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Mini-Review

Discovery of orally active anticancer candidate CFI-400945 derived from biologically promising spirooxindoles: Success and challenges

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ABSTRACT

The identification of novel anticancer agents with high efficacy and low toxicity has always been an intriguing topic in medicinal chemistry. The unique structural features of spirooxindoles together with diverse biological activities have made them promising structures in new drug discovery. Among spirooxindoles, CFI-400945 holds its promise as the first potent PLK4 inhibitor, the fumarate of CFI-400945 has entered phase I clinical trials for the treatment of solid tumors. However, questions remain as to whether PLK4 is the only relevant therapeutic target for CFI-400945. To highlight this significant progress of CFI-400945 in last two years, this review centers on the identification from a focused kinase library, structural optimizations and strategies involved, structure-activity relationships, modes of action, target validation, chemical synthesis and, more importantly, the kinase selectivity between PLK4 and other targets.

1. Introduction

The discovery of new structural scaffolds has recently been recognized as an efficient strategy to find biologically promising molecules that can target some biological sites (e. g. protein–protein interactions) and explore more chemical space [1,2] as some already known scaffolds have failed to target biologically relevant sites, especially the undruggable targets [3]. Spiro compounds have recently attracted considerable attention from medicinal community due to their unique structural features and diverse medicinal properties [4]. It is well believed that spirocyclic compounds have a reduced conformational entropy upon binding to a protein target and conformational restriction, which make them the promising scaffolds in drug discovery [5]. In particular, spirooxindoles with the varied spiro ring fused at the C3 position of the oxindole core (highlighted in bold in Fig. 1) have emerged as attractive synthetic targets because of their prevalence in numerous natural products (e. g. Spirotryprostatin A and B) and biologically active molecules [6,7]. These spirooxindoles seem to be promising candidates for drug discovery, since such molecules incorporate both oxindoles and other heterocyclic moieties simultaneously. Among the spirooxindoles, CFI-400945, as the first potent PLK4 inhibitor discovered in 2013, has entered phase I clinical trials for the treatment of human solid tumors [8] (Fig. 1). To highlight the significant progress in last two years, this review mainly focuses on the identification from a focused kinase library, structural optimization from the starting point and strategies employed, structure-activity relationships (SARs), modes of action, target validation, chemical synthesis and their recent clinical progress. More importantly, the kinase selectivity of CFI-400945 and deficiencies of using xenograft models to predict clinical response are also briefly discussed.

2. Discovery of CFI-400945

The polo-like kinase (PLK) family of highly conserved serine/threonine kinases have been recently recognized as potential anticancer targets with five members (PLKs 1–5) discovered in mammalian cells [9,10]. All PLK members share structurally similar *N*-terminal serine/threonine kinase catalytic domains and a *C*-terminal regulatory domain containing one (for PLK4) or two polo-boxes (for PLKs 1–3) (Fig. 2) [11]. The structural difference in *C*-terminal domains makes them function differently as phosphopeptide binding domains and a homodimerization domain for PLKs 1–3 and PLK4, respectively [12]. There is evidence that PLKs are highly expressed in about 80% human tumors of different origins,

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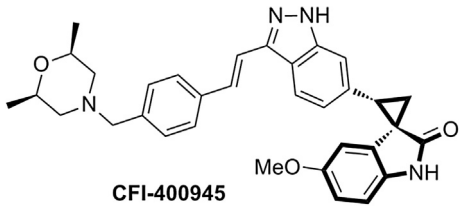


Fig. 1. The chemical structure of CFI-400945.

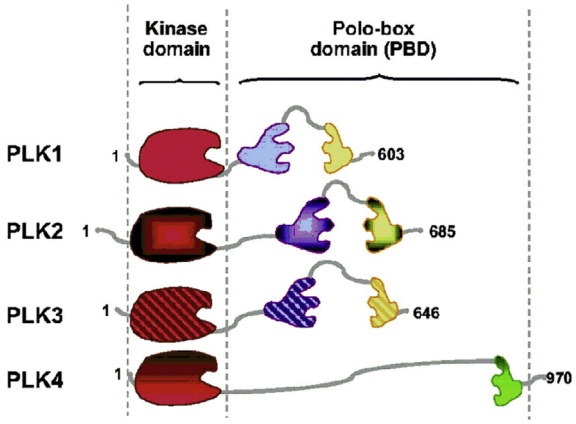


Fig. 2. The structure of polo-like kinase family showing the *N*-/C-terminal domains.

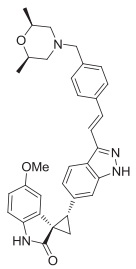
but not in healthy nondividing cells, which makes them attractive and selective targets for developing anticancer drugs [11,13]. Among PLKs [14], PLK1 is the best characterized member with several inhibitors identified which are now in clinical/preclinical development [15–17]. By contrast, other family members, PLK4 in particular, remain largely unknown with very few inhibitors reported. PLK4, as the most structurally divergent polo family member, has recently been reported to be essential for centriole duplication during the cell cycle [18], cytokinesis and maintenance of chromosomal stability [19], and can promote cancer cell invasion [20]. Additionally, RNA interference (RNAi)-mediated depletion of PLK4 in human breast cancers and cell lines was found to be able to prevent centriole duplication [21,22]. All these interesting findings undoubtedly make PLK4 a potential target for cancer therapy.

CFI-400945 stands out among recently discovered PLK4 inhibitors [23] as the potent, orally active PLK4 inhibitor with potent antitumor activity (as shown in Table 1) and well tolerance in breast cancer xenograft models, in particular those deficient in the tumor suppressor PTEN [24,25]. This inhibition depends on the precise control of centriole number, which is achieved through the balance between phosphorylation of downstream substrates and autophosphorylation that regulates PLK4 levels [26–28]. The fumarate of CFI-400945 as a single agent has entered Phase I clinical trials for the treatment of solid tumors (breast cancer particularly) approved by Health Canada and the FDA [29].

Intriguingly, only the (1*R*,2*S*) enantiomer has an excellent binding ability with PLK4 as shown in the binding model. Therefore, the stereoselective synthesis of CFI-400945 is required to construct the chiral centers needed. Pauls's group developed an efficient double S_N2 displacement reaction of a chiral bis-electrophile (compound **6**) with bis-nucleophile (compound **7**) for the stereoselective installation of the desired asymmetric centers [8]. The synthetic route toward CFI-400945 is outlined in Scheme 1; the yield for each step is given under the arrow and the ee value under the structure. Initially, treatment of bromoindazole **1** with benzyl chloride in the presence of *t*-BuOK gave a mixture of *N*2- and *N*1-benzylated **2** and **3** (1:3), which was isomerized exclusively to *N*1-benzylated **3** at 150 °C in excess benzyl chloride (77% yield from compound **1**). Subsequent Suzuki-Miyaura coupling with vinyl boronic acid pinacol ester gave vinyl indazole **4** in 65% yield. Sharpless asymmetric hydroxylation of **4** using AD-mix-α generated diol (*S*)-**5** with a high ee (enantiomeric excess) value (98%), which was then dimesylated to **6** in 87% yield and with an ee value of 99%. Double displacement of the dimesylate **6** with the anionic oxindole **7** proceeded smoothly to give **8** with high enantioselectivity (99.9% ee). Next, the benzyl group in **8** was cleanly removed in the presence of *t*-BuOK in an O_2-saturated solution of THF/DMSO, giving **9** without the loss of enantioselectivity (99.4% ee). By contrast, the catalytic hydrogenation condition caused the partial ring opening of the cyclopropane. Subsequent iodination of **9** using I_2 proceeded smoothly, generating **10** (95% yield, 99.4% ee). The Suzuki-Miyaura coupling of **10** with vinyl boronic acid pinacol ester gave CFI-400945 (**11**) in a moderate yield (48%), which was then treated with fumaric acid in acetone to form the fumarate of CFI-400945. It should be noted that most steps, even the double displacement procedure, in Scheme 1 were performed on a large scale (up to 400 g), which could be potentially used in industrial process.

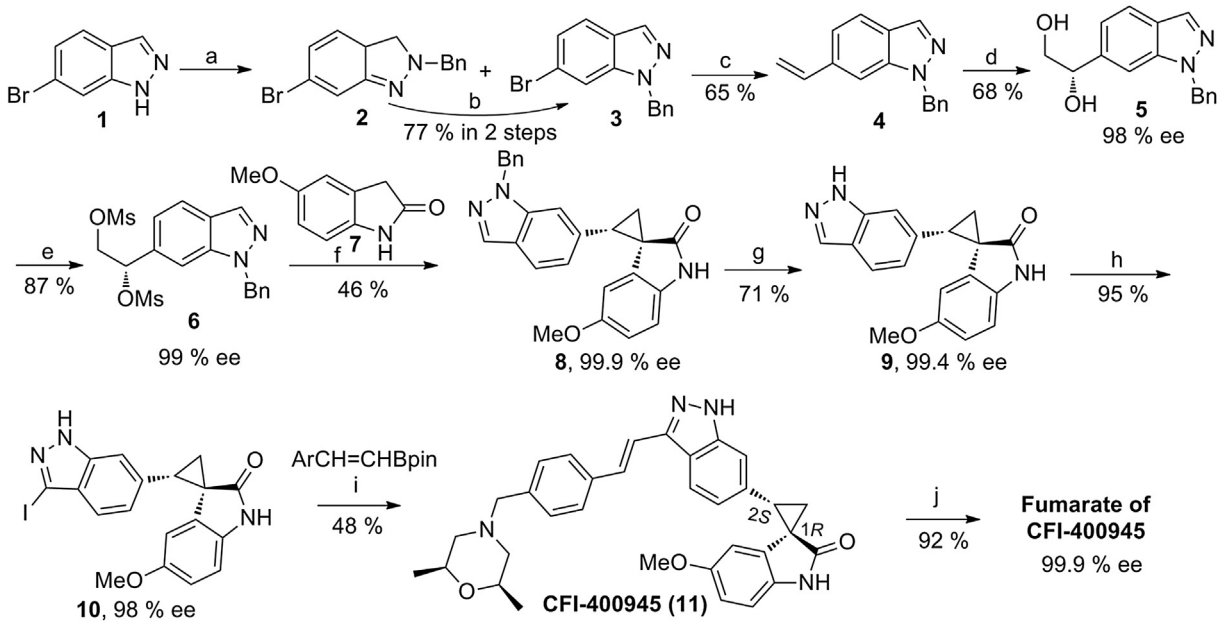
The identification of CFI-400945 came from a drug program initiated by Pauls's group with an aim of finding potent PLK4 inhibitors from a focused kinase library, namely the ligand and homology model-based libraries (7700 compounds in total) as well as about 280 commercial kinase inhibitors (Fig. 3) [23]. The 4-hydroxybenzylideneindolin-2-ones held the most promise after an indirect ELISA assay probably because of the beneficial effects of indolinone NH and phenolic hydroxyl groups for PLK4 inhibition. Among them, indolinone **12** (IC_{50} = 32 μM against PLK4) was chosen as a template for further modifications. The undesirable phenol group of compound **12** having weak interaction with His93

Table 1
In vitro antitumor activity of CFI-400945 against a panel of cancer cell lines.[a]



Breast cancer cell lines (GI_{50}/μM)						
MDA-MB-468	MCF-7	HCC-1954	MDA-MB-231	SKBr-3	Cal-51	BT-20
0.006	0.008	0.005	8.6	5.3	0.26	0.058
Lung (GI_{50}/μM)	Ovarian (GI_{50}/μM)	Colon (GI_{50}/μM)				
A549	OVCAR-3	SW620	Colo-205		HCT116+/+	
0.005	0.018	0.38	0.017		0.005	

[a] Cell growth was determined by measuring total protein content by SRB assay.



Scheme 1. Stereoselective synthesis of CFI-400945. Reagents and conditions: (a) BnCl, DMSO, *t*-BuOK, 4 h; (b) BnCl, 150 °C, 8 h; (c) 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane, $Pd(PPh_3)_2Cl_2$ (2 mol%), K_2CO_3, DME/H_2O, 80 °C, 7 h; (d) $(DHQ)_2PHAL$, $K_2OsO_4 \cdot 2H_2O$ (0.5 mol %), $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C, 5 h; (e) MsCl, TEA, CH_2Cl_2, 0 °C; (f) NaH (60% in mineral oil), THF; (g) DMSO, *t*-BuOK, THF, O_2; (h) I_2, K_2CO_3, DMF; (i) 2:1 PhMe/EtOH, 1 M Na_2CO_3, $Pd(PPh_3)_4$ (5 mol %), microwave 120 °C, 2 h or 1 M Na_2CO_3, LiCl, $Pd(PPh_3)_4$ (2.5 mol %), dioxane, reflux, 18 h; (j) Fumaric acid, acetone, 50 °C.

was replaced by other bioisosteric heterocycles. Compound **13** with an indazole group in place of the phenol group showed significantly increased inhibition against PLK4 with an IC_{50} value of 0.29 μM. Additionally, Johnson et al. reported that Axitinib had an excellent inhibition against PLK4 (IC_{50} = 46 nM, K_i = 4.2 nM) [12]. Inspired by this interesting finding, hybridization of indolinone **13** and Axitinib was carried out by Pauls's group, generating indolinone **14** with a markedly improved inhibition against PLK4 (IC_{50} = 13 nM). Further modifications focusing on variations of substituents on the indolinone ring, the position of the pyridinyl nitrogen and the incorporation of water-solubilizing substituents on the phenyl ring distal from the indazole core revealed that the introduction of the methoxy group at the 5-position of the indolinone ring and solubilizing substituents on the pyridinyl ring not only enhanced growth inhibitory activity but also attenuated CYP450 inhibition, finally yielding indolinone **15** with high potency (IC_{50} = 0.61 nM) and excellent selectivity against other polo family members (>10 μM). Besides, indolinone **15** represented favorably *in vivo* efficacy in the MDA-MB-468 mouse xenograft model compared to the standard VX680.

Although these molecules such as indolinone **15** showed potent PLK4 inhibition, antiproliferative activity and robust tumor inhibition, some drawbacks were also observed in these inhibitors, namely the strong inhibition of CYP450, low pharmacokinetic properties (low oral exposure particularly) and configurational lability [23,30]. So the key questions are to further improve the drug-like properties of these inhibitors through rational modifications. It is envisioned that the excellent CYP450 inhibition of the pyridinyl inhibitors is ascribed to the pyridinyl nitrogen. Therefore, indolinone **16** was designed by changing the pyridinyl to the phenylene group with slightly decreased PLK inhibition (IC_{50} = 4 nM). Besides, the cyclopropane ring, as a biologically important motif in some natural products [31], has been extensively used in drug discovery programs to prepare configurationally restricted pharmaceuticals [32]. It is believed that the bioisosteric replacement of the double bond with a cyclopropane ring would improve the configurational stability and physicochemical properties. Inspired by these interesting findings, compound **7**-based design was performed by Pauls's group through the bioisosteric replacement, yielding racemic indolinone **17** with improved ADME properties and oral exposure (Fig. 3) [30]. In order to increase the kinase selectivity and PK profiles, modifications centering on variations of solubilizing group (dimethylamine, piperidine, piperazine or morpholine) attached to the phenyl ring were carried out, yielding indolinone **18** with the less basic morpholino substituent, which displayed significantly increased oral exposure (C_{max} = 1800 ng/mL, AUC = 4300 ng h/mL). It should be noted that the racemic cyclopropane-linked inhibitors (e. g. indolinones **17** and **18**) showed comparable PLK4 affinity and antiproliferative activity to their alkene-linked congeners but with improved physicochemical, ADME and PK properties.

It is evident that the cyclopropanation of the double bond incorporates two adjacent stereogenic centers. And the modeling studies revealed that the 1*R*, 2*S* enantiomer had preferential affinity on PLK4 over the 1*S*, 2*R* enantiomer. The 1*R*, 2*S* enantiomer of indolinone **18**, namely compound **19**, showed comparable PLK4 inhibition (IC_{50} = 1.4 nM) with high clearance rates in rat (Cl = 3.2 L h/kg). Further modifications focused on maintaining the *in vitro* potency while maximizing PK properties by changing the substituents in the indolinone core and solubilizing groups attached to the phenyl ring, finally yielding the potent, orally active antitumor agent CFI-400945 with the IC_{50} and K_i values of 2.8 and 0.26 nM, respectively (Fig. 3). The methoxy group at the 5-position of the indolinone core was considered to be beneficial for the potency and kinase selectivity. The introduction of the morpholino group could enhance permeability, cell activity and PK parameters. The introduction of the meso dimethyl groups on the morpholine significantly reduced the clearance in rat and dog. Besides, no significant inhibition against PLKs 1–3 was observed for CFI-400945 at a concentration of 50 μM. More importantly, *in vivo* studies showed that CFI-400945 was well tolerated in the MDA-MB-468 mouse xenograft model at a high (9.4 g/kg) and low (3.0 g/kg)

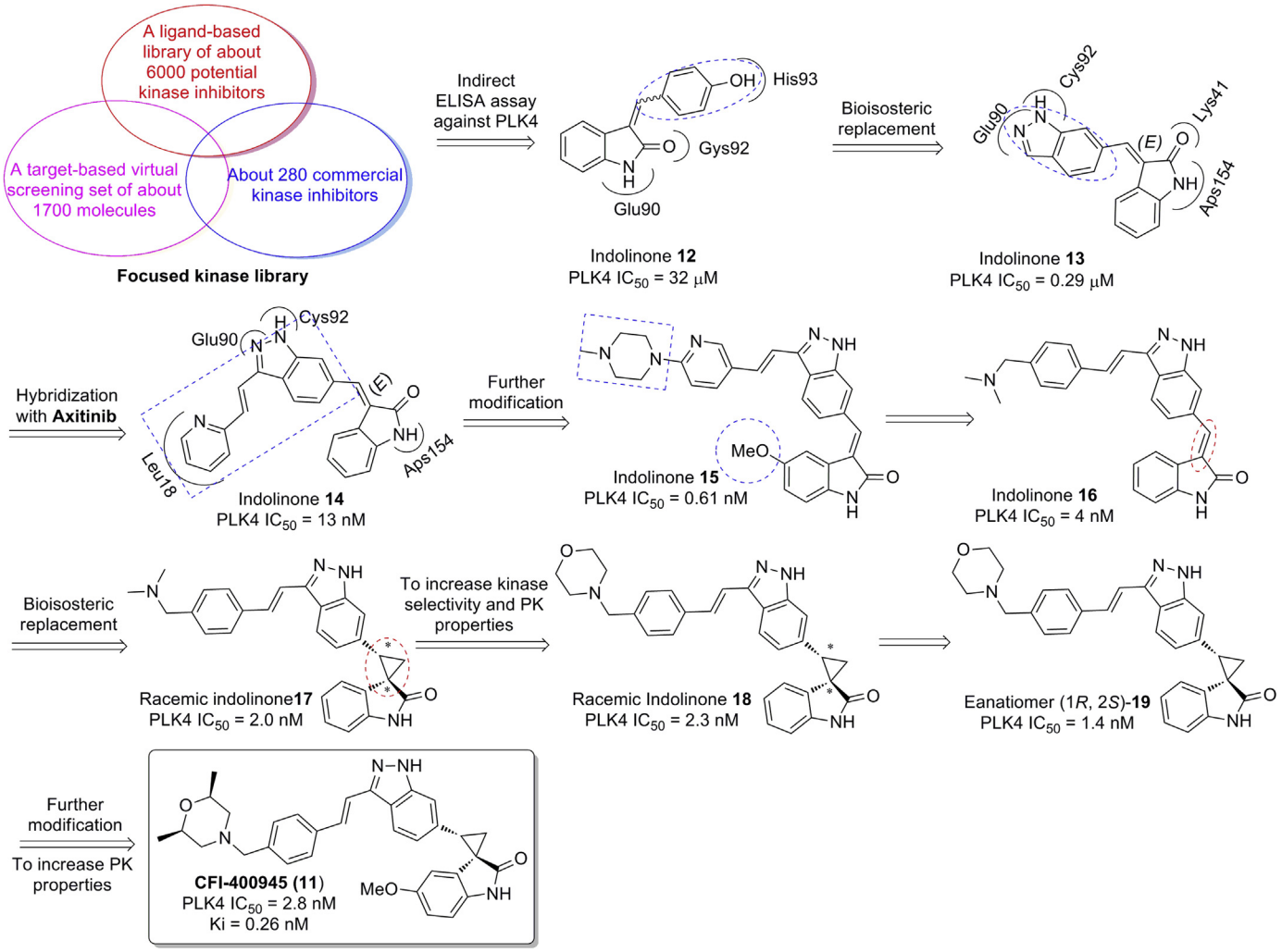


Fig. 3. The discovery of CFI-400945 based on a focused kinase library.

dose, once a day, for 21 days. Additionally, CFI-400945 can also attenuate the growth of breast cell line, as well as other tumor cell lines significantly. Another interesting finding that should be noted here is that a bimodal effect was observed for CFI-400945 on centriole duplication, that is, CFI-400945 can inhibit duplication at high doses while promote duplication at lower doses probably due to the formation of heterodimers of catalytically active and inactive monomers of PLK4 [33].

The binding modes for CFI-400945 in PLK4 active site generated by GlideXP show that two H-bonds bind to the hinge (Glu90 and Gys92) and two H-bonds from the indolinone carbonyl and NH to Lys41 and Gln160, respectively (Fig. 4A). A similar view with a surface representation on the protein is shown in Fig. 4B; there is extensive hydrophobic interaction between the enzyme and the ligand. The morpholine is at the protein-water interface. The methoxy group nests in a groove by the protein backbone and the side chains of Leu143 and Glu96.

CFI-400945, as the first potent PLK4 inhibitor discovered to date, recapitulates the hallmarks of genetic PLK4 inhibition and has entered phase I clinical trials for the treatment of solid tumors. However, the kinase selectivity is the major concern that deserves further attention, namely whether PLK4 is the only relevant therapeutic target for CFI-400945 [33]. The kinase selectivity of CFI-400945 was examined against an array of recombinant protein and lipid kinases and clinically relevant mutant kinases. The results indicated that CFI-400945 selectively inhibited PLK4 in cells, but also had certain activity against AURKB, TRKA, TRKB and Tie2/TEK (only 10 kinases showed more than 50% inhibition among 290 kinases) (Table 2). The cytokinesis failure and subsequent polyploidization by CFI-400945 treatment indicated that the cell death in cancer cell lines was at least partly achieved through inhibition of AURKB. This probably means the co-inhibition of PLK4 and AURKB would be responsible for the activity by CFI-400945, although Mason et al. reported that cancer cells treated with CFI-400945 exhibited effects consistent with PLK kinase inhibition [25]. Besides, no significant inhibition was observed for PLKs 1–3 (IC_{50}s > 50 μM) probably due to the most divergent structure of PLK4 compared to other polo-like kinases 1–3 (Fig. 2). The authors stated that CFI-400945 was ATP competitive with a K_i value of 0.26 nM [25]. Actually, it is quite challenging to achieve target specificity with ATP competitive inhibitors because all kinases share a similar catalytic core. Another interesting but surprising finding is that the greatest growth inhibition was observed in cell lines that were among the most resistant to the growth inhibition by CFI-400945. One explanation is that the loss of PLK4 protein and inhibition of PLK4 kinase activity have different effects on cellular activity. Another possibility is that the co-inhibition of PLK4 and other targets is responsible for the cytostatic effect of CFI-400945.

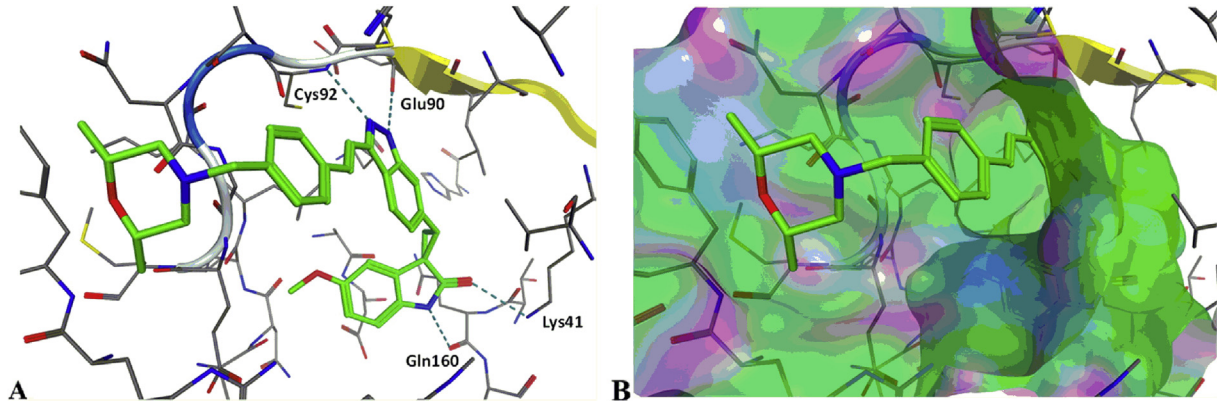


Fig. 4. Binding mode for CFI-400945 generated by GlideXP docking in the PLK4 active site. (A) The left panel shows H-bonds from indolinone carbonyl and NH to Lys41 and Gln160, respectively and H-bonds from indazole to Glu90 and Cys92 of the hinge. (B) The right panel shows a similar view with a surface representation on the protein; morpholine is at protein-water interface; the OMe group nestles in a groove bounded by the protein backbone and side chains.

Apart from the kinase selectivity, another concern that should also be considered is the limitation of using xenograft models to predict clinical response observed in anticancer drug development [34]. Several drugs that show excellent antitumor activity in xenograft models have failed to generate the expected clinical benefits. So these concerns mentioned above still exist and need to be investigated further although a significant progress of CFI-400945 has been made in preclinical studies.

3. Conclusions and outlook

Spirooxindoles have drawn wide attention because of their diverse biological activities and novel structural scaffold. A number of biologically promising molecules have been identified to date. Among these spirooxindoles, three molecules, namely CFI-400945, SAR405838 and KAE609 have entered clinical evaluation for the treatment of human cancers and malaria, respectively. The identification of these three compounds, to some extent, makes spirooxindoles promising scaffolds in drug discovery compared to other heterocyclic scaffolds. The asymmetric synthesis, as a powerful tool, has been extensively employed for the construction of spirooxindoles with multiple chiral centers, yielding some biologically promising molecules. However, numerous spirooxindoles with structural novelty have not been subjected to anticancer evaluation, which restricts the discovery of new anticancer agents. Different from other drug scaffolds, the stereochemistry of spirooxindoles is extremely important for the bioactivity as observed in CFI-400945 and MI-888 with only one enantiomer showing excellent activity.

PLK4 with the most divergent structure compared to PLKs 1–3 has shown its potential as a therapeutic target for cancer treatment. However, very few inhibitors have been reported to be able to inhibit PLK4 potently. CFI-400945, as the first potent PLK4 inhibitor discovered to date, recapitulates the hallmarks of genetic PLK4 inhibition and has entered phase I clinical trials for the treatment of solid tumors, especially those deficient in PTEN. The binding models of CFI-400945 in PLK4 active site give us a clear picture about the potential binding with other relevant inhibitors, which help us to design new PLK4 inhibitors. Additionally, the kinase selectivity (e. g. PLK4 *vs* AURKB) is the main concern that should be paid more attention. CFI-4000945 has been reported to inhibit PLK4 and other targets (AURKB in particular), so questions remain as to whether PLK4 is the only relevant therapeutic target for CFI-400945. The co-inhibition of PLK4 and AURKB would be responsible for the potent antitumor activity by CFI-400945. The discovery of CFI-400945 will encourage medicinal chemists to design more potent inhibitors targeting PLK4, which in turn help us address the concern mentioned above.

Table 2
The kinase selectivity of CFI-400945.

Kinase	PLK4	AURKA	AURKB	FGFR1	SLC34A2-ROS	TIE2/TEK	TRKA	TRKB
EC_{50} (nM)	12.3	510	102	1100	466	117	84	88

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References

[1] H. Zhao, I. Akritopoulou-Zanze, When analoging is not enough: scaffold discovery in medicinal chemistry, Expert Opin. Drug Discov. 5 (2010) 123–134.
[2] P.J. Hajduk, W.R.J.D. Galloway, D.R. Spring, Drug discovery: a question of library design, Nature 470 (2011) 42–43.
[3] M.E. Welsch, S.A. Snyder, B.R. Stockwell, Privileged scaffolds for library design and drug discovery, Curr. Opin. Chem. Biol. 14 (2010) 347–361.
[4] F.-A. Kang, Z. Sui, A diversity-oriented-synthesis protocol for scaffold discovery based on a general synthetic route to spirocycles, Tetrahedron Lett. 52 (2011) 4204–4206.
[5] Y. Zheng, C.M. Tice, S.B. Singh, The use of spirocyclic scaffolds in drug discovery, Bioorg. Med. Chem. Lett. 24 (2014) 3673–3682.
[6] C.V. Galliford, K.A. Scheidt, Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents, Angew. Chem. Int. Ed. 46 (2007) 8748–8758.
[7] B. Yu, D.-Q. Yu, H.-M. Liu, Spirooxindoles: promising scaffolds for anticancer agents, Eur. J. Med. Chem. (2015), http://dx.doi.org/10.1016/j.ejmech.2014.06.056 (in press).
[8] P.B. Sampson, Y. Liu, B. Forrest, G. Cumming, S.-W. Li, N.K. Patel, L. Edwards, R. Laufer, M. Feher, F. Ban, D.E. Awrey, G. Mao, O. Plotnikova, R. Hodgson, I. Beletskaya, J.M. Mason, X. Luo, V. Nadeem, X. Wei, R. Kiarash, B. Madeira, P. Huang, T.W. Mak, G. Pan, H.W. Pauls, The discovery of polo-like kinase 4 inhibitors: identification of (1*R*,2*S*)-2-(3-((*E*)-4-(((cis)-2,6-dimethylmorpholino)methyl)styryl)-1*H*-indazol-6-yl)-5′-methoxyspiro[cyclopropane-1,3′-indolin]-2′-one (CFI-400945) as a potent, orally active antitumor agent, J. Med. Chem. 58 (2015) 147–169.
[9] D.M. Glover, I.M. Hagan, Á.A.M. Tavares, Polo-like kinases: a team that plays throughout mitosis, Genes. Dev. 12 (1998) 3777–3787.
[10] D.M. Lowery, D. Lim, M.B. Yaffe, Structure and function of polo-like kinases, Oncogene 24 (2005) 248–259.
[11] P. Schöffski, Polo-like kinase (PLK) inhibitors in preclinical and early clinical development in oncology, Oncologist 14 (2009) 559–570.
[12] E.F. Johnson, K.D. Stewart, K.W. Woods, V.L. Giranda, Y. Luo, Pharmacological and functional comparison of the polo-like kinase family: insight into

inhibitor and substrate specificity, Biochemistry 46 (2007) 9551–9563.
[13] C. McInnes, M. Mezna, P.M. Fischer, Progress in the discovery of polo-like kinase inhibitors, Curr. Top. Med. Chem. 5 (2005) 181–197.
[14] S.M. Lens, E.E. Voest, R.H. Medema, Shared and separate functions of polo-like kinases and aurora kinases in cancer, Nat. Rev. Cancer 10 (2010) 825–841.
[15] M. Kothe, D. Kohls, S. Low, R. Coli, A.C. Cheng, S.L. Jacques, T.L. Johnson, C. Lewis, C. Loh, J. Nonomiya, A.L. Sheils, K.A. Verdries, T.A. Wynn, C. Kuhn, Y.-H. Ding, Structure of the catalytic domain of human polo-like kinase 1, Biochemistry 46 (2007) 5960–5971.
[16] M. Ahn, Y.-H. Han, J.-E. Park, S. Kim, W.C. Lee, S.J. Lee, P. Gunasekaran, C. Cheong, S.Y. Shin, H.-Y. Kim, E.K. Ryu, R.N. Murugan, N.-H. Kim, J.K. Bang, A new class of peptidomimetics targeting the polo-box domain of Polo-like kinase 1, J. Med. Chem. 58 (2015) 294–304.
[17] M.O. Duffey, T.J. Vos, R. Adams, J. Alley, J. Anthony, C. Barrett, I. Bharathan, D. Bowman, N.J. Bump, R. Chau, C. Cullis, D.L. Driscoll, A. Elder, N. Forsyth, J. Frazer, J. Guo, L. Guo, M.L. Hyer, D. Janowick, B. Kulkarni, S.-J. Lai, K. Lasky, G. Li, J. Li, D. Liao, J. Little, B. Peng, M.G. Qian, D.J. Reynolds, M. Rezaei, M.P. Scott, T.B. Sells, V. Shinde, Q.J. Shi, M.D. Sintchak, F. Soucy, K.T. Sprott, S.G. Stroud, M. Nestor, I. Visiers, G. Weatherhead, Y. Ye, N. D'Amore, Discovery of a potent and orally bioavailable benzolactam-derived inhibitor of polo-like kinase 1 (MLN0905), J. Med. Chem. 55 (2011) 197–208.
[18] R. Habedanck, Y.-D. Stierhof, C.J. Wilkinson, E.A. Nigg, The Polo kinase Plk4 functions in centriole duplication, Nat. Cell. Biol. 7 (2005) 1140–1146.
[19] C.O. Rosario, M.A. Ko, Y.Z. Haffani, R.A. Gladdy, J. Paderova, A. Pollett, J.A. Squire, J.W. Dennis, C.J. Swallow, Plk4 is required for cytokinesis and maintenance of chromosomal stability, Proc. Natl. Acad. Sci. USA. 107 (2010) 6888–6893.
[20] K. Kazazian, R. Xu, F. Zih, C. Rosario, C.J. Swallow, Polo-like kinase 4 (Plk4) promotes cancer cell invasion, J. Am. Coll. Surg. 217 (2013) S128.
[21] J. Sillibourne, M. Bornens, Polo-like kinase 4: the odd one out of the family, Cell. Div. 5 (2010) 25–33.
[22] M. Bettencourt-Dias, A. Rodrigues-Martins, L. Carpenter, M. Riparbelli, L. Lehmann, M. Gatt, N. Carmo, F. Balloux, G. Callaini, D. Glover, SAK/PLK4 is required for centriole duplication and flagella development, Curr. Biol. 15 (2005) 2199–2207.
[23] R. Laufer, B. Forrest, S.-W. Li, Y. Liu, P. Sampson, L. Edwards, Y. Lang, D.E. Awrey, G. Mao, O. Plotnikova, G. Leung, R. Hodgson, I. Beletskaya, J.M. Mason, X. Luo, X. Wei, Y. Yao, M. Feher, F. Ban, R. Kiarash, E. Green, T.W. Mak, G. Pan, H.W. Pauls, The discovery of PLK4 inhibitors: (*E*)-3-((1*H*-Indazol-6-yl)methylene)indolin-2-ones as novel antiproliferative agents, J. Med. Chem. 56 (2013) 6069–6087.
[24] A. Flemming, Cancer: PLK4 inhibitor shows potent antitumour activity, Nat. Rev. Drug. Discov. 13 (2014) 654.
[25] Jacqueline M. Mason, Dan C.-C. Lin, X. Wei, Y. Che, Y. Yao, R. Kiarash, David W. Cescon, Graham C. Fletcher, Donald E. Awrey, Mark R. Bray, G. Pan, Tak W. Mak, Functional characterization of CFI-400945, a Polo-like kinase 4 inhibitor, as a potential anticancer agent, Cancer Cell. 26 (2014) 163–176.
[26] C.W. Brownlee, J.E. Klebba, D.W. Buster, G.C. Rogers, The protein phosphatase 2A regulatory subunit twins stabilizes Plk4 to induce centriole amplification, J. Cell. Biol. 195 (2011) 231–243.
[27] A. Puklowski, Y. Homsi, D. Keller, M. May, S. Chauhan, U. Kossatz, V. Grunwald, S. Kubicka, A. Pich, M.P. Manns, I. Hoffmann, P. Gonczy, N.P. Malek, The SCF-FBXW5 E3-ubiquitin ligase is regulated by PLK4 and targets HsSAS-6 to control centrosome duplication, Nat. Cell. Biol. 13 (2011) 1004–1009.
[28] A. Holland, W. Lan, S. Niessen, H. Hoover, D. Cleveland, Polo-like kinase 4 kinase activity limits centrosome overduplication by autoregulating its own stability, J. Cell. Biol. 188 (2010) 191–198.
[29] For more information about clinical trials of CFI-400945 fumarate, please refer to the National Cancer Institute website (http://www.cancer.gov/drugdictionary?cdrid=754001).
[30] P.B. Sampson, Y. Liu, N.K. Patel, M. Feher, B. Forrest, S.-W. Li, L. Edwards, R. Laufer, Y. Lang, F. Ban, D.E. Awrey, G. Mao, O. Plotnikova, G. Leung, R. Hodgson, J. Mason, X. Wei, R. Kiarash, E. Green, W. Qiu, N.Y. Chirgadze, T.W. Mak, G. Pan, H.W. Pauls, The discovery of Polo-like kinase 4 inhibitors: design and optimization of spiro[cyclopropane-1,3′[3*H*]indol]-2′(1′*H*)-ones as orally bioavailable antitumor agents, J. Med. Chem. 58 (2015) 130–146.
[31] D.Y.K. Chen, R.H. Pouwer, J.-A. Richard, Recent advances in the total synthesis of cyclopropane-containing natural products, Chem. Soc. Rev. 41 (2012) 4631–4642.
[32] F.Z. Gaugaz, M. Redondo-Horcajo, I. Barasoain, J.F. Díaz, A. Cobos-Correa, M. Kaufmann, K.-H. Altmann, The impact of cyclopropane configuration on the biological activity of cyclopropyl-epothilones, ChemMedChem 9 (2014) 2227–2232.
[33] Andrew J. Holland, Don W. Cleveland, Polo-like kinase 4 inhibition: a strategy for cancer therapy? Cancer Cell. 26 (2014) 151–153.
[34] N.E. Sharpless, R.A. DePinho, The mighty mouse: genetically engineered mouse models in cancer drug development, Nat. Rev. Drug. Discov. 5 (2006) 741–754.