitors, we previously reported the development of a series of thiazolopyrimidinone derivatives as micromolar CDC25B inhibitors (Compound **I**, Fig. 1).[16,17] These compounds exhibited cytotoxic activity toward the human cancer cell lines LNCaP (prostate) and MiaPaCa-2 (pancreatic adenocarcinoma) and we also could show that they target CDC25B in cellular assays. Moreover, analysis of the structure-activity relationship in this series underlined the importance of the 4-hydroxybenzylidene-thiazolone moiety for the phosphatase inhibitory activity. Thus, we decided to evaluate the efficiency of compounds containing two 4-hydroxybenzylidene-thiazolone scaffolds toward CDC25B activity (Fig. 1).

Herein, we describe the synthesis and the enzymatic evaluation of bis-thiazolone derivatives as CDC25B inhibitors. To assess their selectivity, we also examined their efficacy on two other protein tyrosine phosphatases, namely PTP1B (Protein Tyrosine Phosphatase 1B) and VHR (Vaccinia virus H1 Related), the latter being a dual-specificity phosphatase. In addition, molecular modeling studies were performed to investigate the binding mode of these new CDC25B inhibitors.

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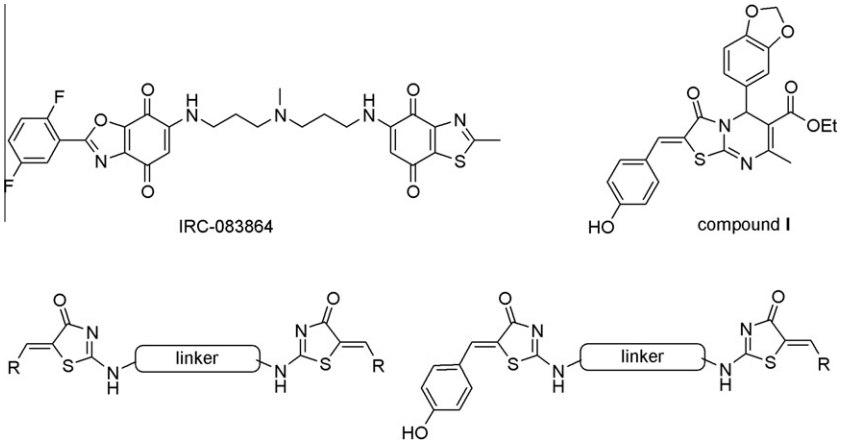


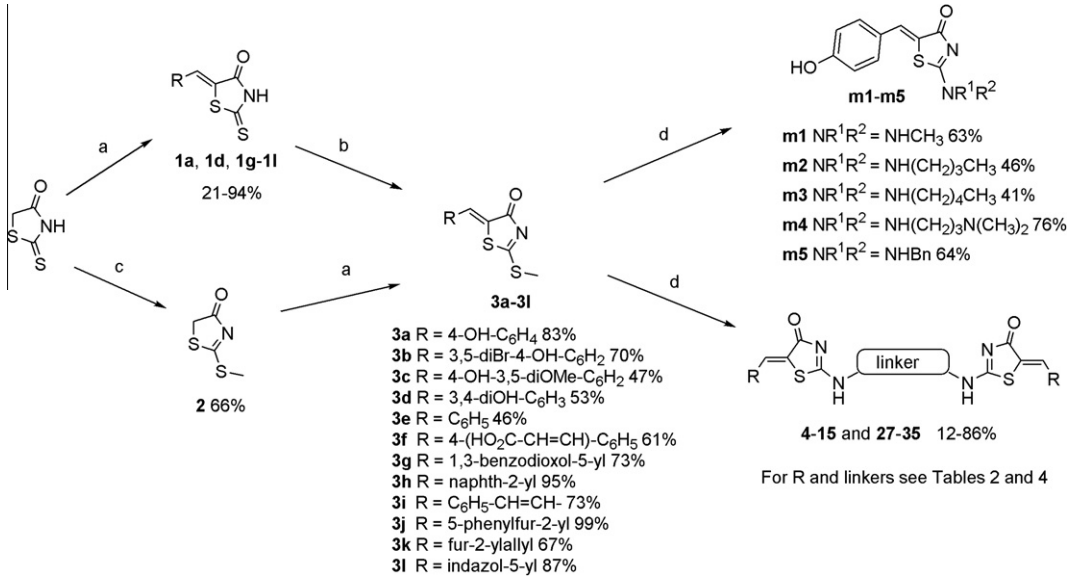
Fig. 1. CDC25 inhibitors and structures of the newly designed inhibitors.

Starting from the thiazolopyrimidinone **I**, we first decided to simplify the chemical structure and conserved only the 4-hydroxybenzylidene-thiazolone moiety. In a first attempt, we thus prepared thiazolones **m1**–**m5** for a preliminary enzymatic evaluation and bis-thiazolones **4**–**15** in order to investigate the nature of the chain linking the two scaffolds (Scheme 1). Synthetic strategies for the preparation of thiazolones are well documented in the literature.[18] Preparation of thiazolones **m1**–**m5** and symmetrical bis-thiazolones **4**–**15** and **27**–**35** was achieved according to reported procedures for the preparation of 2-amino-5-benzylidene-thiazol-4-one derivatives as described in Scheme 1. Rhodanine was condensed with different aldehydes in the presence of piperidine in ethanol to afford intermediates **1a**, **1d** and **1g**–**1l**. Subsequent activation of the thione function was realized *via* the formation of the corresponding methyl thioethers **3a**, **3d** and **3g**–**3l**. An alternative route consisted first in the activation of the thione function which led to the formation of compound **2** followed by Knoevenagel condensation to give compounds **3b**–**3c** and **3e**–**3f**. Thioethers **3a**–**3l** were finally reacted with the selected amines or di-amines in refluxing ethanol to afford the target compounds. All intermediate and final compounds were obtained as a single isomer. A *Z*-configuration of the exocyclic C=C bond was confirmed by the chemical shift value of the methine proton, which was comparable to reported data for analogous derivatives.[19,20]

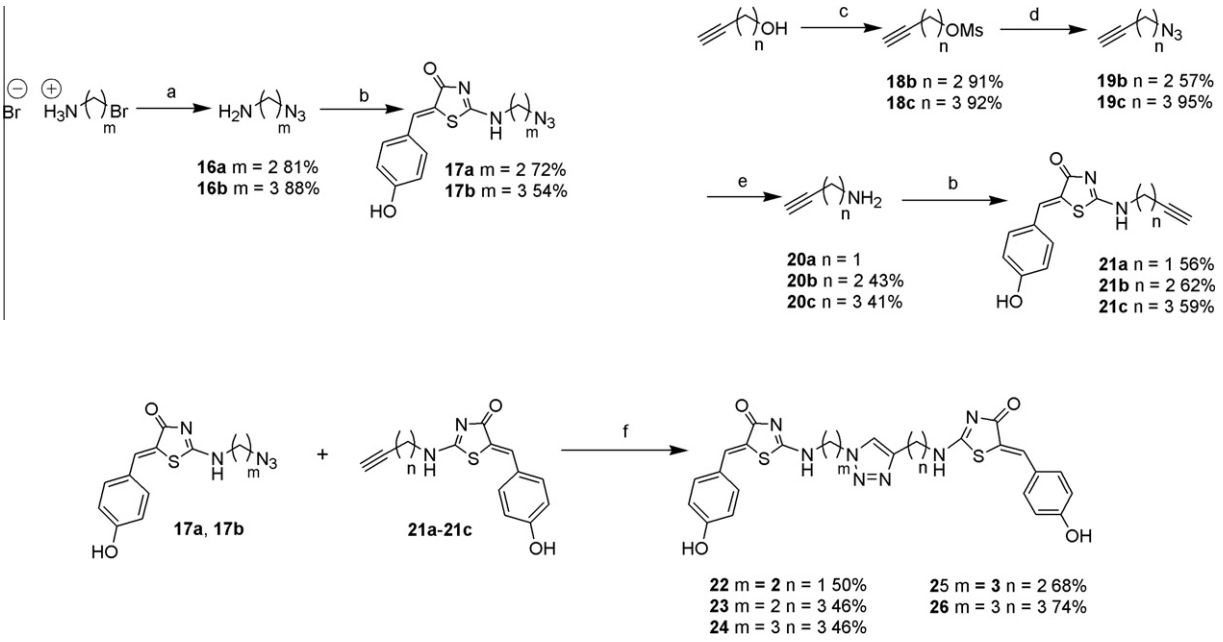
To complete the study concerning the nature of the linker, bis-thiazolones **22**–**26** with a triazole-containing linker were prepared using the well known (3+2) cyclo-addition developed by Huisgen (Scheme 2). Azidothiazolones **17a** and **17b** were obtained by reacting azidoalkylamines **16a** and **16b**[21] with **3a** whereas alkyne derivatives **21a**–**21c** were synthesized in a similar way from the propargylamine hydrochloride **20a** and the alkynes **20b**–**20c** prepared using the method reported by Saito.[22]

Asymmetrical bis-thiazolones **40**–**44** were synthesized according to the route described in Scheme 3. Key intermediate **38** was obtained by introducing successively, the Boc-protected aminoethyl chain and the corresponding free amino ethyl chain on the piperazine ring. Mono-thiazolone **39** was then prepared by reacting amino derivative **38** and **3a**. The Boc group was cleaved using TFA and the selected thiazolones **3b**, **3g**, **3i**, **3k** and **3l** were introduced in a similar way giving asymmetrical dimers **40**–**44**.

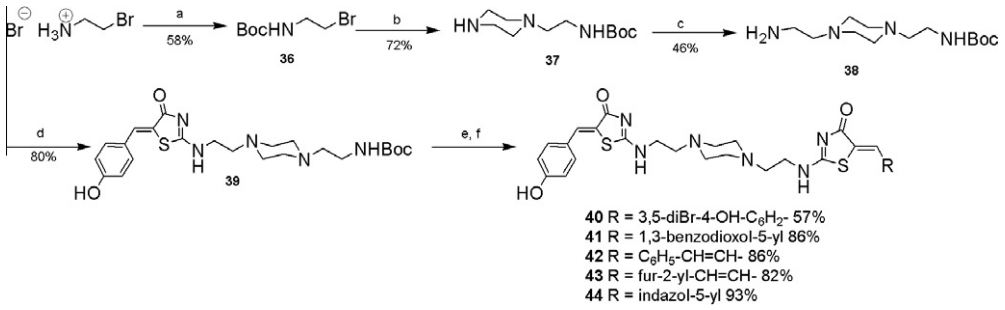
All compounds were assayed for their inhibitory activity against the recombinant fusion protein MBP-CDC25B, PTP1B and VHR



Scheme 1. Reagents and conditions: (a) RCHO, piperidine, EtOH, reflux, 12 h; (b) CH_3I, DIPEA, EtOH, rt, 12 h; (c) CH_3I, aq NaOH (0.5 M), rt, 24 h; (d) R_1R_2NH (1 equiv) or H_2N-linker-NH_2 (0.5 eq), EtOH, reflux, 8 h.



Scheme 2. Reagents and conditions: (a) NaN_3, H_2O, 80 °C, 5 h; (b) **3a**, EtOH, reflux, 12 h; (c) MsCl, Et_3N, Et_2O, 0 °C, 3 h; (d) NaN_3, DMF, 70 °C, 3 h; (e) PPh_3, Et_2O, 0 °C, 3 h; (f) sodium ascorbate (1 equiv), $CuSO_4{\cdot}5H_2O$ (10%), DMF/H_2O, rt, 12 h.



Scheme 3. Reagents and conditions: (a) Boc_2O, Et_3N, MeOH, rt, 18 h; (b) piperazine (4 eq), K_2CO_3, NaI, acetone, reflux, 18 h; (c) 2-bromoethylammonium hydrobromide, K_2CO_3, NaI, MeOH, reflux, 18 h; (d) **3a**, EtOH, reflux, 16 h; (e) TFA, CH_2Cl_2, rt, 30 min; (f) **3b**, **3g**, **3i**, **3k** and **3l**, MeOH, reflux, 16 h.

using fluorescein-3,6-diphosphate as the substrate.[17] As can be seen from the data reported in Table 1, mono-thiazolones **m1**–**m5** were weakly active on CDC25B with percentage of phosphatase activity inhibition between 10% and 45% at the concentration of 100 μM. These compounds showed similar inhibitory activity toward PTP1B but appeared totally inactive on VHR at the same concentration. By contrast and as expected, most of the synthesized bis-thiazolones **4**–**15** showed a large increase of the inhibitory activity on CDC25B (Table 2). Compounds **4**–**9** containing an alkyl chain with 4 to 9 carbon atoms displayed comparable CDC25B inhibitory activity with IC_{50} values between 2.5 and 13.9 μM. Surprisingly, introduction of the aminated linker of IRC-083864 led to a total loss of activity, the corresponding thiazolone **10** showing only an inhibition of 30% of the phosphatase activity at the concentration of 100 μM. A similar result was obtained for compound **11** with two oxygen atoms in the alkyl chain. Bis-thiazolones **12**–**15** with linkers containing aryl or alkyl rings were then prepared to increase the rigidity. All dimers in this sub-series could inhibit CDC25B activity with IC_{50} values in the micromolar range except bis-thiazolone **15** bearing the longer chain which was inefficient at the concentration of 100 μM. Thus, for this set of compounds, the presence of hydrophobic linkers seems crucial for the inhibition of CDC25 enzymatic activity. As regards selectivity, all compounds showed the same inhibitory profile on PTP1B, though they generally appeared less active. Dimers **7** and **14** were the most selective with IC_{50} values of 3.4 and 2.2 μM toward CDC25 versus 30.6 and 46.0 μM toward PTP1B. VHR was the less sensitive enzyme with only bis-thiazolone **9** showing moderate inhibitory activity (IC_{50} = 33 μM). In conclusion, dimerisation of the 4-hydroxybenzylidene scaffold appeared here essential to increase the inhibitory activity toward PTP1B and also, to a less extent, toward VHR.

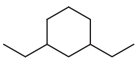
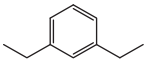
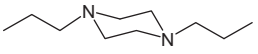
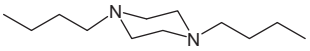
For the bis-thiazolones **22**–**26** with a triazole containing linker, it could be noticed that the inhibitory activity increased with the

Table 1
Inhibitory activities of thiazolones **m1**–**m5**

Compd	$-NR^1R^2$	% of phosphatase inhibition at 100 μM[a]		
		CDC25B	PTP1B	VHR
m1	$-NHCH_3$	10%	32%	2%
m2	$-NH(CH_2)_3CH_3$	20%	35%	0%
m3	$-NH(CH_2)_4CH_3$	20%	35%	0%
m4	$-NH(CH_2)_3N(CH_3)_2$	10%	n.d.	n.d.
m5	–NHBn	45%	46%	8%

[a] Inhibition of the activity of a maltose binding protein (MBP)-CDC25B, PTP1B and VHR recombinant enzymes monitored with fluorescein 3,6-diphosphate (FDP). The 50% inhibitory concentration mean values ± SEM were calculated from at least two, usually three, independent experiments. n.d. not determined.

Table 2
Inhibitory activities of bis-thiazolones **4**–**15**

Compd	Linker	IC_{50} ± SEM (μM) or % of phosphatase inhibition at 100 μM		
		CDC25B	PTP1B	VHR
4	Butyl	8.4 ± 1.6	28.4 ± 7.9	12%
5	Pentyl	13.9 ± 1.2	20.6 ± 6.9	75.8 ± 6.7
6	Hexyl	3.5 ± 1.1	12.4 ± 0.9	26%
7	Heptyl	3.4 ± 1.1	30.6 ± 11.3	0%
8	Octyl	3.9 ± 0.3	11.6 ± 5.9	29%
9	nonyl	2.5 ± 1.0	6.2 ± 2.6	33.1 ± 11.8
10	$-(CH_2)_3N(CH_3)(CH_2)_3$	30%	n.d.	n.d.
11	$-(CH_2)_2O(CH_2)_2O(CH_2)_2-$	12%	n.d.	n.d.
12		6.6 ± 0.3	9.0 ± 1.0	30%
13		7.5 ± 0.6	9.1 ± 0.8	2%
14		2.2 ± 0.3	46.0 ± 2.4	13%
15		28%	n.d.	n.d.

n.d. not determined.

length of the side chains, triazole **26** being the most potent CDC25B inhibitor with an IC_{50} value of 11.2 μM (Table 3). The evaluation on PTP1B revealed that these sub-series was less active since triazoles **23**–**26** showed moderate inhibitory activity at the concentration of 50 μM with percentage of inhibition between 20% and 50%. By contrast with the previous set of dimers, VHR was more sensitive to this set of bis-thiazolones with percentage of inhibition ranking from 38 to 55% at the concentration of 100 μM.

From these results, new symmetrical dimers **27**–**35** were prepared to investigate the importance of the 4-hydroxyphenyl moiety. Since compound **7** appeared to be one of the most selective CDC25 inhibitor, the heptyl chain was chosen to link both thiazolone scaffolds. The enzymatic results are gathered in Table 4. Introduction of 4-hydroxyphenyl derivatives led to dimers **27**–**29** with micromolar IC_{50} values (**27**: IC_{50} = 1.38 μM and **29**, IC_{50} = 2.7 μM), except dimer **28** which was weakly active at the concentration of 100 μM. Thus, the introduction of two bromine atoms or a hydroxyl group at position 3 of the phenyl ring retained the level of inhibitory activity whereas the presence of two methoxy donating groups was detrimental for potent CDC25 inhibition. Suppressing the 4-hydroxy substituent gave dimer **30** with an IC_{50} value of 21 μM, suggesting that the hydroxy group is not crucial for CDC25B inhibitory activity. Replacing the hydroxyl group by the 2-carboxyvinyl moiety led to dimer **31** which could inhibit the activity of the three phosphatases. The effects of bicyclic substituents were then explored by introducing a benzodioxolane moiety which led to the active compound **32** (IC_{50} = 13.8 μM). By contrast, the naphthyl derivative **33** was less active with only 45% of inhibition of CDC25B activity at the concentration of 100 μM. Finally, the presence of the vinyl or the 5-phenylfuryl moieties gave compounds **34** and **35** with micromolar inhibitory activities. As for symmetrical 4-hydroxyphenyl derivatives, this set of compounds was less efficient toward PTP1B, bis-thiazolones **32**, **34** and **35** containing bicyclic substituents or vinyl groups showing an important loss of activity. Similarly to the previous case, symmetric dimers were not able to inhibit VHR activity except bis-thiazolones **27** (31% of inhibition at 10 μM) and **31** (IC_{50} = 12.0 μM). Finally, compounds **34** and **35** are rather selective inhibitors of CDC25B.

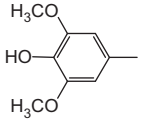
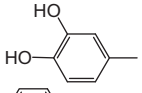
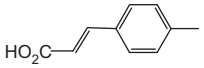
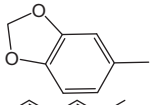
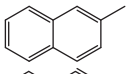
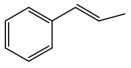
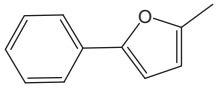
Asymmetrical bis-thiazolone derivatives **40**–**44** containing one 4-hydroxyphenyl moiety were also tested for their anti-phosphatase activity (Table 5). Introduction of previously evaluated

Table 3
Inhibitory activities of bis-thiazolones **22**–**26**

Compd	*m*	*n*	IC_{50} ± SEM (μM) or% of phosphatase inhibition at 100 μM		
			CDC25B	PTP1B[a]	VHR
22	2	1	0%	n.d.	n.d.
23	2	3	48.4 ± 2.9	35%	48%
24	3	1	40.1 ± 5.1	25%	55%
25	3	2	20.6 ± 1.3	20%	38%
26	3	3	11.2 ± 1.3	50%	43%

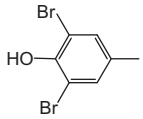
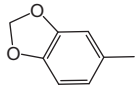
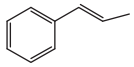
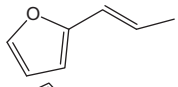
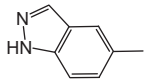
[a] The percentages of inhibition were determined at the concentration of 50 μM. n.d. not determined.

Table 4
Inhibitory activities of bis-thiazolones **27**–**35**

Compd	R	IC_{50} ± SEM (μM) or% of phosphatase inhibition at 100 μM		
		CDC25B	PTP1B	VHR
27	*	1.38 ± 0.1	24.2 ± 4.5	100% 31%[a]
28		49%	2%	22%
29		2.7 ± 0.3	23.4 ± 8.6	38%
30		21.0 ± 6.5	41.3 ± 13.1	28%
31		11.9 ± 1.5	26.9 ± 4.0	12.0 ± 1.4
32		13.8 ± 0.9	30%	27%
33		45%	n.d.	n.d.
34		7.7 ± 1.9	51%	34%
35		2.4 ± 0.1	50%	30%

[a] Tested at the concentration of 10 μM. n.d. not determined.

Table 5
Inhibitory activities of bis-thiazolones **40**–**44**

Compd	R	IC_{50} ± SEM (μM) or% of phosphatase inhibition at 100 μM		
		CDC25B	PTP1B	VHR
40		2.9 ± 0.3	100% 33%[a]	26%
41		4.4 ± 0.5	19%	29%
42		57.3 ± 14.4	13%	23%
43		8.5 ± 2.1	39%	32%
44		2.9 ± 0.8	18%	25%

[a] Tested at the concentration of 10 μM.

substituents such as 3,5-dibromo-4-hydroxyphenyl or benzodioxolyl groups led to compounds **40** and **41** with micromolar IC_{50} values whereas bis-thiazolone **42** showed a weaker affinity with an IC_{50} value of 57.3 μM. Other substituents such as furyl (**43**: IC_{50} = 8.5 μM) or indazolyl (**44**: IC_{50} = 2.9 μM) could also be well tolerated. Replacement of one 4-hydroxyphenyl moiety abolished PTP1B inhibition and led to compounds which are selective inhibitors of CDC25B, except in the case of bis-thiazolone **40**.

The binding mode of bis-thiazolone **7** was further investigated by molecular docking using the CDC25B X-ray structure (PDB code: 1CWT).[23] Among several low-energy poses generated by docking with Surflex-Dock,[24] the selected, after 5 visual analysis, pose (Fig. 2A) suggests that this inhibitor interacts favourably with both catalytic and inhibitor binding sites, which is in agreement with our previously performed docking simulations.[17] The docked pose suggests that the 4-hydroxybenzylidene-thiazolone moieties interact with the active site and the inhibitor binding pocket (swimming-pool). The 4-hydroxyphenyl moieties can form hydrogen bonds with R497 and R482 in the active site and the inhibitor binding site, respectively. The two C=O groups can be involved in hydrogen bonds with Y428 and R548, respectively. The linker is placed in the cleft between the residues R482 and R544 interacting with the hydrophobic patch formed by the β- and γ-CH_2 groups of R479 and the residues Y428, and F543. The binding site of CDC25 is shown in Figure 2B. The analysis of several X-ray structures of the catalytic domain of CDC25B showed that several side chains change the conformations, for example, R544 and R482, thus modifications might be possible in the binding mode. Further, this flexibility may permit the CDC25 binding zone to adopt different conformations that enable dimer molecules with different linker size to act as potent inhibitors. The several polar side chains present in both active site and inhibitor binding site and the hydrophobic patch in the cleft between R544 and R482 suggest that the predicted binding mode is relevant and other similar dimer molecules could bind in both active and inhibitor binding sites.

The effects of increasing concentrations of dithiothreitol (DTT) on the inhibitory activity of the most potent inhibitors **7** and **27** were then explored to investigate their mechanism of action. Enzyme assays were performed by replacing the DTT concentration of 1 mM, normally used under our conditions, by 10 and 20 mM. Results are reported in Table 6. Menadione which is an irreversible quinonoid-based CDC25 inhibitor was also evaluated.[25] As previously reported by us for menadione,[17] an increase in DTT concentration correlated with a decrease in the inhibitory activity. Indeed, menadione could inhibit CDC25 activity with only 14% with a concentration of 20 mM of DTT which is consistent with reactive oxygen species (ROS) generation in vitro. To a less extent, an increase of the IC_{50} values could also be observed for compound **7** which is thus likely to inhibit CDC25 by oxidizing the catalytic cysteine. By contrast, the inhibitory activity of bis-thiazolone **27** was not affected by various concentrations in reducing agent. Thus, compounds **7** and **27** show distinct redox profiles, suggesting different mechanisms of action for the two inhibitors.

In summary, we designed and synthesized new series of symmetrical and asymmetrical bis-thiazolone derivatives. Enzymatic evaluation revealed that dimerisation of the thiazolone scaffold enhanced the potency of the inhibitors. Indeed, most of the dimers displayed micromolar IC_{50} values while the corresponding monomers revealed weakly active at the concentration of 100 μM. This effect could also be observed on protein tyrosine phosphatase PTP1B with symmetrical bis-thiazolones, asymmetrical compounds being inactive. Finally, the dual-specificity phosphatase VHR was the less sensitive protein. We also could show that the most effective CDC25 inhibitor could inhibit phosphatase activity without generating ROS in vitro which is essential for further development of CDC25 inhibitors. The performed docking analysis suggested that dimer compounds can bind simultaneously in the

Table 6
Effect of various concentrations of DTT on the in vitro inhibition of CDC25B

Compd	IC_{50} ± SEM(μM) or% of CDC25 phosphatase inhibition at 100 μM		
	1 mM DTT	10 mM DTT	20 mM DTT
Menadione	2.2 ± 0.6	27%	14%
7	3.4 ± 1.1	16.5 ± 8.0	20.0 ± 9.0
27	1.38 ± 0.1	3.1 ± 2.4	3.2 ± 2.0

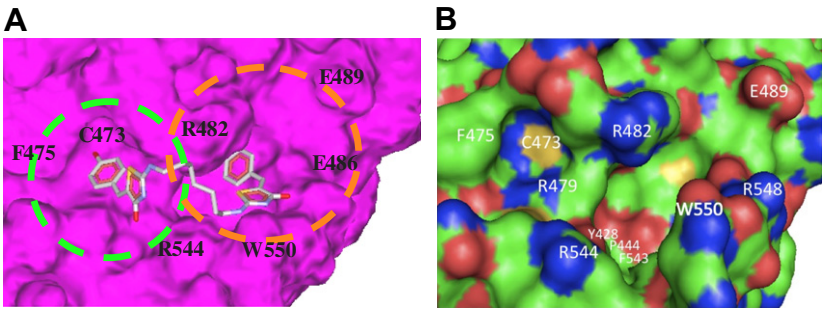


Figure 2. (A) Proposed binding modes for bis-thiazolone **7**. The active site is circled with green dotted line and the inhibitor binding pocket is in orange. (B) The catalytic and inhibitor binding sites are coloured by atom type (PDB code: 1CWT).

active and inhibitor binding sites that is in line with the observed increased inhibitor potency for the synthesized dimer molecules. All together, these findings suggest that dimerisation of known CDC25 inhibitors could be a valuable approach in the search for inhibitors with increased potency.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.072.

References and notes

1. Sun, H.; Tonks, N. K. *Trends Biochem. Sci.* **1994**, *19*, 480.
2. Hunter, T. *Cell* **1995**, *80*, 225.
3. Zhang, Z. Y. *Curr. Opin. Chem. Biol.* **2001**, *4*, 416.
4. Tautz, L.; Pellechia, M.; Mustelin, T. *Expert Opin. Ther. Tar.* **2006**, *10*, 157.
5. Sobhia, M. E.; Paul, S.; Shinde, R.; Potluri, M.; Gundam, V.; Kaur, A.; Haokip, T. *Expert Opin. Ther. Pat.* **2012**, *22*, 125.
6. Nilsson, I.; Hoffmann, I. *Prog. Cell Cycle Res.* **2000**, *4*, 107.
7. Boutros, R.; Dozier, C.; Ducommun, B. *Curr. Opin. Cell Biol.* **2006**, *18*, 185.
8. Galaktionov, K.; Beach, D. *Cell* **1991**, *67*, 1181.
9. Sadhu, K.; Reed, S. I.; Richardson, H.; Russell, P. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 5139.
10. Nagata, A.; Igarashi, M.; Jinno, S.; Suto, K.; Okayama, H. *New Biol.* **1991**, *3*, 959.
11. Boutros, R.; Lobjois, V.; Ducommun, B. *Nat. Rev. Cancer* **2007**, *7*, 495.
12. Kristjandottir, K.; Rudolph, J. *Chem. Biol.* **2004**, *11*, 1043.
13. Galaktionov, K.; Lee, A. K.; Eckstein, J.; Draetta, G. F.; Meckler, J.; Loda, M.; Beach, D. *Science* **1995**, *269*, 1575.
14. Contour-Galcera, M. O.; Sidhu, A.; Prévost, G.; Bigg, D.; Ducommun, B. *Pharmacol. Ther.* **2007**, *115*, 1.
15. Brezak, M. C.; Valette, A.; Quaranta, M.; Contour-Galcera, M. O.; Jullien, D.; Lavergne, O.; Frongia, C.; Bigg, D.; Kasprzyk, P. G.; Prevost, G. P.; Ducommun, B. *Int. J. Cancer* **2009**, *124*, 1449.
16. Montes, M.; Braud, E.; Miteva, M. A.; Goddard, M. L.; Mondesert, O.; Kolb, S.; Brun, M. P.; Ducommun, B.; Garbay, C.; Villoutreix, B. O. *J. Chem. Inf. Model.* **2008**, *48*, 157.
17. Kolb, S.; Mondesert, O.; Goddard, M. L.; Jullien, D.; Villoutreix, B. O.; Garbay, C.; Braud, E. *ChemMedChem* **2009**, *4*, 633.
18. Pulici, M.; Quartieri, F. *Tetrahedron Lett.* **2005**, *46*, 2387.
19. Bourahla, K.; Dercour, A.; Rahmouni, M.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2007**, *48*, 5785.
20. Sing, W. T.; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 91.
21. Carboni, B.; Benalil, A.; Vaultier, M. *J. Org. Chem.* **1993**, *58*, 3736.
22. Saito, Y.; Matsumoto, K.; Bag, S. S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron* **2008**, *64*, 3578.
23. Reynolds, R. A.; Yem, A. W.; Wolfe, C. L., Jr.; Deibel, M. R.; Chidester, C. G.; Watenpaugh, K. D. *J. Mol. Biol.* **1999**, *293*, 559.
24. Jain, A. N. *J. Comput. Aided Mol. Des.* **2007**, *21*, 281.
25. Ham, S. W.; Park, H. J.; Lim, D. H. *Bioorg. Chem.* **1997**, *25*, 33.