Furo[2,3-*d*]pyrimidines and Oxazolo[5,4-*d*]pyrimidines as Inhibitors of Receptor Tyrosine Kinases (RTK)

by **Andreas Martin-Kohler**[a]), **Jörg Widmer**[a]), **Guido Bold***[b]), **Thomas Meyer**[b]), **Urs Séquin***[a]), and **Peter Traxler**[b])

[a]) Departement Chemie der Universität Basel, St. Johanns-Ring 19, CH-4056 Basel (phone: +41 61 267 1110; fax: +41 61 267 1103; e-mail: urs.sequin@unibas.ch)

[b]) *Novartis Pharma AG*, Oncology Research, CH-4002 Basel (phone: +41 61 696 2497; fax +41 61 696 6246; e-mail: guido.bold@pharma.novartis.com)

Receptor tyrosine kinases such as VEGFR2 (vascular endothelial growth factor receptor 2, KDR) or EGFR (epidermal growth factor receptor) play crucial roles in a variety of diseases, such as cancer. Recently, some pyrrolopyrimidines were shown to be potent EGFR inhibitors. Therefore, new types of oxazolo[5,4-*d*]pyrimidines and furo[2,3-*d*]pyrimidines were synthesized (*Schemes 1* and *2*). Appropriately substituted derivatives of these classes of compounds inhibited VEGFR2 and EGFR with IC_{50} values in the low nanomolar range (see *Table*). Generally, the furopyrimidines were somewhat more active than the oxazolopyrimidines. The best inhibitors, **20m**, **20p**, and **20r**, had an IC_{50} of 3 nM towards EGFR and showed a good selectivity, being distinctly less active towards VEGFR2.

Introduction. – Uncontrolled receptor-tyrosine-kinase(RTK)-mediated signaling plays an important role in many pathological conditions, especially in cancer [1][2]. Recently, this was most successfully established by the tremendous responses observed in chronic myelogenous leukemia (CML) patients under treatment with *Glivec*™ [3]. Inhibitors for two other RTKs, vascular endothelial growth-factor receptor 2 (VEGFR2 or KDR; a receptor expressed in endothelial cells of blood vessels [4]) and the epidermal growth-factor receptor (EGFR or HER-1; in cancer cells frequently overexpressed or mutated [5]), are undergoing clinical trials or have already been launched recently. Signaling *via* KDR induces neovascularization of growing tumor tissue, a process that is essential for the development of massive tumors [6]. Mutated forms and/or overexpression of EGFR in cancer cells lead to uncontrolled EGFR activity and, as a consequence, to development and progression of numerous human tumors [5]. Much effort has been applied to the development of synthetic small-molecule inhibitors against either VEGFR2 [7–13] or EGFR [14–18], such as compounds **1**–**6** (*Fig. 1*).

The pyrrolopyrimidines **3**–**5** are potent inhibitors of the EGFR [21]. While sharing many features with other inhibitors (*Fig. 1*), **3**–**5** idiosyncratically have a pyrrole ring fused to the pyrimidine ring. The proper role of the pyrrolo NH moiety of these compounds for binding to the EGFR had not been fully determined. Methylation of the pyrrolo NH leads to a significant drop in activity against EGFR as demonstrated for **7** (IC_{50} = 27 nM) and **8** (IC_{50} = 450 nM) [22]. Whether this is due to steric hindrance or lack of a H-bond remained unclear. To address this issue, we synthesized compounds in which this pyrrolo NH is replaced by an O-atom.

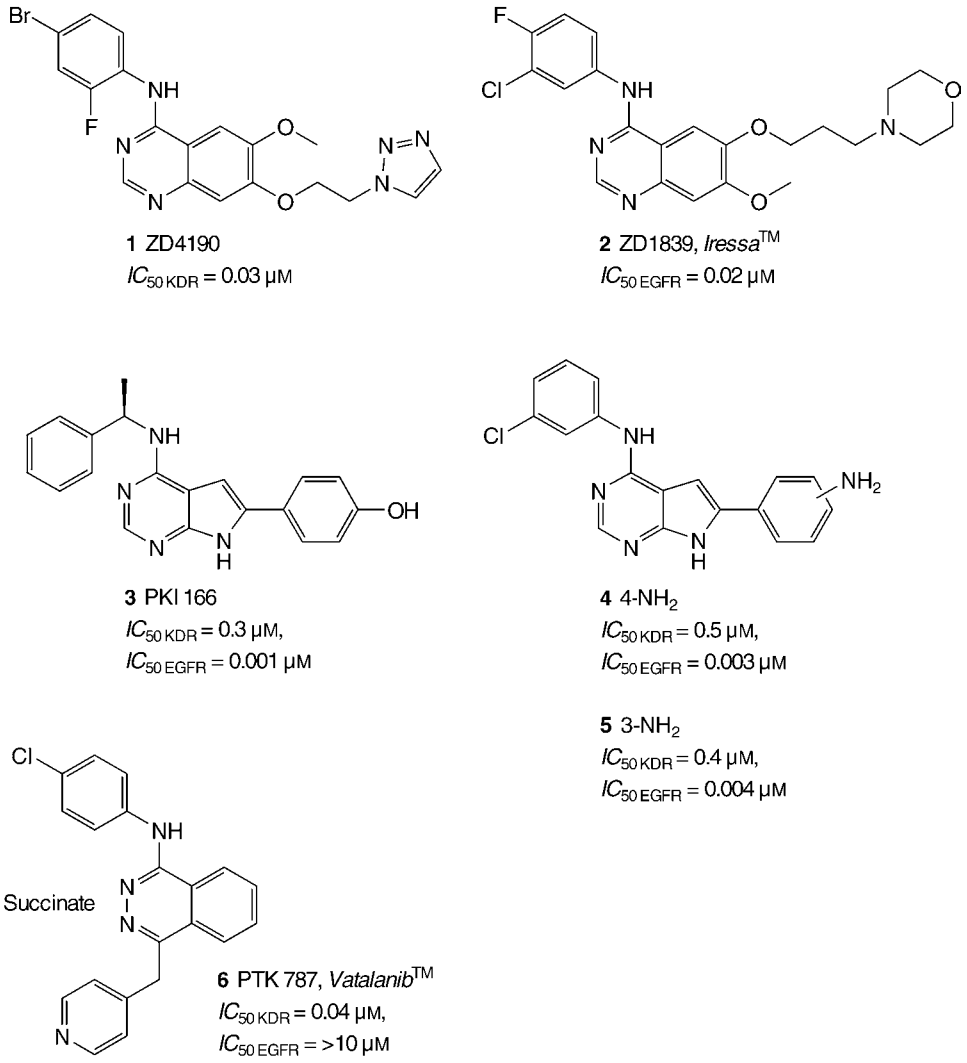
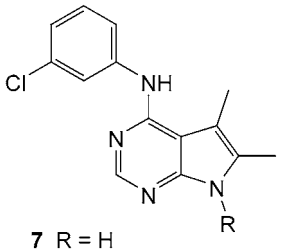


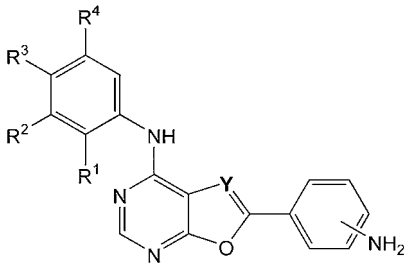
Fig. 1. *VEGFR or EGFR Kinase inhibitors.* IC_{50} values are published as follows: ZD4190 [19], ZD1839 [15], PKI 166 [17], and PTK 787 [20].

Fig. 2 depicts the general structure of the target furopyrimidines (Y = CH) or oxazolopyrimidines (Y = N). Synthetic routes yielding oxazolopyrimidines (Y = N) were described in [23][24], whereas for furopyrimidines (Y = CH), no viable synthetic paradigm was available. Finally, variation of the substituents R^1 – R^4 should allow establishing some structure – activity relationships (SAR).

Syntheses. – *Oxazolo[5,4-*d*]pyrimidines.* Two major routes to 2,7-disubstituted oxazolo[5,4-*d*]pyrimidines have been discussed by *Patil* and *Townsend* [23]. For



7 R = H
8 R = Me



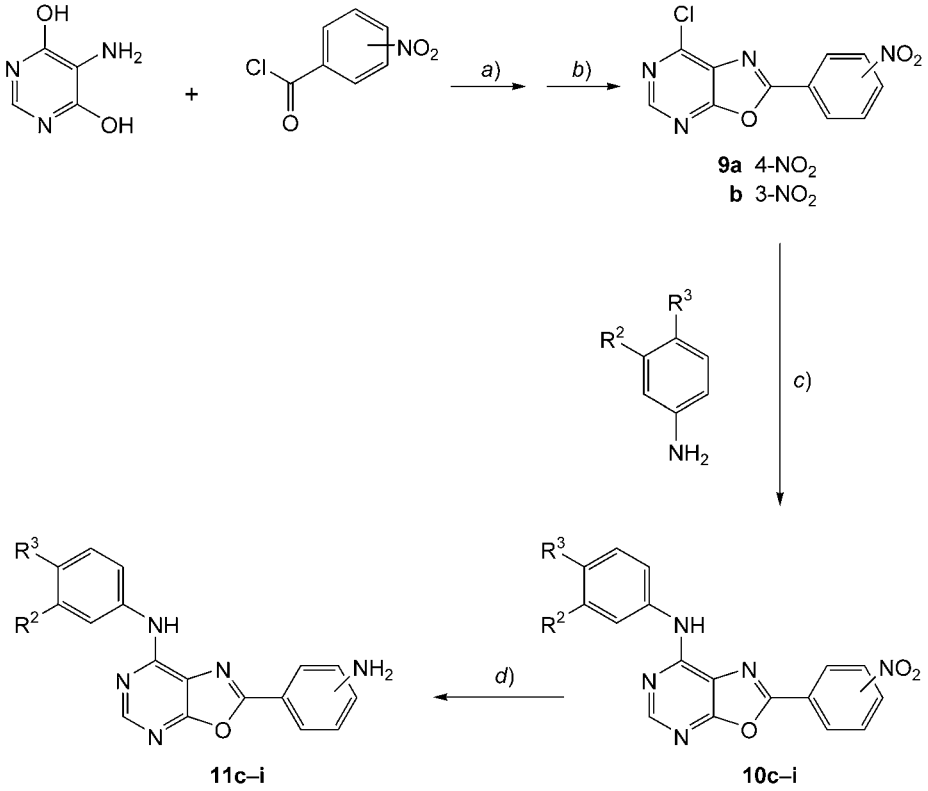
Y = N or CH

Fig. 2. *General structure of target compounds lacking the pyrrolo NH moiety: oxazolo[5,4-*d*]pyrimidines* (Y = N) *or furo[2,3-*d*]pyrimidine* (Y = CH)

stability reasons, these authors favored the methodology published by *Ishidate* and *Yuki* [24], which we followed also. In the published syntheses [23][24], an N-acylation is performed in the appropriate carboxylic anhydride as solvent as well as acylating agent. In our case, the acylation (*Scheme 1*) was carried out with nitrobenzoyl chlorides in pyridine as the solvent. Heating of the resulting intermediate in $POCl_3$ led to simultaneous ring closure to the oxazole system and substitution of the second OH functionality by a Cl-atom, giving rise to **9** in moderate yield. Substitution of the Cl-atom by any desirable aniline furnished compounds of type **10**. These compounds frequently exhibited extremely poor solubilities and were, therefore, often used in the next steps without purification. Reduction of the NO_2 group readily produced the primary amines **11c**–**i**. Due to the poor solubilities of the nitro compounds **10**, 1,3-dimethylimidazolidin-2-one (dimethylethyleneurea, DMEU) was usually used as solubilizer in this reduction step.

*Furo[2,3-*d*]pyrimidines. Korte* and *Trautner* [25] and *Foley* [26] discovered that, after the condensation of cyanoacetates with α-chloro-β-keto esters under basic conditions, the keto nitriles formed swiftly cyclized to stable trisubstituted furan systems when there was a conjugating electron-withdrawing substituent at the C-atom adjacent to the keto function, *e.g.* an ester group. Exploitation of this information granted access to 4,6-disubstituted furo[2,3-*d*]pyrimidines, which were synthesized according to *Scheme 2:* The key to the synthesis is the utilization of this furo-inducing property of an ester group in the starting material **12a**,**b**. The cyanoacetate condensation was carried out according to *Korte* and *Trautner* [25]. However, to

Scheme 1. *Synthesis of (2-Aminophenyl)-7-anilinooxazolo[5,4-*d*]pyrimidines* **11c–i**. For substitution patterns **c–i**, see the *Table*.



a) Reflux, pyridine. *b*) Reflux, $POCl_3$; 56–73% (steps *a* and *b*). *c*) Reflux, BuOH, 3 equiv. of the suitably substituted aniline; 52–84%. *d*) H_2, *Raney*-Ni, THF (+ DMEU); 26–82%.

prevent *retro-Claisen* condensation, EtOH as solvent was replaced by THF. Then, the furans **13a**,**b** were successfully condensed with formamide to yield the fused furopyrimidines **14a**,**b** [27][1]). After saponification of the esters, the resulting carboxylic acids **16a**,**b** were decarboxylated to **17a**,**b** in hot quinoline with Cu_2O as the catalyst as described by *Cohen* and *Schambach* [28]. Activation to the respective formal imidoyl chlorides **18a**,**b** and subsequent substitution of the Cl-atom by anilines produced compounds of type **19**. Reduction of the nitro group in the presence of *Raney*-Ni finally yielded the corresponding amino derivatives **20**.

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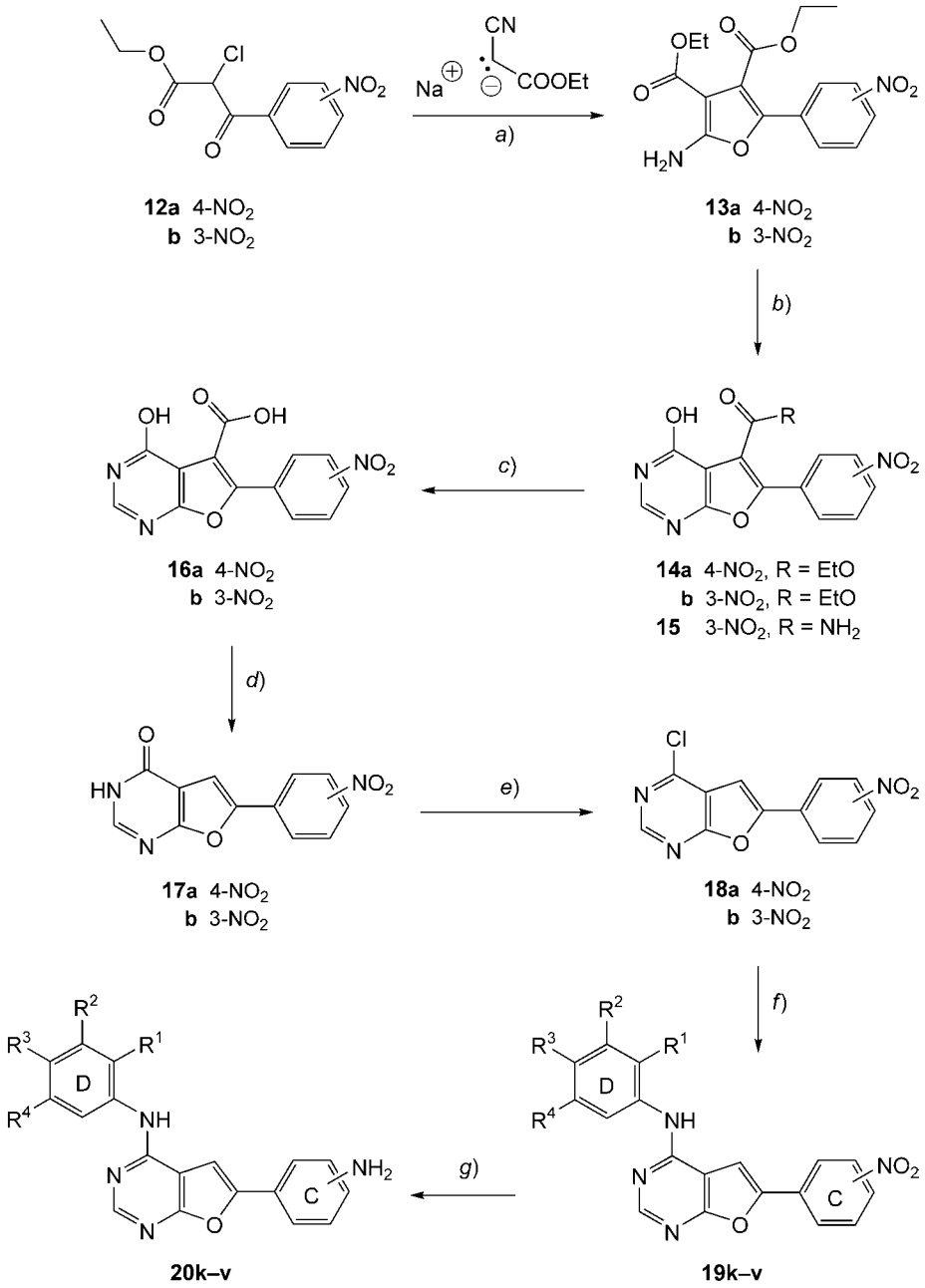
[1]) In the 3-nitro series, reaction of ester **13b** with the NH_3 (resulting from the heat-induced degradation of formamide) to amide **15** (*Scheme 2*) occurred to some extent. Yet **15**, just as ester **14b**, may be converted to the carboxylate in aqueous NaOH solution. Therefore, the crude mixture **14b**/**15** was used without purification in the subsequent saponification.

Scheme 2. *Synthesis of Furopyrimidines* **19k – v** *and* **20k – v**. For substitution patterns **k – v**, see the *Table.*

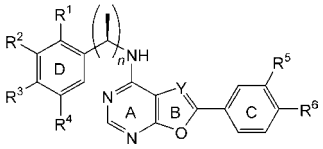


a) THF, 30°; 44%. *b*) Formamide/DMF/formic acid 4 : 2 : 1, 140 – 150°; *ca.* 20 – 40%. *c*) 5% aq. NaOH soln., 100°; 63 – 87%. *d*) Cu_2O, quinoline, 180 – 220°, N_2; *ca.* 49 – 70%. *e*) Reflux, $POCl_3$; *ca.* 23%. *f*) Reflux, BuOH, 3 equiv. of the suitably substituted aniline or amine; 27 – 94%. *g*) H_2, *Raney*-Ni in THF (+ DMEU); 35 – 97% (except for **20v**: 5% due to poor hydrogenation selectivity between the two NO_2 groups).

Results and Discussion. – The IC_{50} values determined for the inhibitory activities towards KDR and EGFR of the furopyrimidines and oxazolopyrimidines synthesized are compiled in the *Table*. For comparison, the activities of the selective KDR inhibitor PTK 787 (**6**), the selective EGFR inhibitor PKI 166 (**3**), and the known RTK inhibitors **1**, **2**, **4**, and **5** were included. Many of the nitrophenyl-substituted compounds synthesized, particularly the oxazolopyrimidines **10**, proved to be inactive and were, therefore, not included in the *Table*.

In contrast to what could have been expected from our former binding hypothesis [22], compounds lacking the pyrrolo NH moiety are indeed potent inhibitors of KDR

Table. IC_{50} *Values for KDR and EGFR Inhibition by Compounds* **1**–**6**, **11c**–**i**, **19k**–**p**, *and* **20k**–**v**



	IC_{50} [μM][a])				Ring D				Ring C	
	KDR	EGFR	Y	*n*	R^1	R^2	R^3	R^4	R^5	R^6
1 [11]	0.03									
2 [15]		0.023								
3[b])	0.3	0.001								
4	0.5	0.003								
5	0.4	0.004								
6[c])	0.04	> 10								
11c	0.3*	0.2*	N	0	H	OH	H	H	NH_2	H
d	0.3*	0.9*	N	0	H	OH	MeO	H	NH_2	H
e	0.5*	0.07*	N	0	H	OH	H	H	H	NH_2
f	0.6*	0.2*	N	0	H	H	OH	H	H	NH_2
g	4*	0.06*	N	0	H	Cl	H	H	NH_2	H
h	7*	0.2*	N	0	H	Cl	H	H	H	NH_2
i	> 50	18	N	0	H	H	Cl	H	H	NH_2
19k	0.04	0.02	CH	0	F	H	Cl	H	H	NO_2
20k	0.7*	0.01*	CH	0	F	H	Cl	H	H	NH_2
19l	> 5	> 5	CH	0	F	H	Cl	H	NO_2	H
20l	0.2*	0.009*	CH	0	F	H	Cl	H	NH_2	H
19m	> 5	0.01	CH	0	H	Cl	H	H	H	NO_2
20m	2*	0.003*	CH	0	H	Cl	H	H	H	NH_2
19n	> 10	0.007	CH	0	H	Cl	H	H	NO_2	H
20n	5*	0.005*	CH	0	H	Cl	H	H	NH_2	H
19o	0.07	0.1	CH	0	H	OH	MeO	H	H	NO_2
20o	0.05*	0.02*	CH	0	H	OH	MeO	H	H	NH_2
19p	> 5	0.01	CH	1	H	H	H	H	NO_2	H
20p	1*	0.003*	CH	1	H	H	H	H	NH_2	H
q	0.06*	0.02*	CH	0	H	OH	Me	H	NH_2	H
r	1	0.003	CH	0	OH	H	H	Cl	NH_2	H
s	3*	0.03*	CH	0	H	NH_2	H	H	H	NH_2
t	0.06*	0.04*	CH	0	H	OH	Me	H	H	NH_2
u	4*	0.05*	CH	0	H	Cl	H	Cl	NH_2	H
v	> 10*	0.005*	CH	0	H	NO_2	H	H	NH_2	H

[a]) Figures marked * are median values of at least three measurements. [b]) Selective EGFR inhibitor [17]. [c]) Selective KDR inhibitor [20].

and EGFR. These findings are consistent with observations for the 4-anilinoquinazoline-structure class as exemplified by ZD4190 (**1**; KDR inhibitor [19]) or ZD1839 (**2**; *Iressa*™; EGFR inhibitor [15]). Neither **1** and **2** possess a moiety enabling H-bond donation. The space filled by the pyrrolo moiety in **4** or **5** is occupied by a benzo moiety in 4-anilinoquinazolines. Conclusively, a H-bonding interaction at this position as postulated for the binding mode of pyrrolopyrimidines is not mandatory for potent kinase inhibition. This makes furo[2,3-*d*]pyrimidines and oxazolo[5,4-*d*]pyrimidines good tyrosine-kinase inhibitors in general. Furopyrimidines are better inhibitors than their oxazolopyrimidine counterparts. This is prominently demonstrated by the EGFR inhibition of **20m** in comparison to **11h**, or by **20n** in comparison to **11g**. Apparently, the N-atom in the oxazolo moiety (position Y, ring B) is not well tolerated by EGFR. We reckon this to be an electronic effect characteristic to EGFR. Or, alternatively, an intramolecular H-bond between the aniline NH functionality and the oxazole N-atom (*Fig. 3*) could hold the molecule in an unfavorable conformation for binding to the enzyme.

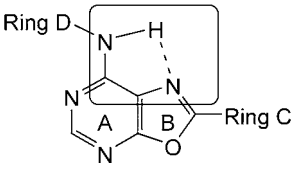


Fig. 3. *Hypothetical intramolecular H-bond in anilino-substituted oxazolo[5,4-*d*]pyrimidines*

The best EGFR inhibitors from the oxazolo[5,4-*d*]pyrimidine series, **11e** and **11g**, are significantly less active than PKI 166 (**3**). However, very potent inhibitors for both kinases with IC_{50} values in the low nanomolar range, and thus comparing favorably with PKI 166 (**3**) or PTK787 (**6**), were found in the furo[2,3-*d*]pyrimidine series. Among them, some are able to selectively inhibit the EGFR, not influencing KDR at concentrations below 1 μM (*e.g.*, **19m**, **19n**, **19p**, **20m**, **20n**, **20p**, **20r**, **20s**, **20u**, or **20v**). Others, such as **19k**, **20o**, **20q**, or **20t** are inhibitors of both, EGFR and KDR. Clearly, the oxazolo[5,4-*d*]pyrimidines and furo[2,3-*d*]pyrimidines presented here make an interesting addition to the known classes of RTK inhibitors.

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Experimental Part

General. Tetrahydrofuran (THF) was freshly distilled over Na under Ar. Flash column chromatography (FC): distilled solvents, SiO_2 (40–63 μm) *Uetikon*. M.p.: *Kofler* hot stage; uncorrected. IR Spectra: *Perkin-Elmer FT-IR 1600*; KBr pellets; ν in cm^{-1}. NMR: *Varian Gemini-300* (300 (^{1}H) and 75 MHz (^{13}C)), *Varian VXR-400* (400 (^{1}H) and 101 MHz (^{13}C)), *Bruker VRX-500* (500 (^{1}H) and 126 MHz (^{13}C)); δ in ppm, J in Hz. MS: *VG 70-250* (EI, 70 eV); *Finnigan MAT 312* (FAB; 3-nitrobenzyl alcohol); *Finnigan-LCQ* system (ESI); *m/z* (rel. %). Elemental analyses: Microlaboratory at the Department of Chemistry of the University of Basel (*W. Kirsch*).

Catalytic Reductions. Raney-Ni *Actimet M* (*Engelhard Corporation*; kindly provided by *P. Schultheiss*, Hydrierlabor *Novartis*, Klybeck, CH-4002 Basel) was washed to neutrality, stored under EtOH (at 2–8°), and used as suspension directly. Reductions were carried out in THF soln., with 1,3-dimethylimidazolidin-2-one

(dimethylethylurea, DMEU) as emulsifier, in the dark under H_2 atmosphere at standard pressure for at least one night with shaking.

*7-Chloro-2-(4-nitrophenyl)oxazolo[5,4-*d*]pyrimidine* (**9a**). The mixture of 5-aminopyrimidine-4,6-diol (6.83 g, 41.8 mmol) [24] and 4-nitrobenzoyl chloride (9.84 g, 52.9 mmol) in abs. pyridine (100 ml; the suspension turned dark red) was refluxed for 1 h under Ar. The solvent was evaporated at 75°. The dark red residue was refluxed in $POCl_3$ (75 ml) under Ar for 1 h. After cooling to r.t., the mixture was concentrated (< 60°) and added slowly with constant stirring to a NaOAc/ice mixture. After complete melting of the ice (*ca.* 30 min), the pH of the suspension was adjusted to 5 by adding NaOAc. The suspension was filtered with suction, washed with H_2O and EtOH, and dried under high vacuum. The residue was heated in EtOH (150 ml), filtered lukewarm with suction, and dried under high vacuum. An amorphous, brown solid (6.5 g, 56%; m.p. 228–230°) was obtained containing **9a**, pure enough for further synthesis. FC (SiO_2, pentane/AcOEt 90:10 → 75:25) yielded colorless to pale yellow needles. M.p. 231°. IR: 3103*w*, 1615*s*, 1585*s*, 1527*s*, 1482*s*, 1421*s*, 1348*s*, 1261*s*, 1160*s*, 1106*s*, 1048*s*, 989*s*, 912*s*, 868*s*, 711*s*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.00 (*s*, H–C(5)); 8.54 (*d*, *J* = 9.3, 2 H); 8.47 (*d*, *J* = 9.1, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 165.2; 161.0; 154.2; 149.9; 149.7; 130.7; 130.3; 129.6; 124.7. EI-MS: 276 (100, M^+), 246 (18), 230 (15), 218 (21), 202 (13), 186 (14), 140 (17), 101 (21), 88 (19), 76 (20), 62 (12), 50 (17). Anal. calc. for $C_{11}H_5ClN_4O_3$ (276.64): C 47.76, H 1.82, N 20.25, O 17.35; found: C 47.54, H 1.96, N 20.08, O 17.23.

*7-Chloro-2-(3-nitrophenyl)oxazolo[5,4-*d*]pyrimidine* (**9b**). A mixture of 5-aminopyrimidine-4,6-diol (2.25 g, 17.7 mmol) [24] and 3-nitrobenzoyl chloride (3.72 g, 20.0 mmol) in abs. pyridine (100 ml) was refluxed for 1 h under Ar. After evaporation at 75°, the residue was dried under high vacuum. The brown-red residue was refluxed for 2 h in $POCl_3$ (*ca.* 100 ml) under Ar. Most of the $POCl_3$ was evaporated (< 60°), and the remaining liquid was very carefully poured under stirring onto NaOAc/ice. After adjusting the pH to *ca.* 5 by adding NaOAc, the suspension was left standing overnight and then filtered with suction. The residue was washed with H_2O, heated in a considerable amount of EtOH, and filtered. The filtrate was left at 2–8° for a week and then filtered with suction and the residue dried under high vacuum: **9b** (3.57 g, 73%) as an ochre, amorphous solid (m.p. 133–135°), usually pure enough for further use. FC (AcOEt/pentane 1:0–2:1) yielded colorless platelets. M.p. 144–147°. IR: 3071*w*, 1622*m*, 1595*s*, 1545*m*, 1523*m*, 1431*w*, 1419*w*, 1375*m*, 1349*s*, 1306*m*, 1271*w*, 1238*w*, 1219*w*, 1164*w*, 1100*m*, 988*m*, 912*m*, 756*s*, 712*s*, 541*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.02 (*s*, H–C(5)); 8.93 (‘*t*’, *J* = 1.9, H–C(2′)); 8.72 (*ddd*, *J* = 8.0, 2.3, 1.0, 1 arom. H); 8.59 (*ddd*, *J* = 8.3, 2.4, 1.0, 1 arom. H); 8.01 (‘*t*’, *J* = 8.1, H–C(5′)). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 165.4; 161.1; 154.0; 149.6; 148.4; 134.0; 131.6; 130.8; 127.7; 126.5; 122.4. EI-MS: 276 (100, M^+), 248 (14), 230 (26), 202 (9), 186 (13), 140 (11), 101 (12), 76 (14). Anal. calc. for $C_{11}H_5ClN_4O_3$ (276.64): C 47.76, H 1.82, N 20.25, O 17.35; found: C 47.75, H 2.10, N 20.03, O 17.33.

General Procedure 1 (*GP 1*): *Reaction of Substituted Anilines with 7-Chlorooxazolo[5,4-*d*]pyrimidines or 4-Chlorofuro[2,3-*d*]pyrimidines*; *3-{[2-(3-Nitrophenyl)oxazolo[5,4-*d*]pyrimidin-7-yl]amino}phenol* (**10c**). A suspension of **9b** (3.57 g, 12.9 mmol) and 3-aminophenol (4.27 g, 39.1 mmol) in BuOH (250 ml) was refluxed for 2 h (orange). After cooling to r.t., the mixture was filtered with suction and the solid washed twice with BuOH and dried under high vacuum (no additional workup): **10c** (2.34 g, 52%), pure enough for further synthesis. M.p.: crystalline platelets above *ca.* 290°, which melted at 307–313°. IR: 3504*w*, 3336*w*, 3088*m*, 1635*s*, 1603*s*, 1529*m*, 1493*s*, 1475*m*, 1352*s*, 1313*m*, 1284*w*, 1181*w*, 1155*m*, 1088*w*, 1049*w*, 711*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.32, 9.45 (2*s*, NH, OH); 8.98 (‘*t*’, *J* = 2.0, H–C(2″)); 8.58 (‘*d*’, *J* = 7.3, 1 H); 8.56 (*s*, H–C(5′)); 8.50 (*m*, 1 H); 7.97 (‘*t*’, *J* = 8.0, H–C(5″)); 7.49 (‘*t*’, *J* = 2.0, H–C(2)); 7.34 (*m*, 1 H); 7.16 (‘*t*’, *J* = 8.1, H–C(5)); 6.55 (*m*, 1 H). EI-MS: 349 (100, M^+), 333 (6), 319 (12), 302 (12), 275 (5), 241 (30), 211 (5), 195 (6), 93 (6), 76 (8), 65 (8), 39 (6). HR-MS: 349.0812 ($C_{17}H_{11}N_5O_4^+$; calc. 349.0811).

*2-Methoxy-5-{[2-(3-nitrophenyl)oxazolo[5,4-*d*]pyrimidin-7-yl]amino}phenol* (**10d**). According to the *GP 1*, with **9b** (866 mg, 3.13 mmol), 5-amino-2-methoxyphenol (1.36 g, 9.77 mmol), and BuOH (100 ml) for 2 h (ochre suspension). Workup: Additional washing with BuOH until apparently all impurities stemming from 5-amino-2-methoxyphenol were washed out and drying under high vacuum gave **10d** (1.00 g, 84%). Pale, yellow-brown-green, amorphous residue. M.p.: at *ca.* 260° crystals, mostly needles, which melted at 323–325°. IR: 3468*s*, 3342*m*, 3095*w*, 2953*w*, 2848*w*, 1639*s*, 1608*s*, 1585*m*, 1535*s*, 1510*s*, 1475*s*, 1441*m*, 1351*s*, 1312*m*, 1286*m*, 1236*m*, 1181*m*, 1161*m*, 1075*m*, 1030*m*, 964*w*, 930*w*, 898*w*, 873*m*, 801*m*, 766*w*, 736*w*, 711*m*, 670*w*, 561*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.19, 9.07 (2*s*, NH, OH); 8.95 (‘*t*’, *J* = 1.8, H–C(2″)); 8.57 (*d*, *J* = 7.8, 1 H); 8.51–8.47 (*m*, 2 H); 7.96 (*t*, *J* = 8.1, H–C(5″)); 7.24 (*d*, *J* = 2.6, H–C(6)); 7.24 (*dd*, *J* = 8.8, 2.6, H–C(4)); 6.93 (*d*, *J* = 8.8, H–C(3)); 3.79 (*s*, Me). EI-MS: 379 (100, M^+), 364 (50), 336 (10), 318 (10), 308 (17), 290 (11), 262 (13). Anal. calc. for $C_{18}H_{13}N_5O_5$ (379.34): C 56.99, H 3.45, N 18.46, O 21.09; found: C 56.91, H 3.60, N 18.50, O 21.01.

*3-{[2-(4-Nitrophenyl)oxazolo[5,4-*d*]pyrimidin-7-yl]amino}phenol* (**10e**). According to the *GP 1*, with **9a** (452 mg, 1.64 mmol), 3-aminophenol (587 mg, 5.38 mmol), and BuOH (100 ml) for 90 min (orange suspension):

10e (414 mg, 72%). Amorphous, violet residue. M.p. $>250°$. IR: 3474*m*, 3336*m*, 3108*w*, 1622*s*, 1606*s*, 1518*s*, 1493*s*, 1406*m*, 1345*s*, 1294*s*, 1179*m*, 1154*m*, 1050*m*, 956*w*, 857*m*, 779*w*, 711*m*, 686*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.35, 9.44 (*s*, NH, OH); 8.52 (*s*, H–C(5′)); 8.45 (*d*, $J=9.2$, 2 H); 8.39 (*d*, $J=9.2$, 2 H); 7.46 (‘*t*’, $J=$ 2.1, H–C(2)); 7.31 (*dd*, $J=8.1$, 1.1, H–C(4)); 7.14 (‘*t*’, $J=8.1$, H–C(5)); 6.53 (*m*, H–C(6)). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.3; 157.3; 156.7; 154.5; 152.7; 149.0; 139.8; 131.6; 129.1; 128.2; 124.6; 117.4; 112.2; 110.7; 108.4. EI-MS: 349 (100, M^+), 321 (15), 302 (18), 274 (5), 241 (38), 195 (12), 120 (6), 104 (7), 93 (8), 76 (9), 65 (9), 39 (7). HR-MS: 349.0819 ($C_{17}H_{11}N_5O_4^+$; calc. 349.0811).

4-{[2-(4-Nitrophenyl)oxazolo[5,4-d*]pyrimidin-7-yl]amino}phenol* (**10f**). According to the *GP 1*, with **9a** (2.22 g, 8.0 mmol), 4-aminophenol (2.58 g, 23.6 mmol), and BuOH (350 ml) for 3 h. Workup: The crude product (2.2 g; m.p. $>300°$) was heated to 70° in 40 ml of 98% EtOH, filtered with suction, and dried under high vacuum: **10f** (2.0 g, 72%). Amorphous solid, pure enough for the intended purposes. M.p. $>300°$. IR: 3360*w*, 3178*w*, 1630*m,* 1607*m*, 1518*m*, 1482*w*, 1348*m*, 1217*m*, 1079*w*, 1045*w*, 855*w*, 710*w*, 516*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 10.25, 9.32 (2*s*, NH, OH); 8.48 (*d*, $J=9.2$, 2 H); 8.45 (*s*, H–C(5′)); 8.40 (*d*, $J=9.1$, 2 H); 7.59 (*d*, $J=$ 8.9, H–C(3)); 6.78 (*d*, $J=9.0$, H–C(2)). FAB-MS: 349 (100, M^+), 321 (13), 302 (14), 241 (33), 195 (14), 120 (10). HR-MS: 349.0809 ($C_{17}H_{11}N_5O_4^+$; calc. 349.0811).

N-*[(3-Chlorophenyl)-2-(3-nitrophenyl)oxazolo[5,4*-d*]pyrimidin-7-amine* (**10g**). According to the *GP 1*, with **9b** (7.14 g, 25.9 mmol), BuOH (300 ml), and 3-chloroaniline (8.1 ml, 77.1 mmol) for 2.5 h (yellow suspension → clear, pale yellow soln.). Workup: The filtrate was stored for 3 d at 2–8° and then filtered with suction, and the resulting residue dried under high vacuum (0.86 g) and combined with the initially obtained bright brown residue (1.81 g). FC (SiO_2, CH_2Cl_2/MeOH 99 : 1 → 96 : 4) yielded **10g** (125 mg, 1%). Amorphous, off-white solid. M.p. 256–260°. IR: 3331*w*, 3093*w*, 1636*s*, 1616*s*, 1593*s*, 1528*s*, 1476*m*, 1427*m*, 1355*s*, 1320*m*, 1080*w*, 1046*w*, 929*w*, 870*w*, 784*m*, 710*m*, 679*m*, 564*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.60 (*s*, NH); 8.96 (‘*t*’, $J=1.9$, H–C(2″)); 8.62 (*s*, H–C(5)); 8.58 (*d*, $J=7.7$, 1 H); 8.49 (*ddd*, $J=8.3$, 2.3, 0.9, 1 H); 8.18 (‘*t*’, $J=2.0$, H–C(2″)); 7.96 (‘*t*’, $J=8.0$, H–C(5″)); 7.88 (*d*, $J=7.7$, 1 H); 7.41 (‘*t*’, $J=8.1$, 1 H); 7.17 (*ddd*, $J=8.0$, 2.0, 0.8, 1 H). EI-MS: 367 (100, M^+), 351 (8), 337 (12), 320 (10), 259 (41), 229 (6), 213 (8), 157 (5), 150 (7), 143(7), 138 (5), 111 (8), 104 (6), 76 (12). HR-MS: 367.0473 (calc. 367.0472). Anal. calc. for $C_{17}H_{10}ClN_5O_3$ (367.76): C 55.52, H 2.74, N 19.04, O 13.05; found: C 55.04, H 2.93, N 19.07, O 12.80.

N-*(3-Chlorophenyl)-2-(4-nitrophenyl)oxazolo[5,4*-d*]pyrimidin-7-amine* (**10h**). According to the *GP 1*, with **9a** (150 mg, 0.54 mmol), 3-chloroaniline (0.17 ml, 1.6 mmol), and BuOH (30 ml) for 2 h (clear, pale yellow soln.). No workup: **10h** (118 mg, 59%), pure enough for the intended purposes. Golden platelets. M.p. 285°. IR: 3289*w*, 3202*w*, 3110*w,* 1641*s*, 1590*s*, 1524*s*, 1476*s*, 1410*m*, 1348*s*, 1314*m*, 1292*m*, 1051*m*, 856*m*, 785*w*, 712*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.70 (*s*, NH); 8.62 (*s*, H–C(5)); 8.49 (*d*, $J=9.2$, 2 H); 8.43 (*d*, $J=9.2$, 2 H); 8.16 (‘*t*’, $J=2.0$, H–C(2′)); 7.87 (*m*, 1 H); 7.41 (‘*t*’, $J=8.1$, H–C(5′)); 7.17 (*ddd*, $J=8.0$, 2.1, 0.9, 1 H). EI-MS: 367 (100, M^+), 339 (12), 320 (11), 259 (43), 213 (11), 150 (16), 104 (11), 76 (15). HR-MS: 367.0475 (calc. 367.0472). Anal. calc. for $C_{17}H_{10}ClN_5O_3$ (376.76): C 55.52, H 2.74, N 19.04, O 13.05; found: C 55.15, H 3.04, N 18.59, O 13.98.

N-*(4-Chlorophenyl)-2-(4-nitrophenyl)oxazolo[5,4*-d*]pyrimidin-7-amine* (**10i**). According to the *GP 1*, with **9a** (1.99 g, 7.2 mmol), 4-chloroaniline (2.75 g, 21.6 mmol), and BuOH (300 ml) for 90 min. Workup: Washing with little MeOH and much EtOH (instead of BuOH) and drying under high vacuum (1.14 g, m.p. $>300°$). The residue was heated in $(CD_3)_2SO$ (*ca.* 400 ml) and filtered hot. From this filtrate, orange-golden platelets crystallized and were dried under high vacuum: **10i** (307 mg, 12%). M.p. *ca.* 300°. IR: 3286*w*, 3198*w*, 3080*w*, 3000*w*, 1635*s,* 1604*m*, 1591*m*, 1577*s*, 1513*s*, 1495*s*, 1472*m*, 1404*m*, 1342*s*, 1306*m*, 1289*m*, 1231*m*, 1105*w*, 1080*m*, 1051*m*, 1028*m*, 712*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.6 (*s*, NH); 8.57 (*s*, H–C(5)); 8.49 (*d*, $J=7.0$, 2 H); 8.43 (*d*, $J=7.5$, 2 H); 7.98 (*d*, $J=9.0$, H–C(2′)); 7.44 (*d*, $J=8.9$, H–C(3′)). EI-MS: 367 (100, M^+), 339 (15), 320 (11), 259 (40), 213 (14), 111 (11), 104 (11), 76 (14). HR-MS: 367.0473 ($C_{17}H_{10}N_5O_3^+$; calc. 367.0472).

General Procedure 2 (*GP 2*): Raney-*Nickel Reduction; 3-{[2-(3-Aminophenyl)oxazolo[5,4*-d*]pyrimidin-7-yl]amino}phenol* (**11c**). A mixture of **10c** (1.8 g, 5.1 mmol), THF (*ca.* 100 ml), and some *Raney*-Ni was shaken overnight and then filtered with suction through *Celite*. Workup: The filtrate was brought to precipitation by adding H_2O (*ca.* 100 ml). After overnight storage at 2–8°, the suspension was filtered with suction. The residue was submitted to FC (adsorption onto SiO_2 (10 g); SiO_2, CH_2Cl_2/MeOH 100 : 0 → 95 : 5): **11c** (91.2 mg, 0.6%). Fine, off-white needles. M.p. 274–278° (partial dec.). IR: 3390*w*, 3307*w*, 1636*s*, 1602*s*, 1464*s*, 1319*m*, 1281*m*, 1184*w*, 1159*w*, 684*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.18, 9.44 (2*s*, NH, OH); 8.49 (*s*, H–C(5′)); 7.47 (‘*t*’, $J=$ 2.1, 1 H); 7.41 (‘*t*’, $J=1.9$, 1 H); 7.39–7.25 (*m*, 3 H); 7.14 (‘*t*’, $J=8.1$, H–C(5)); 6.83 (*ddd*, $J=8.0$, 2.3, 1.0, 1 H); 6.52 (*ddd*, $J=8.1$, 2.4, 0.9, 1 H); 5.55 (*s*, NH_2). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.1; 159.5; 157.4; 153.5; 152.3; 149.5; 140.1; 129.9; 129.1; 126.5; 117.5; 117.2; 114.5; 112.1; 111.7; 110.5; 108.3. EI-MS: 319 (100, M^+), 290 (6), 264

(13), 211 (42), 160 (5), 146 (5), 118 (6), 92 (9), 65 (9). Anal. calc. for $C_{17}H_{13}N_5O_2$ (319.33): C 63.94, H 4.10, N 21.93, O 10.02; found: C 63.10, H 4.31, N 21.84, O 10.26.

*5-{[2-(3-Aminophenyl)oxazolo[5,4-*d*]pyrimidin-7-yl]amino}-2-methoxyphenol* (**11d**). According to *GP 2*, with **10d** (813 mg, 2.14 mmol), THF (*ca.* 50 ml), and DMEU (20 ml), brown-green suspension. Workup: The filtrate was concentrated and brought to precipitation with H_2O (bright, yellow-green), left for 4 h at 2–8°, and filtered with suction. The residue was dried under high vacuum: **11d** (615 mg, 82%). Pale green amorphous solid. M.p. 254–257°. IR: 3376*s*, 3299*m*, 3092*w*, 1635*s*, 1590*s*, 1528*s*, 1478*s*, 1432*s*, 1410*m*, 1320*m*, 1283*s*, 1243*s*, 1214*s*, 1187*m*, 1163*m*, 1136*w*, 1080*m*, 1060*w*, 1033*w*, 970*w*, 926*w*, 901*w*, 869*s*, 788*s*, 682*s*, 574*w*, 511*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.02, 9.04 (2*s*, NH, OH); 8.42 (*s*, H–C(5′)); 7.40–7.34 (*m*, 3 H); 7.29–7.20 (*m*, 2 H); 6.93 (*d*, *J* = 8.8, 1 H); 6.83 (*dd*, *J* = 8.0, 1.0, 1 H); 5.53 (*s*, NH_2); 3.78 (*s*, MeO). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.0; 159.2; 153.6; 152.4; 149.4; 146.2; 144.2; 132.4; 129.9; 126.5; 117.4; 116.8; 114.6; 112.6; 112.3; 111.8; 110.2; 56.0. EI-MS: 349 (100, M^+), 334 (50), 320 (6), 306 (11), 278 (19), 153 (5), 118 (5), 92 (6). Anal. calc. for $C_{18}H_{15}N_5O_3$ (349.35): C 61.89, H 4.33, N 20.05, O 13.74; found (after heating the product for 105 min at 190°/0.05 mbar): C 61.57, H 4.45, N 19.93, O 13.83.

*3-{[2-(4-Aminophenyl)oxazolo[5,4-*d*]pyrimidin-7-yl]amino}phenol* (**11e**). According to *GP 2*, with **10e** (0.574 g, 1.64 mmol), and THF (20 ml). Workup: The filtrate was brought to precipitation by adding H_2O (*ca.* 50 ml). After removal of the light brown precipitate, another dark brown precipitate formed, which was filtered off with suction a few days later (17 mg). Another beige, amorphous precipitate containing **11e** formed, which was collected and dried under high vacuum: 214 mg (41%). M.p. *ca.* 285°. IR: 3476*w*, 3375*m,* 3230*w*, 1625*s*, 1608*s*, 1594*s*, 1560*w*, 1498*m*, 1475*m*, 1443*w*, 1323*m*, 1263*w*, 1174*m*, 1154*w*, 1088*w*, 1040*w*, 911*w*, 833*w*, 769*w*, 684*w*, 558*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.96, 9.39 (2*s*, NH, OH); 8.41 (*s*, H–C(5′)); 7.88 (*d*, *J* = 8.7, H–C(3″)); 7.47 (‘*t*’, *J* = 2.2, H–C(2)); 7.30 (*dd*, *J* = 8.1, 1.1, 1 H); 7.12 (‘*t*’, *J* = 8.1, H–C(5)); 6.72 (*d*, *J* = 8.8, H–C(2″)); 6.48 (*m*, 1 H); 6.08 (*s*, NH_2). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 163.9; 160.2; 157.4; 152.7; 152.4; 151.6; 140.4; 129.0; 128.9; 117.5; 113.6; 112.1; 111.8; 110.2; 108.1. EI-MS: 319 (100, M^+), 290 (6), 264 (44), 237 (16), 211 (50), 173 (7), 160 (10), 146 (10), 120 (7), 104 (11), 92 (10), 65 (16), 39 (8).

*4-{[2-(4-Aminophenyl)oxazolo[5,4-*d*]pyrimidin-7-yl]amino}phenol* (**11f**). According to the *GP 2*, with **10f** (350 mg, 1.0 mmol), THF (100 ml), and DMEU (20 ml) for 72 h (reddish soln.). Workup: The yellow-green filtrate was concentrated and brought to precipitation by adding H_2O (*ca.* 150 ml). This precipitate was collected, washed with H_2O, and dried under high vacuum: 296 mg (92%) of crude product as small needles (m.p. > 300°). The crude product was dissolved in warm THF, the soln. immediately filtered and evaporated, and the resulting reddish residue dried under high vacuum at r.t. and then at 150° for 1 h: **11f** (0.15 g, 47%). Amorphous solid. M.p. > 250°. IR: 3446*w*, 3311*w*, 3194*w*, 1618*s*, 1509*s*, 1483*s*, 1439*m*, 1322*m*, 1312*m*, 1267*m*, 1225*m*, 1171*w*, 1080*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.79, 9.21 (2*s*, NH, OH); 8.30 (*s*, H–C(5′)); 7.85 (*d*, *J* = 8.7, 2 H); 7.58 (*d*, *J* = 8.9, 2 H); 6.75 (*d*, *J* = 8.8, 2 H); 6.71 (*d*, *J* = 8.8, 2 H); 6.03 (*s*, NH_2). ^{13}C-NMR (101 MHz, $(CD_3)_2SO$): 163.4; 159.5; 153.2; 152.3; 152.2; 151.6; 130.2; 128.4; 123.0; 116.5; 114.6; 113.4; 112.0. EI-MS: 319 (100, M^+), 264 (37), 237 (10), 211 (30). HR-MS: 319.1072 ($C_{17}H_{13}N_5O_2^+$; calc. 319.1069).

*2-(3-Aminophenyl)-*N*-(3-chlorophenyl)oxazolo[5,4-*d*]pyrimidin-7-amine* (**11g**). According to *GP 2*, with **10g** (0.46 g, 1.3 mmol), THF (100 ml), and DMEU (10 ml). Workup: The filtrate was evaporated and the residue submitted to FC (SiO_2, CH_2Cl_2/MeOH 100:0 → 95:5). The precipitate formed in the eluates was washed with H_2O and MeOH and dried under high vacuum: **11g** (116 mg, 26%). Microscopically fine colorless needles. M.p. 239–242°. IR: 3383*m*, 3316*m*, 3206*w*, 3011*w*, 1639*s*, 1589*s*, 1482*s*, 1408*m*, 1349*m*, 1318*m*, 1280*m*, 1232*m*, 1170*w*, 1104*m*, 1086*m*, 996*w*, 909*m*, 864*m*, 791*m*, 778*m*, 726*m*, 677*m*, 580*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.51 (*s*, NH); 8.56 (*s*, H–C(5)); 8.71 (‘*t*’, *J* = 2.0, H–C(2″)); 7.88 (*ddd*, *J* = 8.3, 2.1, 0.9, 1 H); 7.43–7.36 (*m*, 3 H); 7.28 (‘*t*’, *J* = 7.8, H–C(5′)); 7.15 (*ddd*, *J* = 8.0, 2.1, 0.9, 1 H); 6.84 (*ddd*, *J* = 8.0, 2.3, 1.1, 1 H); 5.56 (*s*, NH_2). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.2; 159.8; 153.5; 152.0; 149.5; 140.8; 132.8; 130.2; 129.9; 126.4; 122.7; 120.3; 119.3; 117.6; 117.6; 114.6; 111.8. EI-MS: 337 (100, M^+), 282 (12), 229 (48), 151 (14), 92 (14), 84 (12), 49 (15). Anal. calc. for $C_{17}H_{12}ClN_5O$ (337.77): C 60.45, H 3.58, N 20.73, O 4.74; found: C 60.21, H 3.76, N 20.79, O 4.85.

*2-(4-Aminophenyl)-*N*-(3-chlorophenyl)-oxazolo[5,4-*d*]pyrimidin-7-amine Hydrochloride* (**11h** · HCl). To a suspension of **10h** (1.61 g, 4.4 mmol) in conc. HCl soln. (10 ml) and EtOH (10 ml) at r.t., $SnCl_2$ (2.50 g) was added and the mixture heated to *ca.* 80° (water bath). After 100 min, conc. HCl soln. (40 ml) was added and the water bath removed. Once the suspension reached r.t., it was filtered with suction and the amorphous residue dried under high vacuum (1.65 g; m.p. *ca.* 245° (dec.). The residue was resuspended in H_2O, left to stand overnight, and filtered with suction. The resulting residue was dried under high vacuum: **11h** · HCl (1.01 g, 56%) (note: we recommend the more feasible methodology of *GP 2* rather than the $SnCl_2$ procedure). M.p. 260–270° (partial dec.). IR: 3373*m*, 3215*w*, 2863 *m*, 2591*w*, 1637*s*, 1592*s*, 1479*s*, 1426*m*, 1322*w*, 1178*w*, 1081*w*, 1045*w*, 789*w*,

732*w*, 684*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.36 (*s*, NH); 8.50 (*s*, H–C(5)); 8.16 (*m*, H–C(2″)); 7.95 (*d*, *J* = 8.7, H–C(2′)); 7.85 (*dd*, *J* = 2, 0.9, 1 H); 7.34 (‘*t*’, *J* = 8.1, H–C(5″)); 7.12 (*ddd*, *J* = 6.3, 2, 0.9, 1 H); 6.9 (*d*, *J* = 8.8, H–C(3′)); NH_2 signal probably overlapped by the br. H_2O signal at δ 6.4. ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.2; 159.7; 152.8; 151.5; 146.3; 140.9; 132.8; 130.1; 128.9; 122.5; 120.1; 119.1; 117.8; 117.7; 117.1. FAB-MS: 338 (100, M^+), 120 (30), 57 (23), 43 (21).

2-(4-Aminophenyl)-N-*(4-chlorophenyl)oxazolo[5,4-*d*]pyrimidin-7-amine* (**11i**). According th the *GP 2*, with **10i** (0.536 g, 2.93 mmol), DMEU (15 ml), and THF (75 ml) for 22 h. Workup: The filtrate was concentrated, brought to precipitation by adding H_2O, and filtered with suction, the residue dried under high vacuum and redissolved in THF, and the mixture brought to precipitation by adding MeOH. This suspension was filtered with suction and the amorphous residue dried for 1 week under high vacuum: **11e** (256 mg, 52%). M.p.: crystals at *ca.* 290°, which melted at 296–301°. IR: 3412*w*, 3330*w*, 1647*s*, 1611*s*, 1594*s*, 1563*m*, 1495*s*, 1320*m*, 1286*w*, 1258*m*, 1180*w*, 1083*w*, 1042*w*, 818*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.2 (*s*, OH); 8.43 (*s*, H–C(5)); 7.96 (*d*, *J* = 8.8, 2 H); 7.87 (*d*, *J* = 8.7, 2 H); 7.41 (*d*, *J* = 8.9, 2 H); 6.71 (*d*, *J* = 8.7, 2 H); 6.1 (*s*, NH_2). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.0; 160.4; 152.8; 152.3; 151.2; 138.4; 129.0; 128.3; 126.4; 122.2; 117.7; 113.6; 112.0. EI-MS: 337 (100, M^+), 282 (35), 229 (39), 151 (16), 120 (11). HR-MS: 337.0734 ($C_{17}H_{12}ClN_5^+$; calc. 337.0730).

Ethyl 2-Chloro-3-(4-nitrophenyl)-3-oxopropanoate (**12a**). Previously described in [29] (and ref. cit. therein); simplified procedure: Ethyl 3-(4-nitrophenyl)-3-oxopropanoate (100.2 g, 0.42 mol; 1.0 equiv.) was suspended in toluene (350 ml) and treated with SO_2Cl_2 (45 ml, 75 g, 0.55 mol, 1.3 equiv.). The reaction was then performed under slightly reduced pressure (*ca.* 900 hPa). The soln. was stirred on an oil bath (bath temp. *ca.* 80°) for 1 h, upon which the soln. cleared. The heating was switched off after this and the pressure slowly reduced (gas development, slow boiling). After a few hours, the mixture was stored under ambient conditions overnight and then quenched with ice. H_2O was added, the mixture extracted several times with toluene, the combined org. phase washed with H_2O several times and washed neutral (pH *ca.* 7) with sat. $NaHCO_3$ soln., dried ($MgSO_4$), and filtered with suction. The filtrate was evaporated and the residue dried under high vacuum: **12a** (105.1 g, 92%) as a yellow, viscose oil (containing some needles), which was used without further purification.

Diethyl 2-Amino-5-(4-nitrophenyl)furan-3,4-dicarboxylate (**13a**). A soln. of **12a** (105 g, 0.39 mol, 1 equiv.) in freshly distilled THF (600 ml) was kept on a water bath at 35°. Within 6.3 h, finely crushed sodium ethyl cyanoacetate (49.4 g, 0.37 mol, 0.94 equiv.) [25] was added gradually (→ orange soln.). The soln. was stirred overnight under N_2. Then, the solvent was evaporated and the residue extracted with H_2O and CH_2Cl_2. The aq. phase was extracted with CH_2Cl_2, the combined CH_2Cl_2 phase (2 l) washed with H_2O, dried ($MgSO_4$), and evaporated giving rise to a highly viscose mixture, which was recrystallized from toluene (300 ml): **13a** (59.5 g, 44%). Very bright orange needles that were readily soluble in DMF, formamide, acetone, and CH_2Cl_2, fairly soluble (slowly or under mild heating) in ^{t}BuOMe, 1,2-dichloroethane, MeCn > toluene, BuOH > EtOH > MeOH (in decreasing order), poorly soluble in conc. HCl soln. and ligroin, and insoluble in 1M HCl, sat. $NaHCO_3$ soln. 5% NaOH soln., and hexane. M.p. 174–177°. IR: 3450*s*, 3337*s*, 2983*w*, 1735*s*, 1681*vs*, 1654*s*, 1591*vs*, 1543*s*, 1511*s*, 1476*s*, 1458*s*, 1318*vs*, 1264*s*, 1221*s*, 1109*s*, 1067*s*, 1024*s*, 852*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 8.29 (*d*, *J* = 8.9, arom. H); 7.75 (*s*, NH_2); 7.58 (*d*, *J* = 8.9, arom. H); 4.36, 4.17 (*q*, *J* = 7.1, 2 MeC*H*$_2$); 1.31, 1.23 (*t*, *J* = 7.1, 2 *Me*CH_3). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.3; 162.4; 145.3; 135.7; 135.2; 134.4; 124.7; 123.4; 118.7; 88.4; 61.8; 59.4; 14.3; 13.8. FAB-MS: 349 (100, $[M+H]^+$), 348 (90, M^+), 332 (10), 303 (39), 287 (6), 275 (14), 150 (17), 89 (10), 77 (19), 65 (18), 51 (16), 39 (32). FAB-MS (KCl): 387 (25, $[M+K]^+$), 371 (5), 349 (99, $[M+H]^+$), 348 (100, M^+), 332 (11), 303 (43), 287 (7), 274 (11), 150 (15). Anal. calc. for $C_{16}H_{16}N_2O_7$ (348.32): C 55.17, H 4.63, N 8.04, O 32.15; found: C 54.89, H 4.67, N 7.86, O 32.42.

Diethyl 2-Amino-5-(3-nitrophenyl)furan-3,4-dicarboxylate (**13b**). Ethyl 3-(3-nitrophenyl)-3-oxopropanoate (25 g, 0.10 mol) was suspended in toluene (300 ml), and SO_2Cl_2 (12.8 ml, 0.15 mol) was added at r.t. After 5 min, the mixture cleared. Another 10 min later, the reaction was quenched by adding H_2O (150 ml) with cooling in an ice/water bath. The org. layer was washed neutral (pH > 7) with sat. $NaHCO_3$ soln. and H_2O, dried ($MgSO_4$), and filtered with suction. Evaporation of the filtrate gave **12b** (26.51 g, 92%) as an orange oil that was used without further purification.

After dissolution of **12b** (180 g) in THF (400 ml), finely crushed sodium ethyl cyanoacetate (79.6 g, 0.59 mol) was added in small portions with cooling in an ice bath [25] (orange → red). After stirring at 25° for 3 h, the THF was removed and the oily residue taken up in CH_2Cl_2 and H_2O. The org. phase was washed with H_2O (5 ×). The first two H_2O phases were combined and washed back with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$) and filtered with suction, the filtrate evaporated, and the orange oil (227 g) precipitated from *p*-xylene: 61.98 g (25% from ethyl 3-(3-nitrophenyl)-3-oxopropanoate) of **13b**. Yellow, amorphous solid. M.p. 169°. IR: 3419*m*, 3318*m*, 3092*w*, 2986*w*, 2904*w*, 1718*s*, 1678*s*, 1647*s*, 1553*m*, 1528*s*, 1452*m*, 1347*s*, 1329*m*, 1265*s*, 1112*m*, 1030*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 8.23 (‘*t*’, *J* = 2.1, 1 H); 8.11 (*ddd*, *J* = 8.0, 2.3, 1.2, 1 H);

7.81–7.70 (*m*, 2 H); 7.61 (*s*, NH_2); 4.35, 4.17 (2*q*, *J* = 7.1, 2 MeC*H*$_2$); 1.31, 1.23 (2*t*, *J* = 7.1, 2 *Me*CH_2). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 164.2; 162.4; 161.9; 148.2; 136.0; 130.7; 129.9; 129.0; 121.6; 117.6; 116.6; 87.6; 61.6; 59.2; 14.2; 13.7. EI-MS: 348 (100, M^+), 303 (22), 274 (90), 256 (21), 150 (56), 134 (22), 104 (18), 76 (12). Anal. calc. for $C_{16}H_{16}N_2O_7$ (348.32): C 55.17, H 4.63, N 8.04, O 32.15; found: C 55.15, H 4.79, N 8.00, O 32.27.

*Ethyl 4-Hydroxy-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidine-5-carboxylate* (**14a**). Diethyl ester **13a** (7.34 g) was stirred under N_2 at 140° for 14 h in formamide (40 ml), DMF (20 ml), and 98–100% formic acid (10 ml). After cooling to r.t., crystals in a deep red to brown mother liquor were present. This mixture was further cooled in an ice bath. The highly viscose mass was filtered, the residue washed with ^{i}PrOH and hexane, dried under high vacuum (5.6 g), and then heated in EtOH (200 ml), and the hot soln. filtered with suction. The residue obtained was dried under high vacuum: **14a** (1.43 g, 21%). Microscopically small crystals of irregular shape. M.p. 279–282°. IR: 3084*w*, 2994*w*, 2829*w*, 1721*s*, 1684*s*, 1597*m*, 1551*m*, 1512*s*, 1492*m*, 1351*s*, 1322*s*, 1298*m*, 1231*m*, 1076*m*, 1041*m*, 858*m*, 750*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 12.9 (*s*, NH); 8.36 (*d*, *J* = 9.0, 1 H); 8.28 (*s*, H–C(2)); 8.01 (*d*, *J* = 9.1, 1 H); 4.39 (*q*, *J* = 7.1, MeC*H*$_2$); 1.31 (*t*, *J* = 7.1, *Me*CH_2). ^{13}C-NMR (101 MHz, $(CD_3)_2SO$): 164.2; 162.3; 156.8; 148.9; 147.5; 147.4; 133.5; 127.6; 124.1; 113.2; 107.0; 61.8; 13.7. EI-MS: 357 (19, $[M+28]^+$), 329 (100, M^+), 313 (11), 284 (47), 257 (70), 237 (15), 227 (17), 211 (13), 150 (35), 104 (23), 76 (14), 44 (13). FAB-MS (KCl): 368 (35, $[M+K]^+$), 330 (79, $[M+H]^+$), 284 (35), 149 (39), 124 (12), 113 (12), 107 (43), 95 (12), 89 (33), 77 (62), 69 (32), 65 (49), 55 (52), 41 (100). Anal. calc. for $C_{15}H_{11}N_3O_6$ (329.27): C 54.72, H 3.37, N 12.76, O 29.16; found: C 54.66, H 3.46, N 12.81, O 29.27.

*Ethyl 4-Hydroxy-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidine-5-carboxylate* (**14b**) *and 4-Hydroxy-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidine-5-carboxamide* (**15**). Diethyl ester **13b** (72.9 g) was stirred in formamide (200 ml), DMF (100 ml), and 98–100% formic acid (40 ml) under N_2 at 140° for 1 d. After cooling to r.t., the mixture was diluted with H_2O to 2 l and allowed to stand overnight. The precipitate formed was filtered off with suction, air-dried overnight, and then dried under high vacuum. This crude product (79 g) was boiled in MeCN (300 ml), filtered off with suction, washed with ice-cold MeCN, and dried under high vacuum (45 g). The residue was boiled in CH_2Cl_2 (200 ml), filtered off warm with suction, washed with CH_2Cl_2, and dried under high vacuum: **14b**/**15** (32.2 g, 46%) as a bright, gray-brown, and sometimes almost black solid, which was used without further purification. The by-product **15** could be obtained in pure form upon recrystallization from DMF as gray microcrystals of inconsistent shape. From the mother liquors (MeCN, CH_2Cl_2), *ca.* 20% of starting material **13b** was recovered.

Data of **14b**: M.p. 212–220°. IR: 3528*w*, 3246*m*, 3092*m*, 2985*w*, 1936*w*, 1721*s*, 1589*m*, 1543*s,* 1482*m*, 1429*w*, 1378*s*, 1352*s*, 1323*m*, 1287*m*, 1234*m*, 1196*m*, 1076*m*, 1042*s*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 12.87 (*s*, NH, 1 H); 8.60 (*s*, H–C(2′)); 8.34 (*dd*, *J* = 8.2, 2.2, 1 H); 8.28 (*s*, H–C(2)); 8.21 (*d*, *J* = 8.7, 1 H); 7.84 ('*t*', *J* = 8.0, H–C(5′)); 4.38 (*q*, *J* = 7.0, MeC*H*$_2$); 1.29 (*t*, *J* = 7.0, *Me*CH_2). EI-MS: 329 (100, M^+), 284 (40), 268 (12), 257 (84), 237 (17), 211 (21), 150 (49), 134 (12), 127 (14), 104 (25), 76 (24). HR-MS: 329.0645 ($C_{15}H_{11}N_3O_6^+$; calc. 329.0648).

Data of **15**: M.p.: needles at *ca.* 330°, prisms at *ca.* 350°, start of dec. at *ca.* 380°, melting at 390° (dec.). IR: 3338*m*, 3180–2810*w*, 1708*s*, 1676*s*, 1589*w*, 1560*m*, 1526*s*, 1406*w,* 1348*s*, 1220*w*, 1105*w*, 1081*w*, 1041*w*, 920*w*, 899*w*, 880*w*, 803*w*, 740*w*, 676*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 13.2 (*s*, 1 H, exchange with D_2O, NH); 9.5 (*s*, 1 H, exchange with D_2O, $CONH_2$); 8.82 ('*t*', *J* = 2.0, H–C(2′)); 8.36 (*s*, H–C(2)); 8.33 (*dd*, *J* = 8.1, 2.0, H–C(4′), H–C(6′)); 7.80 ('*t*', *J* = 8.1, H–C(5′)); 7.7 (*s*, 1 H, exchange with D_2O, $CONH_2$). ^{13}C-NMR (126 MHz, $(CD_3)_2SO$; assigned by HETCOR): 163.9; 162.2; 159.8; 150.6; 148.2 (C(2)); 147.4; 135.1 (C(6′) or C(4′)); 130.2 (C(5′)); 129.8; 124.3 (C(4′) or C(6′)); 123.9 (C(2′)); 115.1; 105.8. EI-MS: 299 (100, $[M-H]^+$), 253 (41), 150 (35), 134 (27), 104 (27), 76 (23), 44 (29). Anal. calc. for $C_{13}H_8N_4O_5$ (300.23): C 52.01, H 2.69, N 18.66, O 26.65; found: C 51.90, H 2.81, N 18.80, O 26.51.

*4-Hydroxy-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidine-5-carboxylic Acid* (**16a**). A mixture of **14a** (3.0 g, 9.1 mmol) and 5% NaOH soln. (*ca.* 50 ml) was boiled for 50 min. The clear, reddish, hot soln. was filtered with suction and the residue discarded[2]). The filtrate was adjusted to pH 1 by cautiously adding conc. HCl soln. (→ ochre and precipitation). The precipitate was dried under high vacuum: **16a** (2.4 g, 87%). Yellow to beige,

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[2]) Sodium 4-hydroxy-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidine-5-carboxylate can be obtained from this filtrate: Upon cooling to 0°, the salt precipitated as needles, which were collected by filtering over ice and washing with ice-cold H_2O. These yellow-orange needles were dried under high vacuum, upon which they turned blood red. Yield 62%. M.p. > 250° (dec.). IR: 3414*m* (br.), 1595*vs*, 1542*s*, 1508*s*, 1476*m*, 1345*m*, 1180*w*, 1099*w*, 1067*w*, 854*w*, 811*w*. ^{1}H-NMR (300 MHz, D_2O; δ rel. to residual HDO (= 4.79 ppm)): 8.24 (*d*, *J* = 9.2, 2 H); 8.08 (*s*, 1 H); 7.93 (*d*, *J* = 9.2, 2 H). ESI-MS (sample dissolved in MeOH): 299.9 (100, $[M-Na]^-$), 255.9 (23, $[M-CO_2]^-$).

amorphous solid, readily soluble in DMSO, pyridine, and hot 5% NaOH soln., fairly to poorly soluble in 5% NaOH soln. at r.t., and practically insoluble in acetone, toluene, benzene, MeOH, nitromethane, BuOH, 1,2-dichloroethane, THF, and *sym*-collidine. M.p. 300–302° (dec.). IR: 3089*m*, 2843*m*, 1686*s*, 1540*vs*, 1513*vs*, 1474*m*, 1436*m*, 1405*m*, 1341*vs*, 1226*s*, 1110*m*, 1070*m*, 1039*m*, 855*m*, 775*m*, 755*s*, 620*m*, 516*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 13.5 (br. *s*, COOH); 8.40 (*s*, H–C(2)); 8.38 (*d*, $J = 7.0$, arom. H); 8.17 (*d*, $J = 9.1$, arom. H). ^{13}C-NMR (101 MHz, $(CD_3)_2SO$): 164.0; 162.4; 159.3; 149.6; 148.8; 147.7; 133.6; 128.8; 123.9; 113.7; 106.7. EI-MS: 301 (100, M^+), 257 (70), 227 (67), 211 (20), 156 (17), 150 (24), 120 (22), 104 (20), 76 (15), 44 (19). HR-MS: 301.0350 ($C_{13}H_7N_3O_6^+$; calc. 301.0335). Anal. calc. for $C_{13}H_7N_3O_6$ (301.22): C 51.84, H 2.34, N 13.95, O 31.87; found: C 51.70, H 2.53, N 14.15, O 31.88.

*4-Hydroxy-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidine-5-carboxylic Acid* (**16b**). A mixture of **14b** (0.95 g, 3.2 mmol) and 5% NaOH soln. (30 ml) was heated for 30 min to 100°. The black mixture was filtered hot, the residue discarded, and the filtrate allowed to cool. The pH of the filtrate was adjusted to 1 in an ice bath. The brown precipitate formed was collected and dried under high vacuum. The brown, amorphous solid contained **16b** (595 mg, 63%) and was used without further purification. M.p. > 300°. IR: 3448*w*, 3237*m*, 3088*w*, 1752*s*, 1734*s*, 1672*s*, 1531*s*, 1474*m*, 1407*m*, 1381*m*, 1346*s*, 1241*m*, 1211*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 14.4–12.8 (*s*, COOH, OH); 8.82 (*t*', $J = 1.9$, H–C(2′)); 8.42 (*s*, H–C(2)); 8.37–8.34 (*m*, 2 H); 7.85 (*t*', $J = 8.1$, H–C(5′)). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 163.7; 162.1; 159.8; 150.7; 148.6; 147.7; 134.2; 130.4; 129.1; 124.7; 122.8; 112.5; 106.4. MS: 301 (23, M^+), 257 (100), 211 (24), 156 (48), 150 (14), 128 (17), 104 (20), 101 (12), 76 (32), 63 (11), 52 (15), 50 (15), 44 (20).

*6-(4-Nitrophenyl)furo[2,3-*d*]pyrimidin-4-ol* (**17a**). Acid **16a** (21 g) was dissolved in warm pyridine (200 ml). The pyridine was subsequently evaporated at 80°. The mixture of the residue, Cu_2O (1 g), and quinoline (500 ml; dried over $MgSO_4$) was heated under constant N_2 flow for 1 h at 190°. After cooling to r.t., the mixture was poured into 2.5M HCl (1 l), stirred, and filtered with suction. This residue was washed with conc. NH_3 soln. and H_2O. The dark brown, muddy residue was left to dry first at r.t. and then dried under high vacuum: crude **17a** (13 g, *ca.* 70%). Due to low solubilities, the compound was used without further purification. M.p. > 350°. IR: 3073*w*, 2859*w*, 1678*vs*, 1599*s*, 1548*s*, 1514*s*, 1349*vs*, 1218*m*, 1189*m*, 1110*m*, 854*m*, 780*m*, 752*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 12.8 (*s*, NH); 8.33 (*d*, $J = 8.8$, 2 arom. H); 8.23 (*d*, $J = 3.6$, H–C(2)); 8.12 (*d*, $J = 8.6$, 2 arom. H); 7.85 (*s*, H–C(5)). EI-MS: 257 (100, M^+), 241 (9), 227 (18), 211 (19), 156 (22), 128 (7), 104 (9), 52 (7). HR-MS: 257.0429 ($C_{12}H_7N_3O_4^+$; calc. 257.0437).

*6-(3-Nitrophenyl)furo[2,3-*d*]pyrimidin-4-ol* (**17b**). As described for **17a**, with **16b** (25.5 g), pyridine (250 ml), Cu_2O (1 g), and quinoline (250 ml). After cooling, the mixture was poured into 2.5M HCl (1 l), stirred, diluted to 2 l with H_2O, and filtered with suction. The residue was washed with little H_2O (this acidic filtrate was discarded), conc. NH_3 soln. (200 ml), and lots of H_2O. The pH of this second (basic) filtrate was adjusted to 1 with conc. HCl, and the mixture filtered with suction. The residue was dried in an oven at 100° (for at least one night), then under high vacuum. This crude product (18.5 g) was stirred into a considerable amount of sat. $NaHCO_3$ soln. and stored overnight. The resulting precipitate was filtered off with suction and washed with H_2O: crude **17b** (10.5 g, 49%), which was used without further purification (starting material **16b** (2.3 g, 9%) could be recovered by adjusting the pH of the last filtrate to 1 with conc. HCl soln., collecting the precipitate, and drying it under high vacuum). IR: 3091*w*, 2853*w*, 1670*vs*, 1593*w*, 1527*s*, 1496*w*, 1475*w*, 1373*w*, 1348*s*, 1297*w*, 1202*m*, 938*m*, 900*m*, 783*w*, 740*w*, 703*w*, 622*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 12.7 (*s*, NH); 8.58 (*t*, $J = 3.8$, H–C(2′)); 8.29 (*ddd*, $J = 7.8$, 1.8, 1.0, 1 H); 8.20 (*ddd*, $J = 8.4$, 2.3, 1.0, 1 H); 8.19 (*d*, $J = 3.5$, H–C(2)); 7.78 (*s*, H–C(5)); 7.77 (*t*, $J = 8.1$, H–C(5′)). EI-MS: 257 (100, M^+), 241 (7), 227 (8), 211 (22), 156 (23), 128 (7), 104 (7), 76 (9), 52 (6). HR-MS: 257.0436 ($C_{12}H_7N_3O_4^+$; calc. 257.0437).

*4-Chloro-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidine* (**18a**). Crude **17a** (13.5 g) was refluxed in $POCl_3$ (200 ml) for 1.5 h. The mixture was left open at r.t.for three days and then poured very cautiously onto 4 kg of drip-dried ice. After a few hours, the resulting bright brown suspension was filtered with suction. The residue was washed with much H_2O and then air-dried overnight. Additional drying under high vacuum gave crude **18a** (13.8 g, 94%) which was frequently used without purification. We recommend, however, that **18a** be sublimed before use in synthesis as impurities may not easily be removed at a later stage. Sublimation at *ca.* 200°/*ca.* 0.1 mbar yielded **18a**. Bright yellow, noncrystalline needles that are somewhat soluble in DMF and hardly or not at all soluble in acetone, toluene, EtOH, and 1,2-dichloroethane. M.p.: transformation to microscopically small, crystalline needles just before melting at 245° (dec.). IR: 3106*w*, 1593*m*, 1560*s*, 1515*s*, 1430*w*, 1376*w*, 1345*m*, 1250*w*, 1108*w*, 1030*w*, 973*w*, 914*w*, 858*w*, 782*w*, 752*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 8.93 (*s*, H–C(2)); 8.42, 8.33 (*d*, $J = 9.2$, H–C(2′), H–C(3′)); 8.12 (*s*, H–C(5)). EI-MS: 275 (100, M^+), 245 (16), 217 (16), 174 (32), 139 (14). HR-MS: 275.0091 ($C_{12}H_6ClN_3O_3^+$; calc. 275.0097). Anal. calc. for $C_{12}H_6ClN_3O_3$ (275.65): C 52.29, H 2.19, N 15.24, O 17.41; found: C 52.28, H 2.45, N 15.26, O 17.47.

*4-Chloro-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidine* (**18b**). Crude **17b** (11 g) was refluxed in $POCl_3$ (340 ml) for 4 h. The mixture was left to stand at r.t. overnight and then poured slowly and cautiously onto drip-dried ice (5 kg). The resulting bright brown suspension was stored for a few hours under constant surveillance. The precipitate was then filtered off with suction and washed extensively with H_2O. The residue was left to dry under ambient conditions overnight, dried under high vacuum, and subsequently sublimed at *ca.* 200° under high vacuum: **18b** (2.73 g, 23%) as noncrystalline needles (the brown sublimation residue (8.0 g, >72%) contained mostly starting material **17b**). M.p.: transformation to tiny crystalline needles at *ca.* 190° which melted from 196° to 205°. IR: 3114*w*, 3070*m*, 3009*w*, 2867*w*, 1618*w*, 1592*m*, 1565*s*, 1519*vs*, 1469*w*, 1429*m*, 1373*s*, 1359*s*, 1304*m*, 1255*s*, 1228*w*, 1206*m*, 1108*w*, 1046*w*, 972*w*, 923*m*, 900*w*, 878*w*, 807*m*, 780*m*, 753*m*, 740*m*, 677*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 8.87 (*s*, H–C(2)); 8.78 ('*t*', *J* = 1.9, H–C(2′)); 8.46 (*ddd*, *J* = 7.8, 1.8, 1.0, 1 H); 8.33 (*ddd*, *J* = 8.1, 2.3, 0.9, 1 H); 8.09 (*s*, H–C(5)); 7.86 ('*t*', *J* = 8.1; H–C(5′)). EI-MS: 275 (100, M^+), 229 (9), 217 (5), 201 (8), 174 (33), 165 (10), 139 (13). Anal. calc. for $C_{12}H_6ClN_3O_3$ (275.65): C 52.29, H 2.19, N 15.24, O 17.41; found: C 52.18, H 2.33, N 15.49, O 17.51.

N-*(4-Chloro-2-fluorophenyl)-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19k**). According to *GP 1*, with **18a** (1.65 g, 5.9 mmol), 4-chloro-2-fluoroaniline (2.2 ml) and BuOH (100 ml) for 4 h. Workup: The residue was washed with BuOH, MeOH, and *t*BuOMe, dried under high vacuum (→ 1.5 g), and recrystallized from AcOH: **19k** (1.15 g, 51%). Yellow, microscopically fine needles that are well soluble in DMSO and CF_3COOH, fairly soluble in AcOH, and not at all or poorly soluble in acetone, MeOH, and H_2O. M.p. > 250°. IR: 3386*m*, 3110*w*, 3065*w*, 1625*m*, 1599*s*, 1590*s*, 1576*s*, 1506*s*, 1476*m*, 1456*m*, 1414*m*, 1337*s*, 1312*m*, 1286*m*, 1188*m*, 1109*w*, 1067*w*, 1032*w*, 853*w*, 787*w*, 753*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 10.0 (*s*, NH); 8.41 (*s*, H–C(2)); 8.36 (*d*, *J* = 9.1, H–C(2″)); 8.08 (*d*, *J* = 9.0, H–C(3″)); 7.82 ('*t*', *J* = 8.6, H–C(6′)); 7.78 (*s*, H–C(5)); 7.57 (*dd*, *J* = 10.4, 2.4, H–C(3′)); 7.35 (*ddd*, *J* = 8.6, 2.4, 1.1, H–C(5′)). ^{13}C-NMR (126 MHz, $(CD_3)_2SO$; assigned by HETCOR and long-range HETCOR): 166.8 (C(7a)); 155.5 (*d*, *J* = 250.2, C(2′)); 155.4 (C(3)); 154.3 (C(2)); 149.0 (C(1″)); 147.0 (C(4″)); 134.6 (C(6)); 129.5 (*d*, *J* = 9.9); 127.7 (*d*, *J* = 2.1, C(6′)); 125.3 (C(3″)); 125.2 (*d*, *J* = 13.1); 124.6 (*d*, *J* = 3.5, C(5′)); 124.5 (C(2″)); 116.5 (*d*, *J* = 23.7, C(3′)); 103.8 (C(4a)); 103.0 (C(5)). EI-MS: 384 (100, M^+), 365 (86), 354 (21), 349 (42), 319 (36), 303 (20), 247 (11), 180 (13), 156 (14). HR-MS: 384.0419 ($C_{18}H_{10}ClFN_4O_3^+$; calc. 384.0426). Anal. calc. for $C_{18}H_{10}ClFN_4O_3$ (384.75): C 56.19, H 2.62, N 14.56, O 12.48; found: C 55.92, H 2.89, N 14.63, O 12.46.

N-*(4-Chloro-2-fluorophenyl)-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19l**). According to the *GP 1*, with **18b** (4.32 g, 16 mmol), 4-chloro-2-fluoroaniline (5 ml) and BuOH (200 ml) for 3 h (colorless suspension → colorless soln. → yellow suspension). Workup: the crude **19l** (4.3 g, 70%), a very bright yellow cotton-wool-like solid, was recrystallized from AcOH and then dried at 100°/high vacuum overnight: microscopically small needles. M.p.: transformation at *ca.* 260° to somewhat larger needles that melted at 269°. IR: 3410*m*, 3110*w*, 1630*s*, 1610*s*, 1594*s*, 1582*s*, 1526*vs*, 1479*m*, 1458*m*, 1416*m*, 1356*s*, 1190*m*, 1108*w*, 1070*w*, 1043*w*, 934*w*, 904*w*, 844*w*, 809*w*, 782*w*, 741*w*, 536*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 9.9 (*s*, NH); 8.56 (*t*, *J* = 2.0, H–C(2″)); 8.42 (*s*, H–C(2)); 8.31–8.27 (*m*, H–C(4″) and H–C(6″)); 7.850 ('*t*', *J* = 8.0, H–C(5″)); 7.847 ('*t*', *J* = 8.7, H–C(6′)); 7.77 (*s*, H–C(5)); 7.60 (*dd*, *J* = 10.4, 2.4, H–C(3′)); 7.37 (*ddd*, *J* = 8.7, 2.3, 1.0, H–C(5′)). EI-MS: 384 (100, M^+), 365 (90), 354 (20), 349 (43), 335 (14), 319 (29), 303 (18), 247 (12), 180 (10), 156 (10), 151 (15). Anal. calc. for $C_{18}H_{10}ClFN_4O_3$ (384.75): C 56.19, H 2.62, N 14.56, O 12.48; found: C 56.04, H 2.72, N 14.66, O 12.36.

N-*(3-Chlorophenyl)-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19m**). According to *GP 1*, with **18a** (1.80 g, 6.5 mmol), 3-chloroaniline (2.6 ml, 2.55 g, 20.0 mmol) and BuOH (100 ml) for 2 h. No workup: **19m** (2.24 g, 94%). Intensively yellow, granular microcrystals of irregular shape. M.p. 288°. IR: 3278*w*, 3187*w*, 3112*w*, 3014*w*, 1627*m*, 1600*m*, 1584*s*, 1571*s*, 1524*m*, 1473*m*, 1425*m*, 1345*s*, 1313*m*, 1152*w*, 1112*w*, 1072*w*, 1023*w*, 926*w*, 852*w*, 770*w*, 750*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.17 (*s*, NH); 8.57 (*s*, H–C(2)); 8.38 (*d*, *J* = 8.6, 1 H); 8.13 ('*t*', *J* = 2.0, H–C(2′)); 8.10 (*d*, *J* = 8.5, 1 H); 7.86 (*s*, H–C(5)); 7.75–7.12 (*m*, 1 H); 7.43 (*t*, *J* = 8.0, H–C(5′)); 7.18–7.14 (*m*, 1 H). EI-MS: 366 (100, M^+), 350 (12), 336 (21), 319 (21), 258 (8), 229 (11), 142.5 (9), 115 (11), 111 (15), 75 (8). Anal. calc. for $C_{18}H_{11}ClN_4O_3$ (366.77): C 58.95, H 3.02, N 15.28, O 13.09; found (after drying for 19 h at < 150°/high vacuum): C 58.76, H 3.29, N 15.24, O 13.31.

N-*(3-Chlorophenyl)-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19n**). According to *GP 1*, with **18b** (0.87 g, 3.2 mmol), 3-chloroaniline (1.0 ml, 1.2 g, 9.5 mmol), and BuOH (170 ml) for 3 h. Workup: The bright yellow, cotton-wool-like residue was recrystallized from AcOH: **19n** (0.85 g, 73%). Bright yellow, microscopically small, non-crystalline needles. M.p.: transformation to crystalline platelets just below the m.p. (268–270°). IR: 3278*w*, 3186*w*, 3112*w*, 3009*w*, 1629*s*, 1583*vs*, 1523*s*, 1485*s*, 1432*m*, 1346*s*, 1309*m*, 1235*m*, 1150*m*, 938*m*, 772*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$; δ rel. to the solvent (=2.52 ppm)): 10.06 (*s*, NH); 8.56 (*s*, H–C(2)); 8.54 ('*t*', *J* = 2.0, H–C(2″)); 8.27 (*dd*, *J* = 8.1, 2.0, H–C(4″), H–C(6″)); 8.14 (*t*, *J* = 2.0, H–C(2′)); 7.85 ('*t*', *J* = 8.0, H–C(5″)); 7.81 (*s*, H–C(5)); 7.74 (*ddd*, *J* = 8.3, 2.0, 1.0, 1 H); 7.44 ('*t*', *J* = 8.2, H–C(5′)); 7.16 (*ddd*, *J* = 8.0, 2.0,

0.8, 1 H). EI-MS: 366 (100, M^+), 350 (24), 336 (16), 319 (24), 258 (12), 229 (15), 142.5 (19), 115 (13), 111 (13). HR-MS: 366.0503 ($C_{18}H_{11}ClN_4O_3^+$; calc. 366.0520). Anal. calc. for $C_{18}H_{11}ClN_4O_3$ (366.77): C 58.95, H 3.02, N 15.28, O 13.09; found: C 58.76, H 3.15, N 15.41, O 13.16.

*2-Methoxy-5-{[6-(4-nitrophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino}phenol* (**19o**). According to *GP 1*, with **18a** (1.96 g, 7.1 mmol), 5-amino-2-methoxyphenol (2.94 g, 21 mmol), and BuOH (100 ml) for 3 h. Workup: Recrystallization from AcOH yielded **19o** (1.88 g, 70%). Red brown, amorphous solid. M.p. 280–285° (dec.). IR: 3364*m*, 3104*w*, 2929*w*, 1621*m*, 1599*m*, 1579*s*, 1508*s*, 1460*m*, 1340*s*, 1286*w*, 1218*w*, 1180*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.80, 9.15 (2*s*, exchange with D_2O, NH, OH); 8.43 (*s*, H–C(2′)); 8.37, 8.06 (*d*, *J* = 9.0, H–C(3″), H–C(2″)); 7.74 (br. *s*, H–C(5″)); 7.31 (*d*, *J* = 2.5, H–C(6)); 7.14 (*dd*, *J* = 8.7, 2.5, H–C(4)); 6.94 (*d*, *J* = 8.9, H–C(3)); 3.78 (*s*, MeO). EI-MS: 378 (100, M^+), 363 (72), 348 (17), 335 (20), 317 (27), 289 (22), 139 (12). HR-MS: 378.0955 (calc. 378.0964). Anal. calc. for $C_{19}H_{14}N_4O_5$ (378.35): C 60.32, H 3.73, N 14.81, O 21.14; found: C 60.22, H 4.02, N 14.57, O 20.98.

*6-(3-Nitrophenyl)-*N*-[(1*R*)-1-phenylethyl]furo[2,3-*d*]pyrimidin-4-amine* (**19p**). According to *GP 1*, with **18b** (2.43 g, 8.8 mmol), [(1*R*)-1-phenylethyl]amine (4.2 ml), and BuOH (75 ml) for 2.5 h. The clear reaction soln. was concentrated (80°/100 mbar) and then brought to precipitation by adding H_2O (100 ml) and ^{t}BuOMe (300 ml; shaking, brightly yellow precipitate). The two-phase mixture was filtered with suction and the residue dried under high vacuum. Recrystallization from EtOH yielded **19p** (1.78 g, 56%). Brightly yellow needles. M.p. 163–165°. IR: 3407*m*, 3390*m*, 3124*w*, 3086*w*, 3031*w*, 2970*w*, 2929*w*, 1603*s*, 1524*s*, 1490*m*, 1450*m*, 1346*s*, 1294*m*, 1138*m*, 1102*w*, 934*w*, 785*w*, 738*w*, 699*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 8.56 (*s*, H–C(2′)); 8.39 (*d*, *J* = 8.1, NH); 8.23 (*s*, H–C(2)); 8.20–8.15 (*m*, H–C(4′), H–C(6′)); 7.77 ('*t*', *J* = 8.1, H–C(5′)); 7.71 (*s*, H–C(5)); 7.42 (*d*, *J* = 7.6, 2 H); 7.33–7.29 (*m*, 2 H); 7.21 (*tt*, *J* = 7.3, 1.2, 1 H); 5.47–5.43 ('*quint.*', *J* = 7.2, MeC*H*N); 1.54 (*d*, *J* = 7.1, *Me*CHN). EI-MS: 360 (60, M^+), 345 (37), 299 (9), 256 (42), 210 (7), 139 (5), 120 (46), 105 (100), 77 (15). Anal. calc. for $C_{20}H_{16}N_4O_3$ (360.38): C 66.66, H 4.48, N 15.55, O 13.32; found: C 66.43, H 4.62, N 15.61, O 13.37.

*2-Methyl-5-{[6-(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino}phenol* (**19q**). According to *GP 1*, with **18b** (2.43 g, 8.8 mmol), 5-amino-2-methylphenol (3.27 g, 27 mmol), and BuOH (200 ml) for 3 h. Workup: The residue was recrystallized once from AcOH and twice from DMSO: **19q** (869 mg, 27%). Yellow-orange crystals of various shapes. M.p. 280–285°. IR: 3388*m*, 3122*w*, 2922*w*, 1614*s*, 1593*s*, 1526*s*, 1583*m*, 1465*m*, 1420*m*, 1352*s*, 1304*m*, 1178*m*, 1122*m*, 933*w*, 897*w*, 845*w*, 782*m*, 739*m*, 668*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.72, 9.36 (2*s*, NH, OH); 8.50, 8.43 (*s*, H–C(2″), H–C(2′)); 8.25–8.21 (*m*, H–C(4″), H–C(6″)); 7.81 ('*t*', *J* = 8.7, H–C(5″)); 7.75 (*s*, H–C(5′)); 7.36 (*d*, *J* = 1.8, H–C(6)); 7.12 (*dd*, *J* = 8.0, 1.8, H–C(4)); 7.03 (*d*, *J* = 8.3, H–C(3)); 2.09 (*s*, Me). EI-MS: 362 (100, M^+), 346 (17), 332 (42), 315 (27), 77 (11). HR-MS: 362.1001 ($C_{19}H_{14}N_4O_4^+$; calc. 362.1001).

*4-Chloro-2-{[6-(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino}phenol* (**19r**). According to *GP 1*, with **18b** (2.5 g, 9.0 mmol), 2-amino-4-chlorophenol (4 g, 28 mmol), and BuOH (100 ml) for 3.5 h. Workup: The residue was dried under high vacuum (3.05 g) and recrystallized from AcOH: **19r** (1.93 g, 55%). Clear, dark brown prisms. M.p. *ca.* 275° (dec.; sublimation just below the m.p.). ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.25 (*s*, NH); 8.51 (*t*, *J* = 1.9, H–C(2″)); 8.42 (*s*, H–C(2′)); 8.22 (*dd*, *J* = 8.2, 2.1, H–C(4″), H–C(6″)); 7.93 (*d*, *J* = 2.5, H–C(3)); 7.85 (*s*, H–C(5′)); 7.79 ('*t*', *J* = 8.1, H–C(5″)); 7.06 (*dd*, *J* = 8.6, 2.5, H–C(5)); 6.95 (*d*, *J* = 8.6, H–C(6)). EI-MS: 382 (62, M^+), 365 (56), 355 (100), 335 (21), 325 (45), 309 (37), 205 (34), 178 (15), 139 (17), 63 (21), 36 (17). HR-MS: 382.0460 ($C_{18}H_{11}ClN_4O_4^+$; calc. 382.0469).

N-*(3-Nitrophenyl)-6-(4-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19s**). According to the *GP 1*, with **18a** (2.1 g, 7.4 mmol), 3-nitroaniline (3.2 g, 23 mmol), and BuOH (200 ml) for 3 h. No workup: **19s** (2.6 g, 93%). Yellow, amorphous solid. M.p.: tiny needles at *ca.* 300°, m.p. > 350°. IR: 3394*m*, 3106*w*, 3078*w*, 1623*s*, 1595*s*, 1578*s*, 1534*s*, 1510*vs*, 1457*m*, 1346*vs*, 1285*m*, 1243*w*, 1219*w*, 1109*w*, 1070*w*, 1032*w*, 923*w*, 854*m*, 820*w*, 786*w*, 751*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 10.41 (*s*, NH); 8.86 ('*t*', *J* = 2.1, H–C(2′)); 8.60 (*s*, H–C(2)); 8.36 (*d*, *J* = 8.6, H–C(2″)); 8.31–8.27 (*m*, 1 H); 8.09 (*d*, *J* = 8.8, H–C(3″)); 7.93 (*dd*, *J* = 8.1, 1.5, 1 H); 7.84 (*s*, H–C(5)); 7.68 ('*t*', *J* = 8.1, H–C(5′)). EI-MS: 377 (100, M^+), 361 (18), 329 (19), 285 (16), 229 (11). Anal. calc. for $C_{18}H_{11}N_5O_5$ (377.32): C 57.30, H 2.94, N 18.56, O 21.20; found (after drying overnight at *ca.* 175°/high vacuum): C 57.03, H 3.18, N 18.36, O 21.35.

*2-Methyl-5-{[6-(4-nitrophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino}phenol* (**19t**). According to the *GP 1*, with **18a** (2.23 g, 8.1 mmol), 5-amino-2-methylphenol (3.03 g, 25 mmol), and BuOH (170 ml) for 3 h (→ red). No workup: **19t** (2.60 g, 89%). Orange, microscopically small needles. M.p.: transformation at *ca.* 275° (partial dec.) to larger needles that melted at *ca.* 295°. IR: 3388*m*, 3110*w*, 2927*w*, 1619*s*, 1599*s*, 1578*s*, 1518*m*, 1473*m*, 1339*vs*, 1236*w*, 1172*m*, 1108*w*, 1032*w*, 926*w*, 853*w*, 784*w*, 751*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.81, 9.37 (2*s*, NH, OH); 8.44 (*s*, H–C(2′)); 8.36 (*d*, *J* = 9.1, H–C(3″); 8.04 (*d*, *J* = 9.1, H–C(2″)); 7.80 (*s*, H–C(5′)); 7.35 (*d*, *J* = 1.0, H–C(6)); 7.11 (*dd*, *J* = 8.1, 2.3, H–C(4)); 7.03 (*d*, *J* = 8.1, H–C(3)); 2.09 (*s*, Me). EI-MS: 362 (100, M^+), 346

(11), 332 (14), 315 (27), 107 (5), 77 (9). Anal. calc. for $C_{19}H_{14}N_4O_4$ (362.35): C 62.98, H 3.89, N 15.46, O 17.66; found (after drying overnight at *ca.* 175°/high vacuum): C 62.70, H 3.97, N 15.48, O 17.86.

*N-(3,5-Dichlorophenyl)-6-(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19u**). According to *GP 1*, with **18b** (0.82 g, 3.0 mmol), 3,5-dichloroaniline (3.5 g, 21 mmol, 7 equiv.), and BuOH (170 ml), reflux overnight. The mixture was somewhat concentrated, allowed to cool, and then filtered (r.t.) with suction. The solid was washed with BuOH and dried under high vacuum: **19u** (0.68 g, 56%). Microcrystalline platelets. M.p. 212–215°. IR: 3400*m*, 3118*w*, 1626*m*, 1611*s*, 1578*s*, 1527*s*, 1457*s*, 1353*s*, 1082*m*, 843*m*, 785*m*, 738*s*, 671*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 10.13 (*s*, NH); 8.59 (*s*, H–C(2)); 8.52 ('*t*', *J* = 1.9, H–C(2″)); 8.26 (*dd*, *J* = 8.1, 2.0, H–C(4″), H–C(6″)); 7.98 (*d*, *J* = 1.8, H–C(2′)); 7.82 ('*t*', *J* = 8.1, H–C(5″)); 7.75 (*s*, H–C(5)); 7.26 (*t*, *J* = 2.0, H–C(4′)). EI-MS: 400 (100, M^+), 384 (15), 370 (14), 353 (14), 159.5 (14). HR-MS: 400.0133 ($C_{18}H_{10}Cl_2N_4O_3^+$; calc. 400.0130).

N,*6-Bis(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**19v**). According to *GP 1*, with **18b** (1.1 g, 4.0 mmol), 3-nitroaniline (3.8 g, 28 mmol, 7 equiv.), and BuOH (300 ml). BuOH (100 ml) was distilled off and the mixture allowed to cool and then filtered at r.t. with suction. The solid was washed with BuOH and dried under high vacuum: **19v** (1.28 g, 85%). Yellow powder. M.p. 317°. IR: 3375*m*, 3112*w*, 3068*w*, 1612*s*, 1594*s*, 1575*s*, 1526*s*, 1456*s*, 1437*m*, 1347*s*, 1244*w*, 1218*w*, 1068*m*, 937*w*, 801*w*, 788*m*, 742*m*, 671*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 10.35 (*s*, NH); 8.87 ('*t*', *J* = 2.3, 1 H); 8.60 (*s*, H–C(2)); 8.56 ('*t*', *J* = 1.9, 1 H); 8.30–8.26 (*m*, 3 H); 7.92 (*ddd*, *J* = 8.3, 2.3, 0.9, 1 H); 7.84 ('*t*', *J* = 8.1, 1 H); 7.82 (*s*, H–C(5)); 7.68 ('*t*', *J* = 8.2, 1 H). EI-MS: 377 (100, M^+), 361 (17), 347 (5), 330 (22), 285 (18), 257 (7), 229 (12), 197 (5), 139 (8), 115 (5), 76 (9). Anal. calc. for $C_{18}H_{11}N_5O_5$ (377.32): C 57.30, H 2.94, N 18.56, O 21.20; found: C 57.19, H 3.04, N 18.59, O 21.21.

*6-(4-Aminophenyl)-*N*-(4-chloro-2-fluorophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**20k**). According to *GP 2*, with **19k** (0.95 g, 2.5 mmol), THF (50 ml), Et_3N (2 ml; to neutralize traces of AcOH stemming from the previous recrystallization), and DMEU (2 ml). Workup: The filtrate was concentrated and resuspended in H_2O, the pH adjusted to 10 by adding 5% NaOH soln., and the mixture filtered with suction. The residue was washed extensively with H_2O and dried under high vacuum: **20k** (560 mg, 63%). Pale orange amorphous solid that is fairly soluble in DMSO > acetone > ^{i}PrOH > toluene, AcOEt > EtOH (in decreasing order) and poorly soluble in ^{t}BuOMe. For elemental analysis, the product was submitted to FC (acetone soln. adsorbed on SiO_2; SiO_2, pentane/AcOEt 3:2; all fluorescent fractions were collected). M.p.: transformation to microscopically small needles just before melting at 229–232°. IR: 3440*w*, 3408*w*, 3325*w*, 3219*w*, 1625*m*, 1607*s*, 1586*m*, 1504*s*, 1458*m*, 1412*w*, 1356*m*, 1181*m*, 1067*w*, 827*w*, 753*w*, 507*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$; assigned by HETCOR): 9.6 (*s*, NH); 8.27 (*s*, H–C(2)); 7.81 ('*t*', *J* = 8.6, H–C(6″)); 7.55 (*dd*, *J* = 10.4, 2.2, H–C(3″)); 7.51 (*d*, *J* = 8.6, H–C(3′)); 7.33 (*dd*, *J* = 8.6, 1.3, H–C(5″)); 7.10 (*s*, H–C(5)); 6.68 (*d*, *J* = 8.6, H–C(2′)); 5.64 (*s*, NH_2). ^{13}C-NMR (126 MHz, $(CD_3)_2SO$; assigned by HETCOR): 165.8 (C(7a)); 155.3 (*d*, *J* = 249.7, C(2″)); 154.0; 153.2; 151.8 (C(2)); 150.1; 128.8 (*d*, *J* = 9.6); 127.5 (*d*, *J* = 2.4, C(6″)); 125.8 (C(2′)); 125.7 (*d*, *J* = 11.9); 124.5 (*d*, *J* = 3.6, C(5″)); 116.4 (*d*, *J* = 23.7, C(3″)); 115.9; 113.8 (C(3′)); 104.4 (C(4a)); 93.9 (C(5)). EI-MS: 354 (100, M^+), 335 (29), 319 (13), 279 (9), 177 (7), 167.5 (11), 155 (14), 120 (12), 92 (9), 65 (8). Anal. calc. for $C_{18}H_{12}ClFN_4O$ (354.77): C 60.94, H 3.41, N 15.79, O 4.51; found: C 60.89, H 3.66, N 15.58, O 4.76.

*6-(3-Aminophenyl)-*N*-(4-chloro-2-fluorophenyl)-furo[2,3-*d*]pyrimidin-4-amine* (**20l**). According to *GP 2*, with **19l** (2.9 g), THF (80 ml), and DMEU (30 ml). Workup: H_2O (300 ml) was added to the filtrate. The resulting precipitate was filtered off with suction, washed with H_2O, and dried under high vacuum: **20l** (2.58 g, 97%). Colorless, cotton-wool-like solid. M.p. 216°. IR: 3402*w*, 3323*w*, 3317*w*, 3119*w*, 1624*s*, 1606*s*, 1588*s*, 1511*s*, 1466*s*, 1415*m*, 1400*m*, 1355*w*, 1267*m*, 1191*m*, 1066*w*, 940*w*, 856*m*, 779*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.7 (*s*, NH); 8.31 (*s*, H–C(2)); 7.80 ('*t*', *J* = 8.7, H–C(6″)); 7.54 (*dd*, *J* = 10.4, 2.3, H–C(3″)); 7.34 (*s*, H–C(5)); 7.33 (*ddd*, *J* = 8.7, 2.3, 1.0, H–C(5″)); 7.14 ('*t*', *J* = 7.8, H–C(5′)); 7.04 ('*t*', *J* = 1.9, H–C(2′)); 6.96–6.94 (*m*, H–C(6′) or H–C(4′)); 6.61 (*ddd*, *J* = 8.1, 2.3, 1.0, H–C(4′) or H–C(6′)); 5.34 (*s*, NH_2). ^{13}C-NMR (101 MHz, $(CD_3)_2SO$): 167.0; 156.3 (*d*, *J* = 250.0); 155.7; 153.8; 153.3; 150.2; 130.6 (CH); 130.2; 130.1 (*d*, *J* = 10); 128.6 (*d*, *J* = 2.3); 126.5 (*d*, *J* = 12.3); 125.4 (*d*, *J* = 3.1), 117.4 (*d*, *J* = 23.4); 115.7 (CH); 112.9 (CH); 110.2 (CH); 104.9; 98.8 (CH). EI-MS: 354 (100, M^+), 335 (75), 319 (39), 177 (5), 167.5 (16), 155 (8), 120 (5), 92 (11), 65 (7). Anal. calc. for $C_{18}H_{12}ClFN_4O$ (354.77): C 60.94, H 3.41, N 15.79, O 4.51; found: C 60.70, H 3.56, N 15.78, O 4.66.

*6-(4-Aminophenyl)-*N*-(3-chlorophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**20m**). To a suspension of **19m** (1.98 g, 5.4 mmol) in DMEU (50 ml), some *Raney*-Ni suspension was added, and the mixture was shaken overnight under H_2 at 1 atm. The orange suspension was filtered with suction over *Celite* and the residue washed with acetone and DMSO. To the combined filtrates, much acetone was added, and this mixture was then filtered with suction. The resulting residue (0.3 g; consisting of a DMEU polymer pigment) was discarded. The volume of the filtrate was doubled with H_2O. The resulting beige, amorphous precipitate (0.94 g) was submitted to FC (SiO_2, acetone). Fluorescent fractions were filtered (removal of more DMEU polymer colloids), combined,

and evaporated. The residue was dried under high vacuum: **20m** (0.65 g, 36%). (Note: we recommend the *GP 2* instead of the one described). Bright brown, microscopically small needles. M.p. 254° (dec.). IR: 3461*m*, 3370*m*, 3288*w*, 3198*w*, 3116*w*, 1623*s*, 1579*s*, 1518*m*, 1507*w*, 1477*s*, 1458*s*, 1425*m*, 1354*m*, 1296*m*, 1179*m*, 1149*m*, 1072*m*, 1027*w*, 920*w*, 832*m*, 776*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.8 (*s*, NH); 8.40 (*s*, H–C(2)); 8.11 ('*t*', *J* = 2.0, H–C(2″)); 7.72 (*ddd*, *J* = 8.2, 2.2, 0.9, 1 H); 7.50 (*d*, *J* = 8.6, 2 H); 7.37 ('*t*', *J* = 8.1, H–C(5″)); 7.16 (*s*, H–C(5)); 7.08 (*ddd*, *J* = 7.9, 2.0, 0.9, 1 H); 6.67 (*d*, *J* = 8.8, 2 H); 5.64 (*s*, NH_2). EI-MS: 336 (100, M^+), 280 (9), 246 (12), 167.5 (6), 155 (8), 150.5 (7), 120 (6), 92 (5). HR-MS: 336.0782 ($C_{18}H_{13}ClN_4O^+$; calc. 336.0778). Anal. calc. for $C_{18}H_{13}ClN_4O$ (336.78): C 64.20, H 3.89, N 16.64, O 4.75; found: C 63.78, H 4.17, N 16.46, O 5.12.

6-(3-Aminophenyl)-N-*(3-chlorophenyl)furo[2,3*-d*]pyrimidin-4-amine* (**20n**). According to *GP 2*, with **19n** (0.81 g, 2.7 mmol), THF (120 ml), and DMEU (8 ml). The residue on the *Celite* was washed with acetone and H_2O. Workup: The combined filtrates were evaporated (682 mg), the residue heated in EtOH, and the mixture filtered with suction while still hot. From this filtrate, **20n** (0.07 g, 8%) precipitated as amorphous, pale yellow solid (m.p. 244–245°). When H_2O was added at the boiling point of the mother liquor, further **20n** (373 mg, 41%) crystallized as pale yellow, cotton-wool-like solid. IR: 3318*w*, 3201*w*, 3117*w*, 1618*s*, 1605*s*, 1582*s*, 1570*s*, 1512*m*, 1474*s*, 1424*m*, 1356*m*, 1305*m*, 1242*m*, 1150*w*, 1070*w*, 940*w*, 772*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.90 (*s*, NH); 8.47 (*s*, H–C(2)); 8.12 ('*t*', *J* = 2.0, H–C(2′)); 7.73–7.71 (*m*, 1 H); 7.42 (*s*, H–C(5)); 7.39 ('*t*', *J* = 8.1, 1 H); 7.15 ('*t*', *J* = 7.8, 1 H); 7.12–7.09 (*m*, 1 H); 7.05 ('*t*', *J* = 1.8, 1 H); 6.96 (*d*, *J* = 8.1, 1 H); 6.93–6.60 (*m*, 1 H); 5.35 (*s*, NH_2). ^{13}C-NMR (101 MHz, $(CD_3)_2SO$): 166.8; 154.9; 153.8; 153.4; 150.2; 142.0; 133.9; 131.2; 130.7; 130.2; 123.2; 120.4; 119.4; 115.8; 112.8; 110.2; 105.4; 98.8. EI-MS: 335 (100, M^+), 167.5 (10), 150.5 (11), 92 (6). Anal. calc. for $C_{18}H_{13}ClN_4O$ (366.78): C 64.20, H 3.89, N 16.64, O 4.75; found: C 63.80, H 4.07, N 16.38, O 5.18.

5-{[6-(4-Aminophenyl)furo[2,3-d*]pyrimidin-4-yl]amino}-2-methoxyphenol* (**20o**). According to *GP 2*, with **19o** (1.8 g, 4.8 mmol), THF (50 ml), Et_3N (5 ml; added to neutralize traces of AcOH stemming from recrystallization of the starting material), and DMEU (2 ml). The residue on the *Celite* was washed with acetone and H_2O. Workup: The combined filtrates were evaporated, and the crude product was precipitated with H_2O. The precipitate was dried under high vacuum and partly purified by FC (SiO_2, acetone; due to its poor solubility, the crude product (1.33 g) was put onto the column as a solid and then dissolved *in situ* by adding DMSO (100 ml)): **20o** (0.9 g, 54%). Fluorescent, bright brown, amorphous solid. M.p. 261–263°. IR: 3406*w*, 3329*w*, 3275*w*, 3186*w*, 3118*w*, 2835*w*, 1618*s*, 1594*s*, 1506*s*, 1474*s*, 1354*m*, 1288*m*, 1264*m*, 1214*m*, 1170*m*, 1137*w*, 1071*w*, 1030*w*, 923*w*, 849*w*, 778*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.4, 9.1 (2*s*, NH, OH); 8.28 (*s*, H–C(2′)); 7.47 (*d*, *J* = 8.7, H–C(2″)); 7.31 (*d*, *J* = 2.5, H–C(6)); 7.13 (*dd*, *J* = 8.7, 2.5, H–C(4)); 7.05 (br. *s*, H–C(5′)); 6.91 (*d*, *J* = 8.8, H–C(3)); 6.67 (*d*, *J* = 8.6, H–C(3″)); 5.59 (*s*, NH_2); 3.76 (*s*, Me). EI-MS: 348 (100, M^+), 333 (50), 305 (12), 174 (5), 155 (9). HR-MS: 348.1235 ($C_{19}H_{16}N_4O_3^+$; calc. 348.1222).

6-(3-Aminophenyl)-N-*[(1*R*)-1-phenylethyl]furo[2,3*-d*]pyrimidin-4-amine* (**20p**). According to *GP 2*, with **19p** (1.47 g, 4.1 mmol) and THF (50 ml). Workup: The filtrate was evaporated, the residue taken up in ^{t}BuOMe (note: better to use CH_2Cl_2 instead) and extracted with H_2O, the org. phase dried ($MgSO_4$) and evaporated, and the residue dried under high vacuum. The crude product (1.33 g; bright yellow foam) thus obtained was taken up in CH_2Cl_2 and extracted with 18% HCl soln. The aq. phase was neutralized with sat. $NaHCO_3$ soln. and washed with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$) and evaporated: **20p** (1.14 g, 84%). Bright yellow foam. M.p. > 64°. IR: 3340*m* (br.), 3028*w*, 2972*w*, 1600*s*, 1570*m*, 1491*m*, 1466*m*, 1352*m*, 1303*m*, 1228*w*, 1141*m*, 941*w*, 776*m*, 700*m*, 551*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 8.30 (*d*, *J* = 8.0, NH); 8.20 (*s*, H–C(2)); 7.44 (*d*, *J* = 7.5, H–C(2″), H–(6″)); 7.38 (*s*, H–C(5)); 7.35–7.31 (*m*, H–C(3″), H–C(5″)); 7.23 (*tt*, *J* = 7.3, 1.2, H–C(4″)); 7.15 ('*t*', *J* = 7.8, H–C(5′)); 6.94 (*ddd*, *J* = 7.6, 1.6, 1.0, H–C(6′) or H–C(4′)); 6.61 (*ddd*, *J* = 8.0, 2.2, 0.9, H–C(4′) or H–C(6′)); 5.49–5.46 ('*quint.*', *J* = 7.0, MeC*H*N); 5.36 (*s*, NH_2); 1.56 (*d*, *J* = 7.0, *Me*CHN). ^{13}C-NMR (126 MHz, $(CD_3)_2SO$; assignments from HETCOR and APT): 165.6; 156.1; 153.4 (C(2)); 151.2; 149.3; 144.8; 129.68; 129.67 (C(5′)); 128.3 (C(3″)); 126.7 (C(4″)); 126.0 (C(2″)); 114.4, 111.7 (C(4′), C(6′)); 109.1 (C(2′)); 102.6; 98.2 (C(5)); 49.2 (CH); 26.8 (Me). EI-MS: 330 (100, M^+), 315 (44), 226 (69), 199 (13), 155 (10), 120 (39), 105 (61), 77 (13). HR-MS: 330.1479 ($C_{20}H_{18}N_4O^+$; calc. 330.1481).

5-{[6-(3-Aminophenyl)furo[2,3-d*]pyrimidin-4-yl]amino}-2-methylphenol* (**20q**). According to *GP 2*, with **19q** (606 mg, 1.67 mmol), THF (90 ml), and DMEU (10 ml). Workup: After most of the solvent was removed, the filtrate was brought to precipitation by adding H_2O. The off-white precipitate was washed with H_2O and dried under high vacuum: **20q** (431 mg, 78%). Microscopically small crystals. M.p. 233–234°. IR: 3361*m*, 3187*m*, 3027*m*, 1591*vs*, 1550*vs*, 1458*s*, 1437*s*, 1408*s*, 1320*m*, 1285*m*, 1244*w*, 1176*m*, 1119*w*, 1101*w*, 944*w*, 772*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.57, 9.33 (2*s*, OH, NH); 8.36 (*s*, H–C(2′)); 7.37 (*s*, 1 H); 7.36 (*d*, *J* = 2.0, H–C(6)); 7.14 ('*t*', *J* = 7.8, H–C(5″)); 7.10 (*dd*, *J* = 8.1, 2.0, H–C(4)); 7.02–7.00 (*m*, 2 H); 6.94–6.92 (*m*, 1 H); 6.60 (*ddd*, *J* = 8.1, 2.3, 0.8, 1 H); 5.34 (*s*, NH_2); 2.09 (*s*, Me). EI-MS: 332 (100, M^+), 276 (5), 199 (9), 165.5 (6), 158.5 (12), 155 (5), 77 (5). HR-MS: 332.1268 (calc. 332.1273).

*2-{[6-(3-Aminophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino}-4-chlorophenol* (**20r**). According to *GP 2*, with **19r** (1.81 g, 4.7 mmol), THF (150 ml), DMEU (20 ml), and $^{i}Pr_2NH$ (6 ml; added to neutralize potential traces of acid stemming from previous recrystallization). Workup: The dark green filtrate was concentrated and brought to precipitation by adding H_2O. The bright brown, grayish residue was dried under high vacuum: **20r** (1.23 g, 74%). Recrystallization from EtOH gave brown-violet prisms in low yield. M.p. *ca.* 240°. IR: 3399*m*, 2968*w*, 2698*w*, 1612*vs*, 1580*vs*, 1522*s*, 1490*m*, 1461*m*, 1426*s*, 1359*m*, 1302*w*, 1265*m*, 1242*w*, 1194*w*, 1073*w*, 760*m*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$; assigned by COSY, HETCOR, and long-range HETCOR): 10.20, 9.17(2*s*, OH, NH); 8.37 (*s*, H–C(2′)); 7.86 (*d*, *J* = 2.5, H–C(3)); 7.39 (*s*, H–C(5′)); 7.15 (‘*t*’, *J* = 7.8, H–C(5″)); 7.08 (*dd*, *J* = 8.6, 2.6, H–C(5)); 7.04 (‘*t*’, *J* = 1.9, H–C(2″)); 6.96 (*m*, H–C(6), H–C(6″)); 6.61 (*dd*, *J* = 8.0, 2.0, H–C(4″)); 5.37 (*s*, NH_2). ^{13}C-NMR (126 MHz, $(CD_3)_2SO$; assigned by COSY, HETCOR, and long-range HETCOR): 166.0 (C(7′a)); 154.9 (C(4′a)); 153.0 (C(2′)); 152.1 (C(6′)); 149.3 (C(3″) or C(1″)); 149.0 (C(1)); 129.7 (C(5″)); 129.4 (C(1″) or C(3″)); 127.5 (C(2)); 124.8 (C(5)); 124.4 (C(3)); 122.0 (C(4)); 116.9 (C(6)); 114.7 (C(4″)); 111.9 (C(6″)); 109.2 (C(2″)); 103.9 (C(4′)); 98.2 (C(5′)). EI-MS: 352 (100, M^+), 335 (37), 325 (100), 318 (32), 291 (32), 280 (11), 205 (17), 171 (10), 167.5 (13), 155 (15), 120 (10), 92 (14), 65 (10). HR-MS: 352.0733 ($C_{18}H_{13}ClN_4O_2^+$; calc. 352.0727).

N-*(3-Aminophenyl)-6-(4-aminophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**20s**). According to *GP 2*, with **19s** (2.4 g, 6.4 mmol), THF (120 ml), and DMEU (40 ml) for 5 d (every 24 h, further *Raney*-Ni was added). Workup: The filtrate was concentrated and brought to precipitation by adding H_2O. The residue was dried under high vacuum (1.2 g) and suspended in conc. HCl soln. (immediate, intense violet color followed by slow discoloring). To the suspension, H_2O (150–200 ml) was added (pH 1) and then EtOH (150 ml). This mixture was refluxed for several hours and filtered hot with suction. The filtrate was basified with sat. Na_2CO_3 soln. After removal of the EtOH, the suspension (r.t.) was filtered with suction. The beige, amorphous residue was dried under high vacuum: **20s** (0.72 g, 35%). M.p. 225–230°. IR: 3377*m*, 3217*w*, 3034*w*, 1622*s*, 1581*s*, 1523*m*, 1505*s*, 1460*s*, 1401*w*, 1358*m*, 1318*w*, 1287*m*, 1192*w*, 1164*w*, 1073*w*, 1029*w*, 922*w*, 875*w*, 836*w*, 770*m*, 684*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.39 (*s*, NH); 8.31 (*s*, H–C(2)); 7.48 (*d*, *J* = 8.7, H–C(2″)); 7.12 (*s*, H–C(5)); 7.07–7.06 (*m*, H–C(2′)); 6.99 (*t*, *J* = 7.8, H–C(5′)); 6.94–6.91 (*m*, 1 H); 6.67 (*d*, *J* = 8.7, H–C(3″)); 6.33–6.29 (*m*, 1 H); 5.60, 5.10 (*s*, NH_2). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 166.5; 155.0; 153.5; 152.8; 150.8; 149.9; 141.0; 129.7; 126.6; 117.2; 114.8; 110.1; 109.7; 107.3; 105.1; 95.3. EI-MS: 317 (100, M^+), 261 (11), 199 (4), 158 (4), 131 (5), 120 (4), 92 (7), 65 (5). HR-MS: 317.1270 ($C_{18}H_{15}N_5O^+$; calc. 317.1277).

*5-{6-(4-Aminophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino}-2-methylphenol* (**20t**). According to *GP 2*, with **19t** (2.46 g, 6.8 mmol) and THF (180 ml). Workup: To the filtrate, H_2O was added and the forming precipitate was collected. The residue was dried under high vacuum: **20t** (2.11 g, 94%). Off-white, amorphous solid. M.p.: transformation to needles and prisms at *ca.* 265° that decomposed from *ca.* 280° and melted at *ca.* 290° (dec.). IR: 3457*w*, 3389*s*, 3376*s*, 3232*m*, 1616*vs*, 1592*vs*, 1522*s*, 1505*s*, 1470*s*, 1419*s*, 1359*s*, 1299*m*, 1267*m*, 1173*s*, 1123*m*, 1072*w*, 1026*w*, 997*w*, 922*m*, 830*w*, 776*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.48, 9.35 (2*s*, NH, OH); 8.33 (*s*, H–C(2′)); 7.51 (*d*, *J* = 8.5, H–C(2″)); 7.40 (*d*, *J* = 1.7, H–C(6)); 7.15–7.11 (*m*, H–C(3), H–C(5′)); 7.03 (*d*, *J* = 8.2, H–C(4)); 6.70 (*d*, *J* = 8.5, H–C(3″)); 5.62 (*s*, NH_2); 2.12 (*s*, Me). EI-MS: 332 (100, M^+), 276 (7), 262 (7), 199 (9), 158.5 (10), 155 (6), 42 (7). Anal. calc. for $C_{19}H_{16}N_4O_2$ (332.36): C 68.66, H 4.85, N 16.86, O 9.63; found: C 68.53, H 5.09, N 16.55, O 9.90.

*6-(3-Aminophenyl)-*N*-(3,5-dichlorophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**20u**). According to *GP 2*, with **19u** (0.49 g, 1.2 mmol), THF (170 ml), and DMEU (12 ml). Workup: After evaporation of the filtrate, the residue (446 mg) was heated in EtOH and filtered hot with suction (residue discarded). Upon cooling, this filtrate was again filtered several times (residues discarded) and then evaporated. FC (SiO_2, pentane/AcOEt 4:1 → 2:3) of the residue (440 mg) yielded 322 mg that were dissolved in 1,2-dichloroethane/MeOH/H_2O (heating) and filtered cold (residue discarded). H_2O (300 ml) was added to the filtrate, which was then stored openly for a few days. Filtration with suction and washing of the resulting residue with EtOH gave **20u** (48 mg, 11%) as a bright beige, amorphous solid (m.p. 120–125°). The H_2O/EtOH filtrate was filtered the next day, yielding another 118 mg (26%) of **20u** of acceptable purity (beige, pale gray, amorphous solid; m.p. 135–137°). IR: 3386*w*, 3303*w*, 3201*w*, 3117*w*, 1629*s*, 1609*s*, 1579*vs*, 1460*s*, 1409*m*, 1354*m*, 1152*w*, 1115*w*, 1082*m*, 941*w*, 928*w*, 863*w*, 838*w*, 777*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 10.03 (*s*, NH); 8.53 (*s*, H–C(2)); 8.00 (*d*, *J* = 2.0, H–C(2″), H–C(6″)); 7.40 (*s*, H–C(5)); 7.25 (*t*, *J* = 1.9, H–C(4″)); 7.16 (‘*t*’, *J* = 7.8, H–C(5′)); 7.06 (‘*t*’, *J* = 1.9, H–C(2″)); 6.99–6.96 (*m*, 1 H); 6.26 (*ddd*, *J* = 8.0, 2.3, 0.9, 1 H); 5.38 (*s*, NH_2). EI-MS: 370 (100, M^+), 184.5 (11), 92 (10). HR-MS: 370.0392 ($C_{18}H_{12}Cl_2N_4O^+$; calc. 370.0388).

*6-(3-Aminophenyl)-*N*-(3-nitrophenyl)furo[2,3-*d*]pyrimidin-4-amine* (**20v**). According to *GP 2*, with **19v** (1.2 g, 3.2 mmol), THF (170 ml), and DMEU (20 ml). Workup: The filtrate was concentrated and brought to precipitation by adding a considerable amount of H_2O. The precipitate was dried under high vacuum (852 mg)

and submitted to FC (SiO_2, AcOEt/^{t}BuOMe 1:1): **20v** (57 mg, 5%). Orange powder. M.p. > 250°. IR: 3462*w*, 3388*m*, 3329*m*, 3221*m*, 3114*w*, 2923*m*, 2853*w*, 1618*s*, 1586*vs*, 1522*vs*, 1487*s*, 1461*s*, 1396*m*, 1353*s*, 1248*m*, 1079*m*, 782*m*, 733*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 10.21 (*s*, NH); 8.89 ('*t*', *J* = 2.3, 1 H); 8.52 (*s*, H–C(2)); 8.29 (*ddd*, *J* = 8.2, 2.1, 0.9, 1 H); 7.90 (*ddd*, *J* = 8.2, 2.3, 0.9, 1 H); 7.67 ('*t*', *J* = 8.2, 1 H); 7.45 (*s*, H–C(5)); 7.16 ('*t*', *J* = 7.8, 1 H); 7.06 ('*t*', *J* = 1.9, 1 H); 6.98 (*ddd*, *J* = 7.6, 1.8, 1.0, 1 H); 6.62 (*ddd*, *J* = 8.1, 2.3, 1.0, 1 H); 5.37 (*s*, NH_2). EI-MS: 347 (100, M^+), 331 (12), 317 (20), 299 (15), 155 (14). HR-MS: 347.1023 ($C_{18}H_{13}N_5O_3^+$; calc. 347.1018).

Biological Tests. The baculovirus donor vector pfbgx3IGFlRcd was used to generate a recombinant baculovirus that expresses the amino acid region amino acids 670–1210 of the intra-cytoplasmic kinase domains of human HER-1 (EGFR). The HER-1 cDNA fragment was kindly provided by Dr. *N. Hynes*, *FMI*, Basel, Switzerland. The amplified DNA fragments were fused to GST by cloning them into FBG1 as BamHI-EcoRI insertions to yield FBG1-HER-1.

Cell extracts were prepared and loaded onto a glutathione-sepharose (*Pharmacia*) column. After washing, the GST-tagged proteins were then eluted with a glutathione-containing buffer. Purified protein was stored at −70° in elution buffer.

KDR Kinase domains were provided by the lab of Dr. *D. Marmé* (*Tumorbiologiezentrum*, Freiburg, Germany). The glutathione S-transferase (GST) gene from the pAcG1 vector (*Pharmingen*) was excised with EcoRV and EcoRI and inserted into the cloning site of the Fast-Bac baculoviral vector (*GIBCO*) creating a 5530 bp vector with N-terminal cloning sites derived from the pAcG1 fusion vector (FBG0). The C-terminal cloning site may be any cloning site (from the Fast-Bac vector) downstream of the N-terminal cloning site used.

Viruses for each of the kinases were made according to the protocol supplied by *GIBCO*. In brief, transfer vectors containing the kinase domains were transfected into the DH10Bac cell line (*GIBCO*), plated on agar plates containing the recommended concentrations of Blue-Gal, IPTG, kanamycin, tetracycline, and gentamycin. Colonies without insertion of the fusion sequence into the viral genome (carried by the bacteria) are blue. A single white colony was usually picked and viral DNA (bacmid) isolated from the bacteria by standard plasmid mini prep procedures. Sf 9 cells or High Five cells (*GIBCO*) were then transfected in 25-cm^2 flasks with the viral DNA using the cellfectin reagent and protocol supplied with the Bac-to-Bac kit (*GIBCO*). Virus-containing media was collected from the transfected cell culture and used for infection to increase its titer. Virus-containing media obtained after two rounds of infection was used for large-scale protein expression. For large-scale protein expression, 100-cm^2 round tissue culture plates were seeded with 5×10^7 cells/plate and infected with 1 ml of virus-containing media (about 5 MOIs). After 3 days, the cells were scraped off the plates and centrifuged at 500 r.p.m. for 5 min.

Cell pellets from 10–20 100-cm^2 plates were resuspended in 50 ml of ice-cold lysis buffer (25 mM *Tris*·HCl (pH 7.5), 2 mM EDTA, 1% NP-40, 1 mM DTT, 1 mM PMSF). The cells were stirred on ice for 15 min and then centrifuged at 5000 r.p.m. for 20 min. The supernatant was loaded onto a 2-ml glutathione-sepharose column and washed three times with 10 ml of 25 mM *Tris*·HCl (pH 7.5), 2 mM EDTA, 1 mM DTT, and 200 mM NaCl. The GST-tagged proteins were then eluted by 10 applications (1 ml each) of 25 mM *Tris*·HCl (pH 7.5), 10 mM reduced glutathione, 100 mM NaCl, 1 mM DTT, and 10% glycerol and stored at −70°.

The assays of KDR contained in a final volume of 30 µl 200–1800 ng of enzyme protein (depending on the specific activity), 20 mM *Tris*·HCl (pH 7.6), 3 mM $MnCl_2$, 3 mM $MgCl_2$, 1 mM DTT, 10 µM Na_3VO_4, 3 µg/ml of poly(Glu,Tyr) 4:1, and 8 µM ATP (γ-[^{33}P]-ATP 0.1 µCi). Assays with purified GST-HER-1 were carried out in a final volume of 30 µl containing 20 mM *Tris*·HCl (pH 7.6), 10 mM $MgCl_2$, 0.01 mM Na_3VO_4, 1% DMSO, 1 mM DTT, 3 µg/ml of poly(Glu,Tyr) 4:1, and 10 µM ATP (γ-[^{33}P]-ATP 0.1 µCi). The assay was performed in 96-well plates for 20 min at r.t. and then stopped by addition of 25 µl of 0.25M EDTA (pH 7.0). An aliquot of 40 µl was spotted with a multichannel dispenser on *Immobilon-P* membranes mounted in a *Millipore Microtiter* filter manifold connected to a low-vacuum source. After elimination of liquid, the membrane was transferred to a sequence of four washing baths containing 0.5% H_3PO_4 soln. and one with EtOH (shaking incubation for 10 min each), dried, and mounted onto a *Hewlett-Packard TopCount* manifold, 10 µl of *Microscint*® was added, and the sample was counted with a *TopCount NXT* counter (*Perkin-Elmer*). IC_{50} values were calculated by linear regression analysis of the percentage inhibition of each compound in duplicate, at four concentrations (usually, 0.01, 0.1, 1, and 10 µM).

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