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Structure–activity relationships of 6-(2,6-dichlorophenyl)-8-methyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones: Toward selective Abl inhibitors

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ABSTRACT

We report the design, synthesis, and structure–activity relationship (SAR) of a series of novel pyrido[2,3-*d*]pyrimidin-7-one compounds as potent Abl kinase inhibitors. We evaluate their specificity profile against a panel of human recombinant kinases, as well as their biological profile toward a panel of well-characterized cancer cell lines. Our study reveals that substitutions in the 3- and 4-positions of the phenylamino moiety lead to improved potency and improved selectivity both in target-based and cell-based assays. Altogether, our results provide an insight into the SAR of pyrido[2,3-*d*]pyrimidin-7-ones for the development of drug candidates with improved potency and selectivity for the targeted treatment of CML.

Chronic myeloid leukemia (CML) is a clonal hematopoietic malignancy that accounts for up to 20% of adult leukemias. The pathological hallmark of CML is the Philadelphia chromosome present in >90% of patients. The Philadelphia chromosome results from a translocation between chromosomes 9 and 22, leading to the juxtaposition of the Abelson tyrosine kinase (Abl) and breakpoint cluster (Bcr) genes. The resulting Bcr–Abl fusion gene encodes for the constitutively active Bcr–Abl tyrosine kinase, responsible for growth factor-independent cell growth and resistance to apoptosis. Both lead to the uncontrolled proliferation of myeloid cells. Imatinib mesylate (Gleevec™, Fig. 1) is a 2-phenylaminopyrimidine Bcr–Abl inhibitor approved by the FDA for the treatment of CML and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL). Although an initial response is achieved with Imatinib in patients, resistance may develop in advanced phases of CML because of the appearance of mutations in Bcr–Abl, leading to patient relapse. Therefore, novel agents able to overcome resistance to Imatinib such as the Bcr–Abl inhibitor Dasatinib[1] (Fig. 1) are needed for the effective treatment of CML.

Pyrido[2,3-*d*]pyrimidines were originally characterized as inhibitors of the fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGFR), and Src protein tyrosine kinases.[2–4] Members of this chemical class have been shown to be potent inhibitors of the Abl and Bcr–Abl tyrosine kinases and to induce apoptosis of the CML cell line K562.[5–7] Importantly, derivatives of pyrido[2,3-*d*]pyrimidines such as the pyrido[2,3-*d*]pyrimidin-7-one [PD166326] **1** (Fig. 1) are active both in Imatinib-sensitive and in resistant cancer cell lines expressing mutant Bcr–Abl,[8,9] and PD166326 has demonstrated marked antileukemic activity in vivo.[10] Pyrido[2,3-*d*]pyrimidin-7-ones therefore constitute an attractive class of drug candidates for the treatment of sensitive and refractory CML. While pyrido[2,3-*d*]pyrimidine-based tyrosine kinase inhibitors have been described as pan-kinase inhibitors, to our knowledge SAR studies aimed at characterizing and improving the selectivity of PD166326 analogs toward Abl has not been reported. In an attempt to fill this gap, we embarked in the design of novel pyrido[2,3-*d*]pyrimidin-7-one derivatives. The co-crystal structure of **1** with Abl kinase reveals a feature that we decided to exploit in the design of a focused library of pyrido[2,3-*d*]pyrimidin-7-ones: a solvent accessible opening in the back end of the ATP-binding site may tolerate additional functional groups (Fig. 2A). The C-2 phenylamino moiety protrudes from the binding pocket and is solvent-exposed (Fig. 2B). Molecular modeling and docking studies show that the 3- or 4-position on this arene (Fig. 2B) can be functionalized with a variety of groups that may improve solubility and kinase selectivity without decreasing Abl binding affinity. For this reason, we decided to explore the structure–activity relationship of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-one derivatives substituted at positions-3 and -4 of the arene as an avenue in the search of more selective Abl inhibitors (Fig. 1). For this goal, we generated 19 new compounds by coupling

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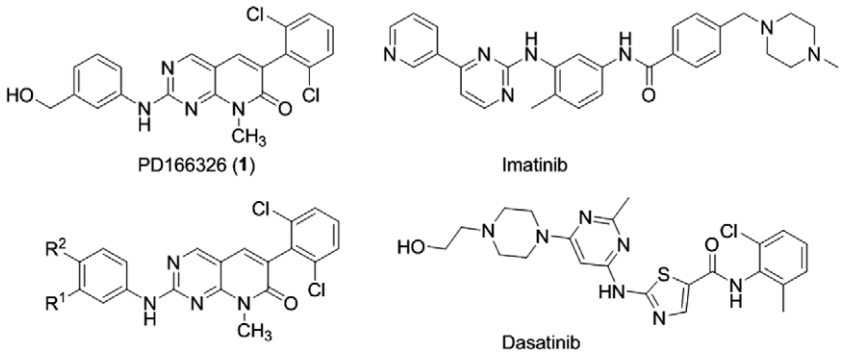


Figure 1. Structure of PD166326 (**1**) and general structure of the 19 derivatives of our 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-one focused library.

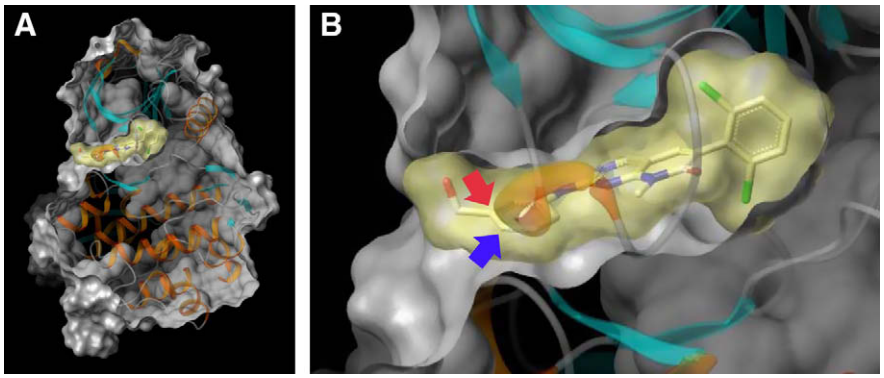
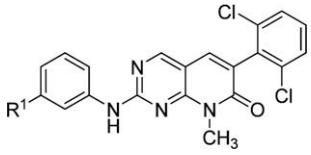


Figure 2. X-ray structure rendering of PD166326 (**1**) co-crystallized with Abl kinase. (A) Overall view. (B) View centered on PD166326. The red and blue arrows indicate the 3- and 4-positions on the C-2 phenylamino moiety, respectively.

a variety of aniline derivatives with 6-(2,6-dichlorophenyl)-2-methanesulfonyl-8-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one. Compounds **1**–**19** were synthesized using methods previously described.[2,11]

Table 1 summarizes the potency of R^1 derivatives with substituents in the 3-position of the phenylamino moiety toward Abl. As expected, we found using a coupled assay previously described[12] that the IC_{50} of the reference compound PD166326 **1** toward Abl was in the same range as previously reported (2.8 vs 8 nM).[9] Interestingly, polar substituents increased the potency of R^1 derivatives (**5** > **2** > **4**,) compared to **1**, while substituting the hydroxyl moiety of **1** with a methyl group induced a 10-fold loss in activity toward Abl. Of note, we have identified two analogs with a slightly improved potency compared to the reference compound PD166326: the amino-(**5**) and hydroxyl-(**2**) substituted R^1 derivatives. Table 2 summarizes the potency toward Abl of R^2 derivatives with substituents in the 4-position of the phenylamino moiety. Similarly to R^1 derivatives, we observe a higher potency for those derivatives substituted with polar groups (**8** > **13** = **17** > **7** > **12**) compared to hydrophobic substituents (**9** > **10** > **11**). For example, a 10-fold difference in potency is observed between the R^2 derivative **13** substituted with an amino group compared to the fluoro derivative **10**. In addition, for the R^2 amino derivatives, a loss of potency is observed when the amino group in this position is capped with hydrophobic moieties such as acetate (**14**), chloroacetamide (**15**), or *N*-*tert*-butoxycarbonylaminopropanamide (**18**). In contrast, when this amino group is substituted with a polar moiety such as a propanediol (**17**), no loss of potency is observed. As a confirmation of our observations, we observe a good correlation ($R^2 = 0.7$) between the potency of our derivatives toward Abl and their *c* log *P* (Fig. 3); potency decreases as hydrophobicity increases, and the most potent compound we have identified (**8**) is also the most hydrophilic

Table 1
2-(Phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones: variation of 3-phenyl substituents



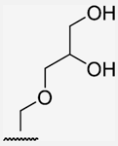
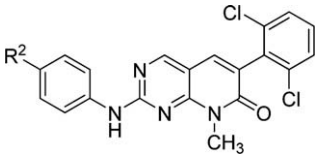
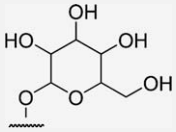
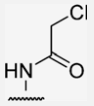
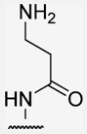
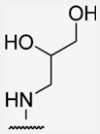
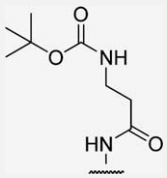
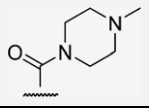
Compound	R^1	Abl IC_{50} (nM)	*c* Log *P*
2		2.6 ± 0.4	4.5
1		2.8 ± 0.6	4.1
3		22 ± 10	6.2
4		4.9 ± 1.2	3.3
5		2.5 ± 0.4	3.9
6		5.0 ± 0.6	4.1

Table 2
2-(Phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones: variation of 4-phenyl substituents



Compound	R^2	Abl IC_{50} (nM)	*c* Log *P*
7		5.3 ± 0.6	4.5
8		1.4 ± 0.1	3.0
9		13 ± 3.2	6.3
10		21 ± 14	5.3
11		30 ± 20	5.6
12		8.2 ± 1.0	4.3
13		2.3 ± 0.5	3.9
14		4.8 ± 0.6	4.1
15		7.6 ± 1.9	4.8
16		4.7 ± 0.9	3.6
17		2.3 ± 0.5	3.6
18		12 ± 7	5.4
19		3.6 ± 0.1	4.4

(Fig. 3). Altogether, our results strongly suggest that polar substituents in positions-3 and -4 of the phenylamino moiety improve the potency of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-one derivatives. Furthermore, we conclude that position-4 tolerates bulky groups, since analog **8** substituted with a glycoside in this position is the most potent derivative that we have identified; analog **8**, with an IC_{50} of 1.4 nM toward Abl, has a twofold increased potency compared to the reference compound PD166326. Our observations therefore validate our hypothesis that positions-3 and -4 of the aminophenyl moiety tolerate additional functional groups; polar substituents in these positions actually improve the potency of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-one derivatives.

While the activity of PD166326 (**1**) toward Abl and Src is well documented, we sought to assess a broad specificity profile for this compound, as well as for the new analogs we have synthesized. For this purpose, we constituted a panel of six human recombinant kinases: five tyrosine kinases (Abl, PDGFR, VEGFR, Src, and C-kit) and one serine/threonine kinase (p38-α). As expected, **1** was potent toward PDGFR and Src tyrosine kinases, with an IC_{50} of 45 and 43 nM for these kinases, respectively (Table 3). Importantly, we found that the reference compound **1** inhibits p38-α and VEGFR quite potently in addition to Abl (IC_{50} = 140 nM and 281 nM, respectively), while it is significantly less potent toward C-Kit, with an IC_{50} of 636 nM. To our knowledge, this observation constitutes the first report of the inhibitory activity of PD166326 toward the serine/threonine p38-α kinase, while inhibition of p38-α kinase by other pyrido[2,3-*d*]pyrimidine compounds has been previously described.[13] This result underlines the importance of our study, as a better understanding of the SAR of pyridopyrimidinones is necessary to design more selective derivatives. As predicted, all members of our focused library potently inhibit Abl, with their IC_{50} ranging from 1.4 to 30 nM. However, their compared selectivity toward Abl, PDGFR, and p38-α varied, and they were generally less potent toward VEGFR and C-Kit (Table 3). The selectivity of our analogs toward Abl compared to p38-α ranged from 2- to 72-fold. Interestingly, we identified a clear trend among the new compounds we have synthesized: the selectivity of R^2 derivatives for Abl compared to p38-α was from 2- to 25-fold, while it ranged from 34- to 72-fold for R^1 derivatives. This important observation strongly suggests that substitutions in the 3-position of the phenylamino moiety increase the selectivity of pyridopyrimidinone derivatives for Abl compared to p38-α. We found that analog **2** had a similar potency toward Abl compared to the reference compound PD166326 **1**, but was roughly twofold more selective for Abl versus PDGFR and VEGFR, and had no activity toward C-Kit. Analog **2** is the most selective derivative we have identified, with a selectivity ratio for Abl versus other kinases ranging from 17 to greater than 385-fold (Table 3); this result constitutes a significant improvement compared to the selectivity profile of the reference compound **1**. We conclude that the important SAR we have defined should allow the design of pyridopyrimidinone derivatives with greatly enhanced selectivity for the Abl kinase.

To test the biological relevance of our findings we performed the cytotoxicity profiling of our pyridopyrimidine derivatives against a panel of seven well-characterized cancer cell lines, using an assay we had previously reported.[14] As expected, the 19 derivatives of our focused library are extremely potent toward the CML cell lines K562, MEG-01, KU812, and Kasumi-4, which are Philadelphia chromosome positive (Table 4); most derivatives have an IC_{50} lower than 10 nM toward these cell lines. We also found that all compounds were potent toward ALL-3 cells, derived from a patient with acute lymphoblastic leukemia treated at MSKCC and characterized as Philadelphia chromosome positive. Interestingly, while ALL-3 cells were refractory to Imatinib (IC_{50} = 333 nM, Fig. 4), we found that the reference compound PD166326 **1** was potent toward these cells (IC_{50} = 7.7 nM, Fig. 4), as well as Dasatinib

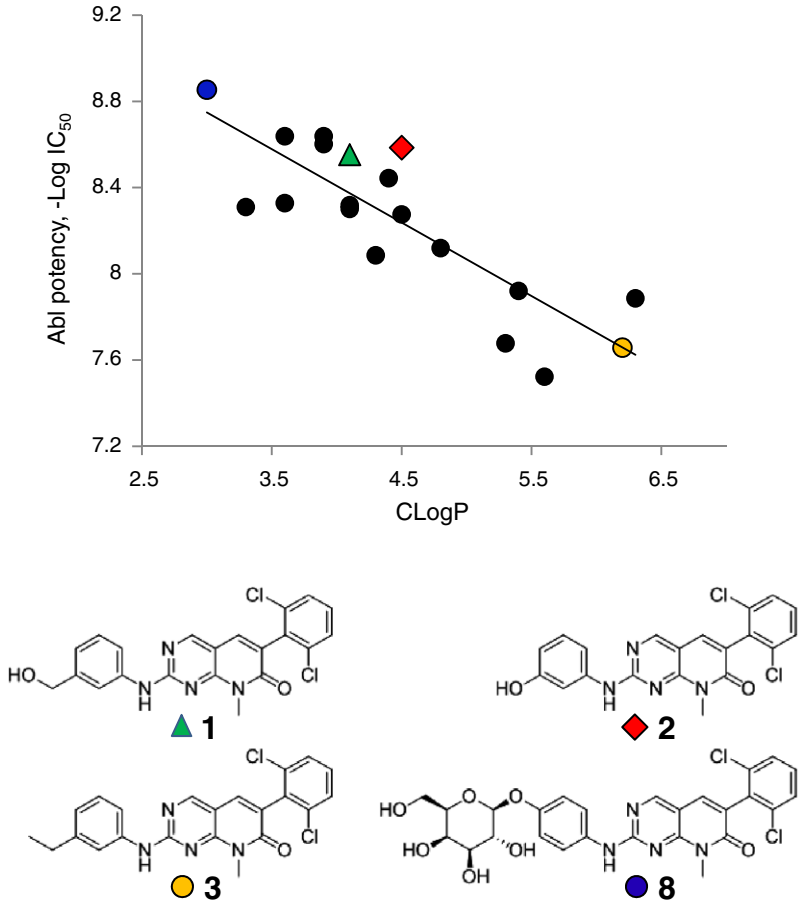


Figure 3. Influence of the hydrophobicity of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-one compounds on their potency toward Abl. Highlighted compounds: **1** (PD166326), Abl IC_{50} = 2.8 ± 0.6 nM, *c* log *P* = 4.1; **2**, Abl IC_{50} = 2.6 ± 0.4 nM, *c* log *P* = 4.5; **3**, Abl IC_{50} = 22 ± 10 nM, *c* log *P* = 6.2; **8**, Abl IC_{50} = 1.4 ± 0.1 nM, *c* log *P* = 3.0.

Table 3
Summary of the kinase specificity profile of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones

	Compound	Abl IC_{50} (nM)	p38-α IC_{50} (nM)	PDGFR IC_{50} (nM)	Src IC_{50} (nM)	VEGFR IC_{50} (nM)	C-Kit IC_{50} (nM)
R^2 derivatives	**10**	21	50 (2)	47 (2)	921 (44)	N.E.	290 (14)
	19	3.6	10 (3)	14 (4)	35 (10)	44 (12)	235 (65)
	16	4.7	34 (7)	26 (6)	18 (4)	104 (22)	239 (51)
	8	1.4	15 (11)	15 (11)	30 (21)	69 (49)	250 179)
	12	8.2	110 (13)	83 (10)	9.2 (1)	245 (30)	N.E.
	17	2.3	32 (14)	42 (18)	38 (17)	158 (69)	421 (183)
	11	30	488 (16)	500 (17)	492 (16)	546 (18)	N.E.
	9	13	224 (17)	203 (16)	341 (26)	296 (23)	766 (59)
	15	7.6	135 (18)	111 (15)	433 (57)	292 (38)	N.E.
	7	5.3	105 (20)	82 (15)	223 (42)	455 (86)	N.E.
	13	2.3	51 (22)	30 (13)	36 (16)	51 (22)	491 (213)
	14	4.8	108 (23)	158 (33)	43 (9)	159 (33)	N.E.
	18	12	299 (25)	311 (26)	213 (18)	415 (35)	N.E.
R^1 derivatives	**3**	22	752 (34)	244 (11)	234 (11)	354 (16)	N.E.
	1	2.8	140 (50)	45 (16)	43 (15)	281 (100)	636 (227)
	6	5	251 (50)	98 (20)	150 (30)	59 (12)	N.E.
	5	2.5	133 (53)	24 (10)	38 (15)	47 (19)	N.E.
	4	4.9	330 (67)	87 (18)	66 (13)	297 (61)	N.E.
	2	2.6	187 (72)	76 (29)	43 (17)	552 (212)	N.E.

N.E.: no effect; IC_{50} > 1000 nM; (x): selectivity ratio for Abl.

(IC_{50} = 0.4 nM, Fig. 4). This result was expected since ALL-3 cells express Bcr–Abl, and confirms the previous observation that pyridopyrimidine derivatives are active in Imatinib-resistant cell lines.[8,9] Importantly, most compounds in our library had potent cytotoxic activity toward ALL-3 cells—including analog **2** with the improved kinase selectivity profile (IC_{50} = 37 nM, Fig. 4)—highlighting the great potential of the class of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones as drug candidates for patients refractory to Imatinib. When we assessed the cytotoxicity of our novel derivatives toward the human acute T-cell leukemia cell line Jurkat and the human Mantle cell lymphoma NCEB-1 cell line—both Philadelphia chromosome negative—as a control, we found

Table 4
Summary of the cell-based antitumor activity of 2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones

Compound	Ph + CML					Ph + ALL	Ph-leuk.	Ph-lymp.
	Abl IC_{50} (nM)	K562 IC_{50} (nM)	MEG-01 IC_{50} (nM)	KU812 IC_{50} (nM)	Kasumi-4 IC_{50} (nM)	ALL-3 IC_{50} (nM)	Jurkat IC_{50} (nM)	NCEB-1 IC_{50} (nM)
8	1.4	<10	<10	<10	<10	55	N.E.	N.E.
13	2.3	<10	<10	<10	<10	165	6500	N.E.
17	2.3	25	<10	<10	<10	15	N.E.	N.E.
5	2.5	<10	<10	<10	<10	135	N.E.	N.E.
2	2.6	<10	<10	<10	<10	35	5000	N.E.
1	2.8	<10	<10	<10	<10	<10	2100	N.E.
19	3.6	<10	<10	<10	<10	<10	900	N.E.
16	4.7	350	<10	<10	<10	165	3600	N.E.
14	4.8	<10	<10	<10	<10	35	N.E.	N.E.
4	4.9	<10	<10	<10	<10	<10	4200	N.E.
6	5	<10	<10	<10	<10	35	4600	N.E.
7	5.3	<10	<10	<10	<10	55	1500	5300
15	7.6	<10	<10	<10	<10	45	660	N.E.
12	8.2	<10	<10	<10	<10	200	3700	N.E.
18	12	90	<10	<10	<10	2800	N.E.	N.E.
9	13	<10	<10	<10	<10	545	1300	N.E.
10	21	<10	<10	<10	<10	170	3700	N.E.
3	22	60	25	<10	<10	650	N.E.	N.E.
11	30	55	35	<10	<10	790	N.E.	N.E.

CML: chronic myelogenous leukemia, ALL: acute lymphoblastic leukemia, leuk.: leukemia, lymph.: lymphoma.

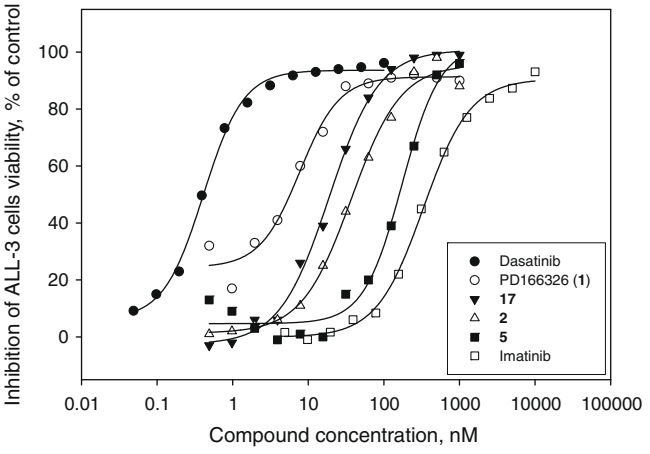


Figure 4. Dose–response of selected compounds in the Alamar Blue assay toward ALL-3 cells. Dasatinib, IC_{50} = 0.4 nM; PD166326 (**1**), IC_{50} = 7.7 nM; **17**, IC_{50} = 15 nM; **2**, IC_{50} = 35 nM; **5** IC_{50} = 135 nM; Imatinib, IC_{50} = 333 nM.

as expected that none of the compounds we tested had potent cytotoxic activity toward these cells. This result indicates that our new derivatives are selective toward Philadelphia chromosome positive cells, emphasizing their potential for the targeted therapy of CML patients.

In summary, our study proved successful, in that we have identified more potent and more selective analogs of PD166326 among our focused library of 19 novel pyrido[2,3-*d*]pyrimidin-7-one derivatives. In addition, we have defined clear trends in the SAR for this class of compounds that should lead to the discovery of novel drug candidates with improved potency and selectivity profile for the targeted therapy of CML.

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