N7-Substituted-5-aryl-pyrrolo[2,3-d]pyrimidines Represent a Versatile Class of Potent Inhibitors of the Tyrosine Kinase c-Src

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Abstract: 5-Aryl-pyrrolo[2,3-d]pyrimidines incorporating different N^7-substituents have been prepared and evaluated for their inhibitory potency towards the tyrosine kinase c-Src. Optimization of these compounds resulted in highly potent c-Src inhibitors, some (e.g. **4g**, **6g**, **7h**, **8l**) with excellent specificity towards other receptor and nonreceptor tyrosine kinases. In addition compounds **4g**, **5b** and **5c** are characterized by a good pharmacokinetic profile.

Involvement of the protein tyrosine kinase $pp60^{c\text{-}Src}$ (c-Src) has been postulated for several diseases that have severe implications in humans, like osteoporosis, colon cancer, bone metastasis formation in breast cancer and most recently stroke just to mention a few [1, 2]. The analysis of mutant mice with a disrupted c-Src gene clearly demonstrated that c-Src plays a unique and crucial role for osteoclast function [3, 4]. Despite high expression of c-Src in osteoclasts, platelets and brain, c-Src deficient mice show no other phenotype than disregulated bone resorption leading to osteopetrosis. This finding initiated interest in different approaches to inhibit c-Src activity with the perspective of a potential therapy of diseases associated with low bone mass [5].

c-Src is composed of three structural domains [6] all are being explored for selective inhibition with small molecules [5]. Interruption of signal transduction mediated through protein-protein interactions, predominantely through Src homology-2 (SH2) [5, 7, 8] or Src homology-3 (SH3) [5] domains, represents one way to interfere with signalling. The other prominent approach to inhibit c-Src activity utilizes compounds which target the catalytic domain. Depending on their site of action such agents are divided into substrate-based or ATP-competitive inhibitors, with the majority of inhibitors targeting the ATP binding site [5, 9-12]. Of this latter type N^7-substituted-5-aryl-pyrrolo[2,3-d]pyrimidines Fig. (**1**) represent one of the most extensively characterized family of compounds. [9, 10, 13]. The corresponding compound CGP76775 reduces serum calcium concentration in an IL-1β-induced hypercalcemia model in mice and most significantly, it is orally active in a long term model of osteoporosis (ovariectomized rats) [14]. We report herein on the optimization of 7-substituted-5-aryl-pyrrolo[2,3-d]pyrimidines towards potency, specificity as well as physicochemical properties that allow oral administration of these inhibitors in the corresponding disease animal models.

How the position of substituents on both phenyl rings on 5,7-diphenyl-pyrrolo[2,3-d]pyrimidines influences the inhibitory potency is outlined with representative examples (entries **1a- h**) in Table 1. No substituents are tolerated in the 2'-position on either phenyl ring without substantially decreasing potency. This finding can be interpreted either as a direct result of limited space for 2'-substituents in the ATP binding site of c-Src or as a consequence of the increased twisting of the phenyl rings out of the pyrrolopyrimidine plane leading to unfavorable interactions with the protein surface. At the 5-phenyl ring , which according to CAMM locks into a hydrophobic pocket inside the ATP binding site, only small substituents in 3'- and 4'-position are tolerated. In contrast to the 3'- and 4'-positions of the N^7-phenyl ring, which allow for broad variations since these substituents presumably reach the water exposed surface of the enzyme. Therefore, physicochemical properties can be optimized by attaching polar and under physiological conditions charged moities at this part of the molecules without affecting their potency. Interestingly, modifications at this site can in addition influence the specificity profile of the inhibitors in the desired direction. The specificity assays include the receptor tyrosine kinases for EGF-R and Kdr, the non-receptor tyrosine kinase v-Abl as well as the serine/threonine kinase Cdc-2.

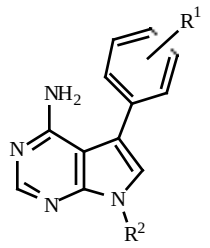

Fig. (1).

The importance of hydrogen bond formation for ATP competitive kinase inhibitors is well documented [15- 18]. The possibility for the proper formation of at least one hydrogen bond, but preferrably a hydrogen bond donor-acceptor pair, is required for good inhibition as illustrated in Fig. (**2**) and demonstrated with compounds **2a- g** in Table 1. Entries **2a** and **2b**, adopting predominantely the carbonyl tautomeric form, lead to inverted hydrogen bond pairing capabilities and are only marginally active. The same is

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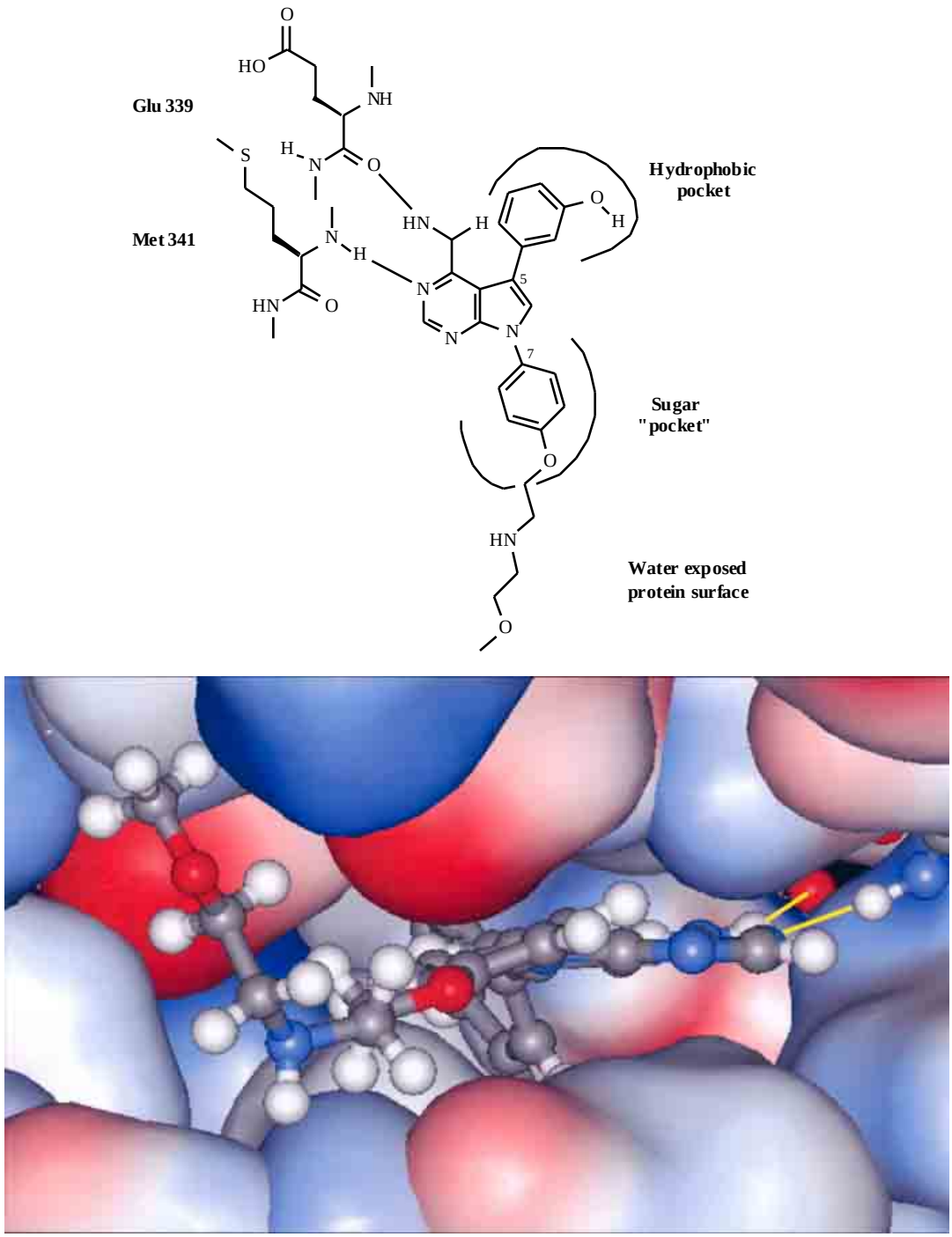
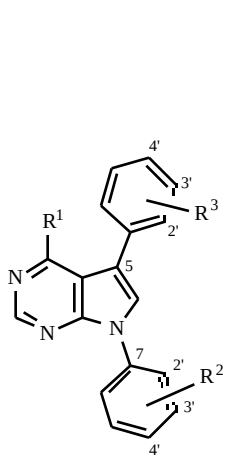


Fig. (2). Proposed binding mode of compound **4a** at the ATP binding site.

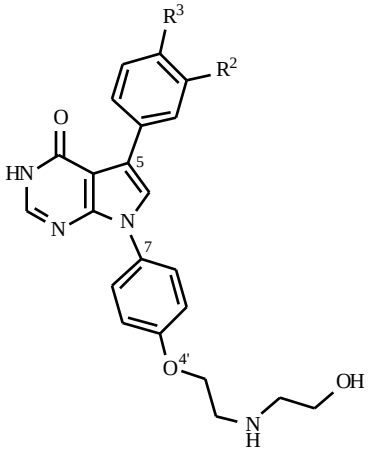
observed with compound **2c**, where methylation of the amine results again in a dramatic loss of inhibitory potency. Entries **2d** and **2e** allow the formation of one hydrogen bond, which leads in the case of **2e** to a still potent inhibitor.

Compounds **2f- m** with an amino-substituent in the 4 position demonstrate the potencies which can be achieved with the 5,7-diphenyl-pyrrolo[2,3-d]pyrimidines if both hydrogen bonds can be formed. While keeping the polar substituent in the 4‘ position on the N^7- phenyl ring constant, the influence of several substituents on phenyl 5 on the inhibitory potency can be shown. Most pronounced effects are seen with hydroxy-substituents in 3‘- (**2g**) and to a smaller degree in 4‘- position (**2k**), these hydroxy-derivatives are generally low- to subnanomolar inhibitors. This effect is not unique to c-Src as illustrated by the selectivity profile, which shows a comparable boost in potency on most other kinases tested, including the serine/threonine kinase Cdc-2 (e.g. **2g**). In addition and indeed not surprising, compounds incorporating a 3‘- or 4‘- OH substituent at the 5-phenyl ring have a poor

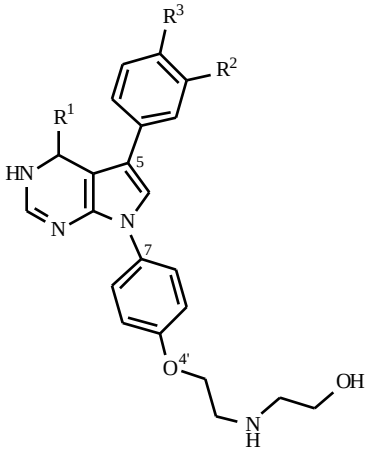
Table 1. Positional Effects of Substituents on 5,7-Diphenyl-pyrrolo[2,3-d]pyrimidines 1 and 2



1a-h



2a, 2b



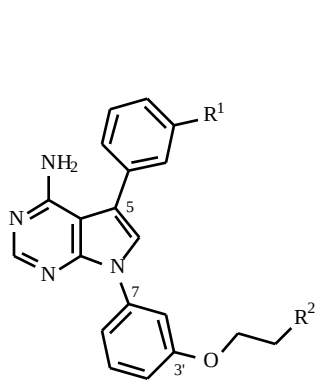
2c-l

Cpd.	R^1	R^2	R^3	c-Src[a] [μM]	EGF-R[b] [μM]	Kdr[c] [μM]	v-Abl[d] [μM]	Cdc-2[e] [μM]
1a	NH_2	H	H	0.1	0.5	0.5	0.02	54
1b	NH_2	H	2'-CH_3	6.0	2.65	n.d.[f]	n.d.[f]	90.0
1c	NH_2	H	3'-OCH_3	0.05	0.5	>1.0	0.06	43.0
1d	NH_2	H	4'-OCH_3	0.15	0.35	0.2	0.4	>10.0
1e	NH_2	H	4'-COOEt	10.0	1.3	1.1	>10.0	>10.0
1f	NH_2	2'-$CH_2NH(CH_2)_2OH$	H	5.0	6.4	n.d.[f]	n.d.[f]	>10.0
1g	NH_2	3'-$CH_2NH(CH_2)_2OH$	H	0.01	3.4	3.6	n.d.	>10.0
1h	NH_2	4'-$CH_2NH(CH_2)_2OH$	H	0.03	1.4	n.d.[f]	1.0	82.5
2a	-	OMe	H	>10	>10	>1	>10	>10
2b	-	OH	H	>10	>1000	>1	6.3	>10
2c	NHMe	OMe	H	>10	8.6	>1	>10	>10
2d	H	OMe	H	>10	1.6	>1	>10	>10
2e	H	OH	H	0.04	0.41	>1	1.7	n.d.[f]
2f	NH_2	OMe	H	0.02	0.09	0.9	0.01	>10
2g	NH_2	OH	H	0.0003	0.08	0.07	<0.001	0.35
2h	NH_2	F	H	0.022	0.17	1.0	0.36	>10
2i	NH_2	Cl	H	0.023	0.11	n.d.[f]	0.39	>10
2k	NH_2	H	OH	0.003	0.11	0.64	0.2	>10
2l	NH_2	Cl	F	0.015	0.09	1.0	0.18	>10
2m	NH_2	F	F	0.015	0.35	1.0	0.12	>10

[a]Inhibition of c-Src enzyme activity in the liquid phase tyrosine phosphorylation assay. IC_{50} values are the mean of 2 experiments carried out in duplicate, individual data points in each experiment were within 3-fold range with each other. [b]Inhibition of epidermal growth factor receptor (EGF-R) tyrosine kinase enzyme activity. [c]Inhibition of Kdr tyrosine kinase enzyme activity. [d]Inhibition of v-Abl tyrosine kinase enzyme activity. [e]Inhibition of Cdc-2 serine/threonine kinase enzyme activity. [f]Not determined

pharmacokinetic profile (*cf.* Table 3, **2g**) . Methoxy- or halogen-substituted derivatives **2f, 2h, i** and **2l, m** on the other hand represent potent inhibitors in the low nanomolar range with an attractive selectivity profile. This finding is further substantiated with a subset of compounds bearing a 3-methoxy substituent at the 5-phenyl ring and various ethyloxy-amines at the 4-position of the N^7-phenyl ring (Table 2, entries **4d- k**) leading to potent inhibitors of c-Src with 20- to 100-fold selectivity over the kinases which were routinely tested for specificity. As indicated above, it is remarkable, that some of these changes affect the specificity profile despite the fact that according to our model, the substituents at the 4'-position at the N^7-phenyl ring point towards the surface of the enzyme and are not interacting

Table 2. Inhibition of c-Src Enzyme Activity and Selectivity Profile of 5,7-Diphenyl-pyrrolo[2,3-d]pyrimidines 3 and 4



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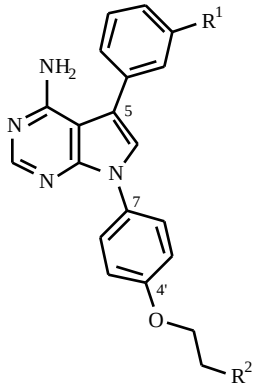

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Cpd.	R^1	R^2	c-Src[a] [μM]	EGF-R[b] [μM]	Kdr[c] [μM]	v-Abl[d] [μM]	Cdc-2[e] [μM]
3a	OH	Imidazol (N1)	<0.001	0.42	0.09	<0.01	3.7
3b	OH	$NH(CH_2)_2OMe$	0.008	0.39	n.d.[f]	<0.01	>10
3c	OMe	Imidazol (N1)	0.03	n.d. [f]	1.0	n.d. [f]	n.d. [f]
3d	OMe	$NH(CH_2)_2OMe$	0.17	2.3	>1	n.d. [f]	>10
4a	OH	$NH(CH_2)_2OMe$	<0.001	<0.3	0.16	0.02	n.d. [f]
4b	OH	NMe_2	0.0003	0.09	0.03	0.001	0.4
4c	OH	Imidazol (N1)	<0.001	0.27	0.05	<0.01	0.5
4d	OMe	NMe_2	0.015	0.14	1.0	0.1	>10
4e	OMe	$NH(CH_2)_2OH$	0.02	0.09	0.9	0.01	>10
4f	OMe	Pyrrolidine (N)	0.025	0.12	>1	0.13	>10
4g	OMe	$NH(CH_2)_2OMe$	0.027	0.26	2.7	0.18	>10
4h	OMe	$NMe(CH_2)_2OMe$	0.03	0.09	0.5	0.1	>10
4i	OMe	$NHCH_2CONHMe$	0.04	0.19	1.0	0.29	>10
4j	OMe	$N(CH_2)_3CH_3$	0.06	0.18	1.0	0.16	>10
4k	OMe	Imidazol (N1)	0.14	1.6	1.0	0.19	>10
4l	OEt	$NH(CH_2)_2OH$	>1000	2.2	>1	2.3	>10

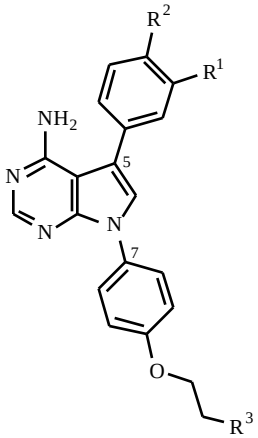
[a]Inhibition of c-Src enzyme activity in a liquid phase tyrosine phosphorylation assay. IC_{50} values are the mean of 2 experiments carried out in duplicate, individual data points in each experiment were within 3-fold range with each other. [b]Inhibition of epidermal growth factor receptor (EGF-R) tyrosine kinase enzyme activity. [c]Inhibition of Kdr tyrosine kinase enzyme activity. [d]Inhibition of v-Abl tyrosine kinase enzyme activity. [e]Inhibition of Cdc-2 serine/threonine kinase enzyme activity. [f]Not determined.

with the binding pocket. One possible explanation could be that they interfere not only with ATP binding but in addition with substrate binding, which would be expected to lead to specificity towards other kinases, considering their individual substrates.

Relevant pharmacokinetic data of some 5,7-diphenyl-pyrrolo[2,3-d]pyrimidines are outlined in Table 3. As already indicated above the phenolic hydroxy-group at the 5-phenyl ring leads to low oral bioavailability and in addition high clearance (data not shown), most likely due to fast metabolic conversion. However, methoxy- as well as fluoro-substituents, blocking this well known metabolic pathway, gave much better pharmacokinetic properties. In addition, a free hydroxy group in the side chain has a negative impact on the oral bioavailability and on the clearance. (*cf.* Table 3, **4e** *vs* **4g** and **5a** *vs* **5b**). The 3‘,4‘-difluoro-derivatives without free hydroxy substituents (*cf.* Table 3, **5b** and **5c**) show good oral bioavailability around 40% and satisfactory C_{max} values. In addition, most compounds inhibit c-Src mediated phosphorylation of FAK in intact cells [14] in the submicromolar range as indicated in Table 3. Overall, compounds like **4g** and **5b, c** are suitable candidates for further profiling in *in vivo* animal models of osteoporosis or cancer therapy.

Further modification of **1a** focused on the replacement of the N^7-phenyl ring by acyclic aliphatic and cyclic groups and

Table 3. Cellular Activity, Additional Specificity and PK of Selected 5,7-Diphenyl-pyrrolo[2,3-d]pyrimidines



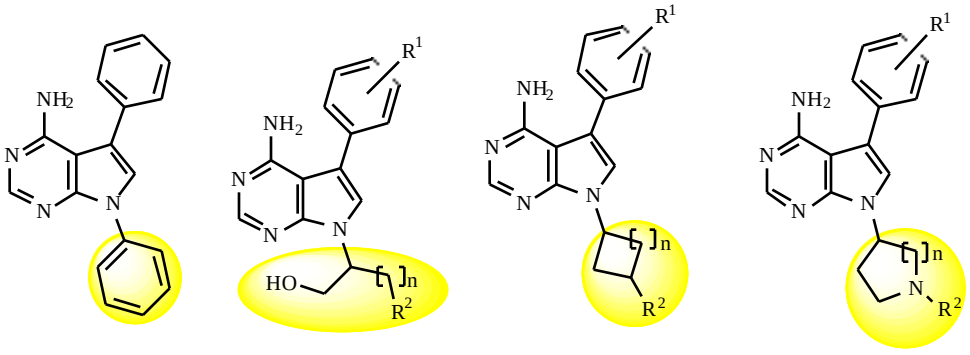
Cpd.	R^1	R^2	R^3	c-Src [a] Enz. [μM]	c-Src[b] cell [μM]	Csk[c] cell [μM]	lck[d] [μM]	F [%]	C_{max} [μM]	CL [ml/min]
2g	OH	H	$NH(CH_2)_2OH$	0.0003	0.02	0.6	0.03	< 5	nd[e]	nd[e]
4e	OMe	H	$NH(CH_2)_2OH$	0.02	0.1	2.7	0.22	< 10	< 0.3	nd[e]
4g	OMe	H	$NH(CH_2)_2OMe$	0.027	0.1	2.6	0.36	40	3.4	6
4f	OMe	H	Pyrrolidine (N)	0.025	0.1	1.9	0.14	20	0.5	20
5a	F	F	$NMe(CH_2)_2OH$	0.01	0.6	6.4	0.1	15	0.5	31
5b	F	F	$NMe(CH_2)_2OMe$	0.05	1.1	4.3	0.24	40	3.8	5
5c	F	F	Pyrrolidine (N)	0.02	0.5	5.0	0.05	35	1.1	12

[a]Inhibition of c-Src enzyme activity in the liquid phase tyrosine phosphorylation assay. IC_{50} values are the mean of 2 experiments carried out in duplicate, individual data points in each experiment were within 3-fold range with each other. [b]Inhibition of c-Src mediated phosphorylation of Fak in IC8.1 fibroblasts [14]. [c]Inhibition of Csk tyrosine kinase mediated c-Src phosphorylation in IC8.1 fibroblasts [14]. [d]Inhibition of lck tyrosine kinase enzyme activity. [e]Not determined

our approaches in this area are summarized in Fig. (**3**) . In our proposed binding mode for **1a** (*cf.* Fig. (**2**)) the N^7-phenyl ring is located within the pocket that is usually occupied by the ribose moiety of ATP [19]. Substitution of the N^7- phenyl ring by open chain sugar analogs as in **5** and **6**, by carbacycles as in **7** or by heterocycles as in **8** was expected to increase potency and solubility of our lead compound **1a**.

Introduction of a polyhydroxylated, non-cyclic substituent at N^7 in compounds of type **5** (Table 4) resulted in sub-μM inhibitors of c-Src. Surprisingly **5a** proved to be slightly more potent than **5c** and **5d**, usually the introduction of a 3-OH or 4-OMe substituent at the 5-phenyl ring led to an increase in inhibitory potency as outlined for the 5,7-diphenyl-pyrrolo[2,3-d]pyrimidines (*cf.* Table 1). Extension of the N^7-methyl-propane-1,3-diol substituent in **5a** by one carbon to the N^7-ethyl-propane-1,3-diol derivative **5b** resulted in a more than 10-fold loss in potency.

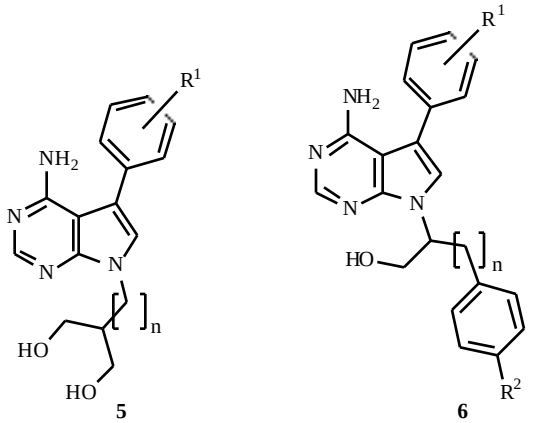
In compounds **6** [9] we consider the substituent at N^7 as an open chain sugar analog still incorporating the 7-phenyl ring of our lead structure **1a**. Optimization of these analogs involves variation of the distance between N^7 and the phenyl ring of the phenyl-hydroxyalkyl moiety and the introduction of substituents at either one or both of the phenyl rings.



1a **5/6** **7** **8**

Fig. (3). Replacement of the N^7-phenyl ring.

Table 4. Inhibition of c-Src Enzyme Activity and Selectivity Profile of N^7-Alkyl-5-aryl-pyrrolo[2,3-d]pyrimidines 5 and 6



Cpd.	R^1	R^2	n	c-Src[a] IC_{50} [μM]	EGF-R[b] IC_{50} [μM]	Kdr[c] IC_{50} [μM]	v-Abl[d] IC_{50} [μM]	Cdc-2[e] IC_{50} [μM]
5a	H	-	1	0.2	n.d.[k]	6.0	n.d.[k]	n.d.[k]
5b	H	-	2	2.3	n.d.[k]	n.d.[k]	n.d.[k]	n.d.[k]
5c	4-OH	-	1	0.45	2.4	n.d.[k]	n.d.[k]	n.d.[k]
5d	3-OMe	-	1	0.35	n.d.[k]	>1	0.94	>10
6a[f]	H	H	0	4.9	n.d.[k]	n.d.[k]	n.d.[k]	n.d.[k]
6b[g]	H	H	0	0.48	n.d.[k]	n.d.[k]	n.d.[k]	n.d.[k]
6c[h]	H	H	1	0.6	0.44	n.d[k]	10.5	>100
6d[h]	H	H	2	4	n.d.[k]	>1	n.d.[k]	n.d.[k]
6e[h]	H	OH	1	1.9	13.2	>1	2.2	>10
6f[h]	H	OMe	1	>1	14.4	>1	>10	>10
6g[h,i]	3-OH	OMe	1	0.042	3.4	>1	0.34	>10
6h[h]	3-OMe	OMe	1	1	9.7	n.d.[k]	0.68	>10

[a]Inhibition of c-Src enzyme activity in the liquid phase tyrosine phosphorylation assay. IC_{50} values are the mean of 2 experiments carried out in duplicate, individual data points in each experiment were within 3-fold range with each other. [b]Inhibition of epidermal growth factor receptor (EGF-R) tyrosine kinase enzyme activity. [c]Inhibition of Kdr tyrosine kinase enzyme activity. [d]Inhibition of v-Abl tyrosine kinase enzyme activity. [e]Inhibition of Cdc-2 serine/threonine kinase enzyme activity. [f]S-Enantiomer. [g]R-Enatiomer. [h]Racemate. [i]IC_{50} for lck inhibition = 2.85 μM. [k]Not determined

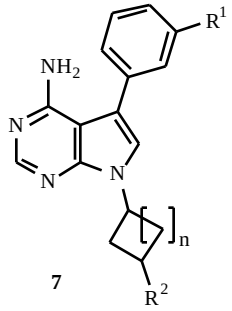
Considering derivatives **6a- d** with unsubstituted phenyl rings, only **6b** (n= 0; R-enantiomer) and **6c** (n= 1; racemate) show sub-μM activity. Introduction of a 4-hydroxy- or 4-methoxy group at the phenyl ring in the phenyl-hydroxyalkyl moiety (**6c** → **6e**, **6f**) led to a drop in potency. A dramatic improvement in inhibitory activity was achieved by introducing a 3-OH substituent at the 5-phenyl ring of **6f** (→ **6g**), resulting in a nM inhibitor of c-Src with a remarkable selectivity toward EGF-R (80-fold) and some selectivity towards v-Abl (8-fold). Most interestingly, **6g** also exhibits an excellent (68-fold) selectivity towards lck, a src family kinase.

Table 5 summarizes the c-Src inhibitory activity of compounds of structures **7** and **8** bearing carbacycles or heterocycles as N^7- substituents. Carbacycles represent more direct mimics of the ribose moiety of ATP than the above described open chain sugar analogs.

N^7-cycloalkyl-5-phenyl-pyrrolo[2,3-d]pyrimidines **7a- c** are all sub-μM inhibitors of c-Src [20]. Derivatives **7d**, **e** incorporating a 3-hydroxymethylcyclobutyl substituent at N^7 show improved potency. Introduction of a 3-OH substituent on the 5-phenyl ring of **7d**, **e** → **7h**, **i** resulted in low nM inhibitors. As further illustrated by the data given in Table 5 the cis- and trans-racemates **7d, f, h** and **7e, g, i** respectively, inhibit c-Src in the same potency range however, their selectivity profile differs. The cis-racemate **7h** was found to be the most selective compound from this series.

Substitution of the N^7-phenyl ring in **1a** by polar heterocyclic moieties was assumed to enable additional interactions with polar amino acid side chains within the sugar pocket and to lead to improved solubility. As illustrated by the data summarized in Table 5 N^7-heterocyclic-5-aryl-pyrrolo[2,3-d]pyrimidine derivatives **8**

Table 5. Inhibition of c-Src Enzyme Activity and Selectivity Profile of N^7-Cycloalkyl-5-aryl-pyrrolo[2,3-d]pyrimidines 7 of N^7-Heterocyclyl-5-aryl-pyrrolo[2,3-d]pyrimidines 8



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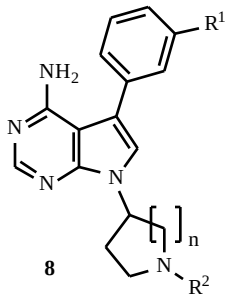

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Cpd.	R^1	R^2	n	c-Src[a] IC_{50} [μM]	EGF-R[b] IC_{50} [μM]	Kdr[d] IC_{50} [μM]	v-Abl[c] IC_{50} [μM]	Cdc-2[e] IC_{50} [μM]
7a	H	H	0	0.25	2.1	n.d.[k]	n.d.[k]	60
7b	H	H	1	0.11	0.73	0.35	0.09	>10
7c	H	H	2	0.14	0.5	0.43	0.14	>10
7d[f]	H	CH_2OH	1	0.032	1.8	0.44	0.27	>10
7e[g]	H	CH_2OH	1	0.054	1.1	0.47	0.08	>10
7f[f]	OH	CO_2CH_3	1	0.004	0.22	0.03	0.009	9
7g[g]	OH	CO_2CH_3	1	0.003	0.3	0.04	0.01	1.3
7h[f,h]	OH	CH_2OH	1	0.001	0.29	0.03	0.04	1.9
7i[g]	OH	CH_2OH	1	0.003	0.17	0.03	0.01	0.75
8a[i]	OMe	H	1	0.053	1.12	>1	1.4	80
8b[i]	OH	H	1	0.006	1.53	0.46	0.29	n.d.[k]
8c[i]	OMe	$CH_2CO_2CH_3$	1	0.05	0.83	1	0.59	>10
8d[i]	OH	$CH_2CO_2CH_3$	1	0.003	0.74	0.24	0.054	4
8e[i]	OMe	$CH_2CON(CH_3)_2$	1	0.1	0.9	>1	0.77	>10
8f[i]	OH	$CH_2CON(CH_3)_2$	1	0.009	0.61	0.38	0.14	7
8g	OMe	$CH_2CO_2CH_3$	2	0.084	1.47	1	1	>10
8h[h]	OH	$CH_2CO_2CH_3$	2	<0.001	0.8	0.39	0.056	3.6
8i	OMe	$CH_2CON(CH_3)_2$	2	0.067	0.75	>1	0.51	n.d.[k]
8k	OH	$CH_2CON(CH_3)_2$	2	0.003	0.5	0.24	0.12	4.3
8l[h]	OMe	$(CH_2)_2N(CH_3)(CH_2)_2OH$	2	0.006	0.29	1	0.36	>100
8m[h]	OMe	$(CH_2)_2NH(CH_2)_2OCH_3$	2	0.015	0.31	>1	0.26	>100
8n[h]	OMe	$(CH_2)_2N(CH_3)(CH_2)_2OCH_3$	2	0.047	0.93	>1	0.5	>10

[a]Inhibition of c-Src enzyme activity in the liquid phase tyrosine phosphorylation assay. IC_{50} values are the mean of 2 experiments carried out in duplicate, individual data points in each experiment were within 3-fold range with each other.[b]Inhibition of epidermal growth factor receptor (EGF-R) tyrosine kinase enzyme activity. [c]Inhibition of v-Abl tyrosine kinase enzyme activity. [d]Inhibition of Kdr tyrosine kinase enzyme activity. [e]Inhibition of Cdc-2 serine/threonine kinase enzyme activity. [f]Cis-racemate. [g]Trans-racemate. [h]IC_{50} (μM) for the inhibition of lck: **7h** = 0.57; **8h** = 0.29; **8l** = 0.34; **8m** = 0.62; **8n** = 0.72. [i] Racemate. [k]Not determined.

[10] represent a series of highly potent c-Src inhibitors. Compounds **8b**, **8d**, **8f**, **8h** and **8k** bearing a 3-OH substituent at the 5-phenyl ring are generally not only the more potent c-Src inhibitors than their O-methylated analogues **8a**, **8c**, **8e**, **8g** and **8i**, in addition they also display a superior selectivity profile. However, as already mentioned above the phenolic derivatives show very unfavorable PK profiles. We therefore investigated the 3-OMe derivatives **8l- n** which have a large substituent incorporating a basic nitrogen, attached at the piperidine nitrogen. **8l – n** are all low nanomolar c-Src inhibitors, exhibiting good to excellent selectivity for c-Src over EGF-R (20- to 48-fold), Kdr (21- to 166-fold), v-Abl (10- to 60-fold), Cdc-2 (>200-fold) and as well towards the src family kinase lck (15- 56-fold). These 7-pyrrolidinyl- and 7-piperidinyl-5-aryl-pyrrolo[2,3-d]pyrimidines represent novel,

extremely potent and remarkably selective inhibitors of the tyrosine kinase c-Src.

In summary, four different types of N^7-substituted 5-aryl-pyrrolo[2,3-d]pyrimidines are described as inhibitors of the tyrosine kinase c-Src. In the 5,7-diphenyl-pyrrolo[2,3-d]pyrimidines series substituents on either phenyl ring have an impact on the potency as well as on the selectivity of these inhibitors. Optimization of the substitution pattern at the 5- as well as at N^7-phenyl ring led to highly potent and extremely selective compounds. Eventually fine tuning of the pharmacokinetic profile allowed the testing of some canditates in *in vivo* models of osteoporosis by oral administration.

Replacement of the N^7-phenyl ring by sugar surrogates, as open chain sugar mimics, carbacycles and heterocycles resulted in novel pyrrolo[2,3-d]pyrimidines, some with good to excellent inhibitory potency against c-Src and a remarkable selectivity profile towards other receptor- and nonreceptor tyrosine kinases as well as selectivity against the src family kinase lck.

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