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Urea derivatives of STI571 as inhibitors of Bcr-Abl and PDGFR kinases

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Abstract—The constitutively active Abl kinase activity of the Bcr-Abl oncoprotein is causative for chronic myelogenous leukemia. Urea derivatives, structurally related to the therapeutic agent STI571, have been identified, which potently inhibit the tyrosine kinase activity of recombinant Abl. In particular a dimethylamino-aniline derivative (**18**) inhibited c-Abl transphosphorylation with an IC_{50} value of 56 nM. Although this activity was not translated into cellular activity against the constitutively activated oncogenic Bcr-Abl, a number of compounds from this series potently inhibited cellular PDGFR autophosphorylation. It was also possible to differentiate between c-Abl and PDGFR kinase inhibition, with compound **22** being selective towards Abl and **23** selective for PDGFR.

STI571 (imatinib; Glivec®/Gleevec®) is a potent and selective inhibitor of Bcr-Abl kinase and as such is an effective therapy for chronic myelogenous leukemia (CML).[1–3] Although STI571 is an ATP-competitive inhibitor (K_i 85 nM),[4] X-ray crystallographic studies have revealed that it binds to an inactive, non-ATP-binding conformation of the Abl kinase domain (Fig. 1).[5,6] This binding mode can account for the overall selectivity of STI571 as a kinase inhibitor, since whereas the active conformations of the catalytic sites of human protein kinases (518 in total)[7] are highly conserved, there is significant diversity among their inactive conformations.[8] When bound to Abl, STI571 makes H-bond interactions with the backbone-NH of Met318, the side chain oxygen of Thr315, the side chain carboxylate of Glu286, the backbone-NH of Asp381 and the backbone carbonyls of Ile360 and His361, together with a large number of van der Waals contacts (Fig. 1). In the original design concept for STI571,[9] the *N*-methylpiperazine moiety was incorporated into the molecule to impart good solubility and oral bioavailability, in the belief that it extended towards the proteins exterior rather than being embedded in the catalytic site, and consequently would not directly influence drug binding. Therefore, since the structure activity surrounding the *N*-methylpiperazine group had not been extensively investigated, we hypothesised that the potency of the molecule might be enhanced by replacing it with an alternative binding group. As a design strategy we replaced the key amide pharmacophore element in STI571 with a urea moiety, with the reasoning that this group would maintain the H-bond interactions to Glu286 and Asp381 and, via the preferred *E*,*E*-conformation, allow us to explore new binding interactions. The urea *N*-substituents were selected to probe for binding interactions, to explore conformational space and to incorporate a basic centre, which would make salt formation possible, thereby facilitating drug formulation and oral absorption. This focussed library was prepared by parallel synthesis and the compounds were evaluated for their effects on Abl/Bcr-Abl kinase activity in both cell-free and in cellular assays. The key findings from this study are presented in this letter.

Compounds **6**–**27** were prepared by the route illustrated in Scheme 1. The phenylamino-pyrimidine core structure **4** was prepared using a variation of the Principal synthesis,[10] involving reaction of the enamine derivative of the β-aldehydoketone **3** with the guanidine **2**. The guanidine **2** was readily available from the commercially available aniline **1**, via reaction with cyanamide, followed by catalytic hydrogenation. Aminoformylation of 3-acetylpyridine with DMF–dimethylacetal furnished

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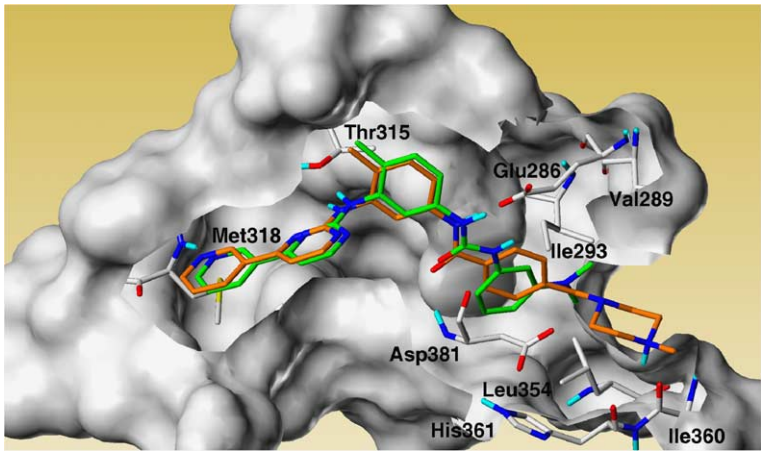
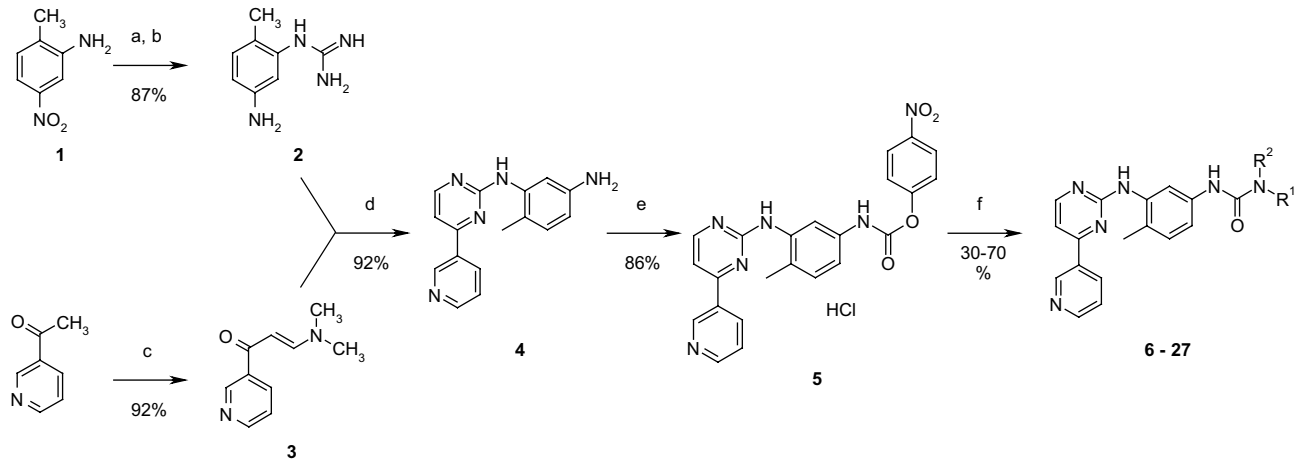


Figure 1. Details of the binding of STI571 (gold; X-ray crystal structure) and compound **18** (green; binding model) to the Connolly solvent-accessible surface (probe radius 1.4 Å) of the c-Abl kinase domain. Residues in the binding site that would be in front of the picture (mainly from the glycine-rich or P-loop), or behind, are not shown for clarity. STI571 interacts with the protein via hydrogen bonds, involving (from left to right): Met318, Thr315, Glu286, Asp381, His361 and Ile360, and packing interactions with Phe317, Phe382, Val256, Tyr253, Ile313, Lys271, Met290, Val299, Ala380 and Val289. Compound **18** is believed to bind to Abl via hydrogen bonds to Met318, Thr315, Glu286 and Asp381, and packing interactions to Phe317, Phe382, Val256, Tyr253, Ile293, Leu354, Leu298 and Val289.



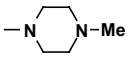
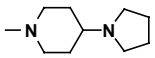
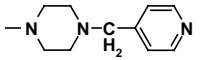
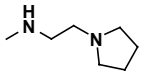
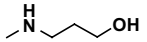
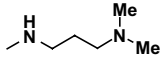
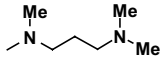
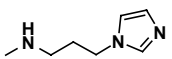
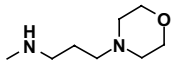
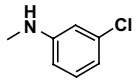
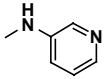
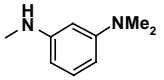
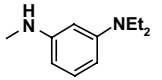
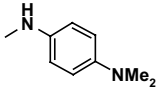
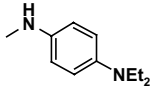
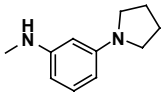
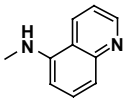
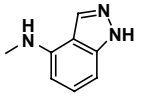
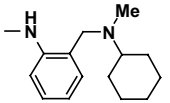
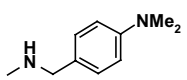
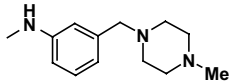
Scheme 1. General synthesis of ureas, **6**–**27**. Reagents and conditions: (a) H_2NCN, HCl, H_2O, *n*-butanol, 150 °C; (b) H_2, Pd/C, *n*-butanol; (c) $Me_2NCH(OMe)_2$, xylene, 140 °C; (d) *n*-butanol, 70 °C; (e) 4-$O_2NC_6H_4OCOCl$, CH_2Cl_2, rt; (f) R^1R^2NH, Et_3N, DMF, 20–40 °C.

3. For the parallel synthesis of the urea library, the 4-nitrophenylcarbamate derivative **5** was selected on the basis of its reactivity, together with the stability and crystallinity of the hydrochloride salt.[11] The addition of a variety of amines to a solution of **5** in DMF, containing triethylamine at 20–40 °C, then provided the desired urea derivatives. The ureas were isolated by extraction, and purified by chromatography/recrystallisation.[12]

The ureas were first evaluated in a filter binding assay, for their effects at a concentration of 10 μM on the trans-phosphorylation of a poly-AEKY substrate catalysed by the recombinant GST-fusion Abl kinase domain at 5 μM [ATP].[13,14] For compounds showing >70% inhibition, full dose–response curves were generated, from which IC_{50} values were calculated. Selected compounds were also evaluated for their effects on p210 Bcr-Abl auto-phosphorylation in transfected 32D murine myeloid progenitor cells,[15,16] with the IC_{50} values for Bcr-Abl inhibition being calculated from the dose–response curves.

Effects of compounds on PDGF-BB stimulated PDGFR autophosphorylation were evaluated using a capture ELISA assay with lysates from A31 cells (ATCC CCL-163), grown close to confluency in 96-well plates. After starving (overnight) and incubation with test compounds (90 min), the cells were stimulated with PDGFBB (BACHEM AG, Switzerland) followed by cell lysis. The lysates were transferred to black ELISA plates precoated with a rabbit polyclonal antibody (Upstate 06-495) specific for both PDGFR-α and PDGFR-β. The phosphorylation of the captured PDGFR protein was quantified using a phosphotyrosine specific Ab (PY20), directly labelled with alkaline phosphatase (AP) and a chemiluminescent AP-substrate. IC_{50} values for the inhibition of ligand induced PDGFR

Table 1. Comparison of the effects of the urea derivatives **6**–**27** on the kinase activity of recombinant Abl, cellular Bcr-Abl and cellular PDGFR, expressed either as percent inhibition at 10 μM or as IC_{50} values[a]

No.	R	Abl		Bcr-Abl	PDGFR	No.	R	Abl		Bcr-Abl	PDGFR
		%	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)			%	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)
6		78	790 930	>10000 *n* = 1	63 ± 15 *n* = 3	**7**		36	n.d.	>5000 *n* = 1	132 ± 21 *n* = 3
8		35	n.d.	n.d.	176 ± 32 *n* = 3	**9**		51	n.d.	n.d.	256 ± 46 *n* = 3
10		34	n.d.	>9000 *n* = 1	655 ± 83 *n* = 3	**11**		44	n.d.	n.d.	>3000 *n* = 3
12		24	n.d.	n.d.	>1600 *n* = 3	**13**		22	n.d.	n.d.	381 ± 22 *n* = 3
14		63	n.d.	n.d.	>1300 *n* = 2	**15**		49	n.d.	n.d.	414 ± 85 *n* = 3
16		84	110 175	1003 *n* = 1	17 ± 3 *n* = 5	**17**		74	1000 760	n.d.	96 ± 7 *n* = 3
18		90	56 39	573 ± 55 *n* = 3	26 ± 7 *n* = 3	**19**		97	280 330	>1000 *n* = 1	47 ± 6 *n* = 3
20		n.d.	>5000 *n* = 1	>10000 *n* = 2	1730 ± 520 *n* = 3	**21**		n.d.	>3400 *n* = 1	>10000 *n* = 2	2025 ± 475 *n* = 3
22		96	52 110	720 ± 145 *n* = 3	>2500 *n* = 3	**23**		45	n.d.	n.d.	64 ± 3 *n* = 3
24		52	n.d.	n.d.	375 ± 33 *n* = 3	**25**		81	870 *n* = 1	n.d.	100 ± 16 *n* = 3
26		36	n.d.	n.d.	236 ± 25 *n* = 3	**27**		45	n.d.	n.d.	192 ± 25 *n* = 3

[a] IC_{50} values represent drug concentrations (nM) required to inhibit enzyme activity by 50%. Where compounds displayed potent inhibition of Abl, IC_{50} values were duplicated, and for potent inhibition of either Bcr-Abl or PDGFR activity determinations were replicated and data are expressed as mean IC_{50} values ± SEM (*n* determinations).

autophosphorylation were calculated from the dose–response curves by graphical extrapolation.

The structures of the urea derivatives (compounds **6**–**27**) and their effects on c-Abl, Bcr-Abl and PDGFR kinase activity are shown in Table 1. STI571 was employed as a positive control in each assay and exhibited IC_{50} values of 166 ± 21 ($n = 23$), 192 ± 6 ($n = 88$) and 74 ± 11 ($n = 11$) for the inhibition of recombinant c-Abl, cellular Bcr-Abl and cellular PDGFR, respectively. In general, ureas derived from nonaromatic amines were relatively inert against Abl kinase activity. The most potent compounds were the 1,3-diaminobenzene derivatives **18** and **22**, which both inhibited c-Abl more potently than STI571, displaying IC_{50} values of 56 and 52 nM, respectively. Since the 3-chlorophenyl derivative **16** also displayed relatively high activity (IC_{50} 110 nM), the basicities of the anilines (pyridine pK_a 5.2 for **17**, *N*,*N*-dimethylaniline pK_a 5.15 for **18**, *N*,*N*-diethylaniline pK_a 6.61 for **19**, 1-phenylpyrrolidine pK_a 9.7 for **22**),[17] probably does not influence their activity, and it is rather their shape and lipophilicity, which governs drug binding. This is supported by the observation that the more bulky diethylamino compound, **19**, was less active than **18**, and that the 1,4-disubstituted analogues **20** and **21**, were devoid of activity.

Molecular modelling studies provide a rationale for the observed SAR. For these studies, the compounds were constructed in Macromodel,[18] and docked manually into the ATP-binding site of c-Abl using the coordinates of human Abl in complex with STI571.[4] Energy minimisation of the complexes was performed using the AMBER* force field,[19] in conjunction with the GB/SA water solvation model.[20] Only residues of the ATP pocket within 6 Å of the initial position of the ligand were included in the calculations. Docking was based upon the design hypothesis and confirmed that compounds such as **18** could adopt a binding mode very similar to that of STI571, with both urea-NH moieties participating in a bifurcated H-bond with the side chain carboxylate of Glu286, the urea-CO forming an H-bond to the backbone-NH of Asp381 and the *meta*-dimethylaminophenyl group making close hydrophobic contacts with Ile293, Leu354, Leu298 and Val289 (Fig. 1). The limited size of the hydrophobic pocket defined by these lipophilic residues, also provides an explanation for the reduced activity against Abl observed for the *meta*-diethylamino compound, **19**, and the loss of activity observed for the *para*-substituted compounds, **20** and **21**, as well as those ureas, **23**–**27**, derived from bulkier anilines

Bcr-Abl is a fusion protein in which the Abl tyrosine kinase domain is constitutively activated. The catalytic sites of both the Abl and the Bcr-Abl tyrosine kinases are identical in sequence, and the enhanced activity of the latter is believed to be due to the loss of regulatory domains, present in the N-terminus of Abl but absent in the fusion protein.[21,22] Consequently, compounds capable of inhibiting the tyrosine kinase activity of Abl, should show similar activity against Bcr-Abl. However, despite showing good potency against Abl in the cell-free assay, neither **18** or **20**, nor any of those compounds with intermediate activity, maintained their activity against Bcr-Abl catalysed autophosphorylation in the cellular assay (Table 1).

The lack of Bcr-Abl activity is unlikely to be due to an inability of the compounds to penetrate 32D cells, since many of the compounds inhibited PDGFR autophosphorylation in A31 cells with activities similar to those of STI571 (Table 1). Potent PDGFR inhibitors were derived from both aliphatic amines such as **6**, as well as from anilines. There were no obvious structure–activity trends evident for this activity, which did not correlate with c-Abl inhibition.[23] This lack of structure–activity is consistent with the urea terminal *N*-substituent being orientated towards the proteins exterior via the hydrophilic channel, similar to that originally proposed for the interaction of STI571 with Abl.[9] Alternatively, this could be due to the cavities, which accommodate the aniline group in PDGFR and Abl having different shapes. In Abl amino acid residues Ile293, Leu298 and Val289 line this cavity, but in the case of PDGFR the equivalent residues are Leu, Ile and Ile, respectively. Furthermore, in the PDGFR family of tyrosine kinases, residues of the juxtamembrane domain proximal to this region might also interact with the urea-*N* substituents.[24]

PDGFR inhibition is potentially beneficial in a range of diseases, and STI571 has demonstrated clinical benefit in a number of PDGFR-driven malignancies.[25] Consequently, some of the representative PDGFR inhibitors were evaluated for their pharmacokinetic properties following oral administration to mice. Despite having few violations of the Lipinski rules and polar surface areas >150 Å^2,[26,27] their pharmacokinetic profiles were unattractive, either as a result of short plasma half-life (e.g., **6** and **18**) or poor oral absorption (e.g., **23**; Table 2).

In summary, this study shows that there is scope to replace the *N*-methylpiperazine moiety in STI571 with

Table 2. Comparison of lipophilicity, polar surface area and plasma concentrations of parent compound following administration of a single oral doses of either **6**, **18** or **23** to naïve mice[a]

No.	clog P[b]	PSA (Å^2)[c]	C_{max} (μM)	t_{max} (min)	C_{120} (μM)
6	3.42	83.04	4.32 ± 1.24	30	0.51 ± 0.12
18	4.75	95.07	1.37 ± 0.55	30	0.30 ± 0.05
23	5.20	104.72	0.17 ± 0.02	30	0.05 ± 0.01

[a] Different groups of female OF1 mice ($n = 4$) received an oral dose of 20 mg/kg of each compound, formulated in NMP/PEG300 (10:90 v/v; final solution 2 mg/mL). At allotted times, mice were sacrificed, blood was removed, and the concentration of compound was determined by reverse-phase HPLC. The pharmacokinetic parameters, C_{max} (maximum plasma concentration at time t_{max}; mean ± SEM) and C_{120} (plasma concentration 120 min after gavage; mean ± SEM) were derived from the mean values and determined by inspection of the data. Data are expressed as mean ± SEM, $n = 4$.

[b] Calculated octanol/water distribution coefficient calculated by CLOGP progam (Biobyte, v. 4.71).

[c] Calculated polar surface area.[27]

alternative pharmacophore elements and, that it is possible to identify compounds based upon this scaffold, which differentiate between the Abl and PDGFR kinases. Although in this series of ureas, potent inhibitors of recombinant c-Abl were identified, the cellular activity against Bcr-Abl kinase was lower by a factor of $\geqslant$10-fold. The reason for this discrepancy is unclear. Although a number of the ureas were potent inhibitors of PDGFR and c-Kit kinases, their pharmacokinetic profiles were unattractive and they were not developed further.

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11. The pivotal urethane **5** was prepared as follows: The amine **4** (1.0 g, 3.61 mmol) was added to a stirred solution of 4-nitrophenylchloroformate (0.87 g, 4.32 mmol) in CH_2Cl_2 (26 mL) at 0 °C over 30 min. After stirring for 2 h at room temperature, the precipitate was filtered off, washed with CH_2Cl_2 and dried to yield the HCl salt **5** (1.5 g, 86% yield) as an orange powder: NMR (DMSO-d_6) δ 2.21 (s, 3H), 7.19–7.24 (m, 2H), 7.53–7.57 (m, 3H), 7.90 (br s, 1H), 7.94 (dd, J = 8.1 Hz, J = 5.4 Hz, 1H), 8.29 (m, 2H), 8.60 (d, J = 5.1 Hz, 1H), 8.92 (d, J = 5.4 Hz, 1H), 8.95 (d, J = 8.1 Hz, 1H), 9.16 (br s, 1H), 9.40 (m, 1H) and 10.47 (br s, 1H).
12. As a typical example, urea **18** was prepared as follows: 3-Amino-*N*,*N*-dimethylaniline dihydrochloride (0.287 g, 1.375 mmol) and triethylamine (0.87 mL, 6.25 mmol) was added to a stirred mixture of **5** (0.6 g, 1.25 mmol) in DMF (5 mL). After stirring for 4 h at 40 °C, the solvent was evaporated off under reduced pressure and the residue was treated with aqueous 1 N NaOH and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and the solvent was evaporated off to give a residue, which was chromatographed (silica gel; CH_2Cl_2–MeOH) to afford **18** as a yellow crystalline solid (323 mg, 59% yield): mp 229–231 °C; NMR (DMSO-d_6) δ 2.18 (s, 3H), 2.84 (s, 6H), 6.32 (dd, J = 8.3, J = 2.4 Hz, 1H), 6.67 (dd, J = 7.9 Hz, J = 1.2 Hz, 1H), 6.91 (t, J = 2.1 Hz, 1H), 7.02 (t, J = 8.1 Hz, 1H), 7.09 (s, 2H), 7.40 (d, J = 5.2 Hz, 1H), 7.49 (dd, J = 8.0 Hz, J = 4.7 Hz, 1H), 7.76 (br s, 1H), 8.45–8.52 (m, 4H), 8.65 (dd, J = 4.8 Hz, J = 1.6 Hz, 1H), 8.89 (br s, 1H) and 9.24 (dd, J = 2.3 Hz, J = 0.7 Hz, 1H). Anal. ($C_{25}H_{25}N_7O$) C, H, N.
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23. The compounds were also evaluated against the third target of STI571, c-Kit, in GIST882 cells (derived from a human gastrointestinal stromal tumor and which express a c-Kit isoform carrying a mutation within Exon 13 leading to constitutive activation of the receptor kinase). In terms of activity (mean IC_{50}, $n \geqslant 3$) only compounds **6** (560 nM), **16** (80 nM), **17** (411 nM), **18** (93 nM), **19** (180 nM) and **23** (108 nM), showed significant activity at concentrations below 2 μM (STI571: IC_{50} 96 ± 12 nM; n = 7). For method see: Mestan, J.; Kempf, D.; Goutte, G.; Fletcher, J. A.; Manley, P. W. *Blood* **2003**, *102*(11), 169b.
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