# Structure-Based Design and Synthesis of the First Weak Non-Phosphate Inhibitors for IspF, an Enzyme in the Non-Mevalonate Pathway of Isoprenoid Biosynthesis

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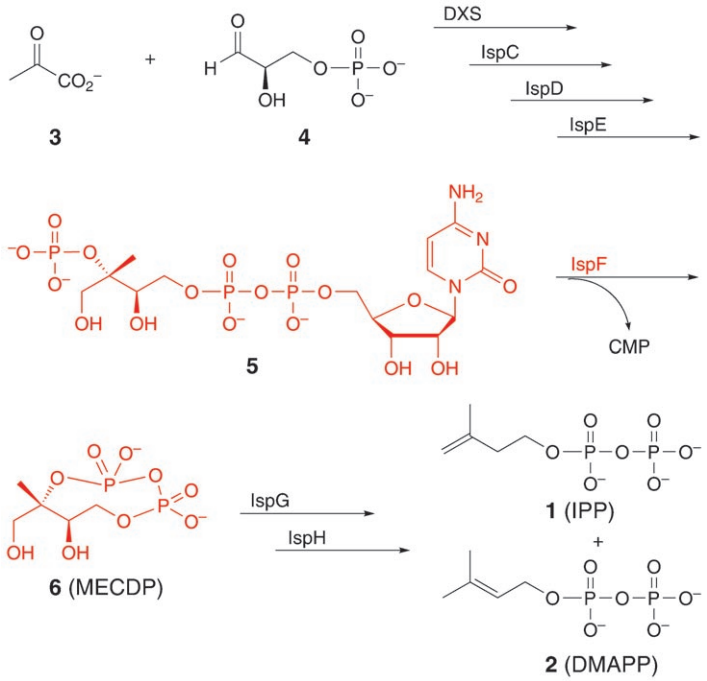
In this paper, we describe the structure-based design, synthesis, and biological evaluation of cytosine derivatives and analogues that inhibit IspF, an enzyme in the non-mevalonate pathway of isoprenoid biosynthesis. This pathway is responsible for the biosynthesis of the $C_5$ precursors to isoprenoids, isopentenyl diphosphate (IPP, **1**) and dimethylallyl diphosphate (DMAPP, **2**; *Scheme 1*). The non-mevalonate pathway is the sole source for **1** and **2** in the protozoan *Plasmodium* parasites. Since mammals exclusively utilize the alternative mevalonate pathway, the enzymes of the non-mevalonate pathway have been identified as attractive new drug targets in the fight against malaria. Based on computer modeling (*cf. Figs. 2* and *3*), new cytosine derivatives and analogues (*Fig. 1*) were selected as potential drug-like inhibitors of IspF protein, and synthesized (*Schemes 2–5*). Determination of the enzyme activity by $^{13}$C-NMR spectroscopy in the presence of the new ligands showed inhibitory activities for some of the prepared cytosine and pyridine-2,5-diamine derivatives in the upper micromolar range ($IC_{50}$ values; *Table*). The data suggest that it is possible to inhibit IspF protein without binding to the polar diphosphate binding site and the side chain of Asp56′, which interacts with the ribose moiety of the substrate and substrate analogues. Furthermore, a new spacious sub-pocket was discovered which accommodates aromatic spacers between cytosine derivatives or analogues (binding to 'Pocket III') and rings that occupy the flexible hydrophobic region of 'Pocket II'. The proposed binding mode remains to be further validated by X-ray crystallography.

**1. Introduction.** – Caused by the protozoan *Plasmodium* parasites, malaria is one of the most important tropical diseases, infecting 300–500 million and killing 1–3 million people annually [1]. To combat the rapidly growing resistance of the *Plasmodium* parasites against currently available antimalarial agents, there is ongoing search for new drugs with a novel mode of action.

In the early 1990s, the non-mevalonate pathway for the biosynthesis of the $C_5$ precursors to isoprenoids, isopentenyl diphosphate (IPP; **1**) and dimethylallyl diphosphate (DMAPP; **2**), was discovered [2]. The non-mevalonate pathway starts with the condensation of pyruvate (**3**) and glyceraldehyde 3-phosphate (**4**). The

cyclization of 4-(diphosphocytidyl)-2*C*-methyl-D-erythritol 2-phosphate (**5**) to the cyclic diphosphate intermediate 2*C*-methyl-D-erythritol 2,4-cyclodiphosphate (MECDP; **6**) is catalyzed by the fifth enzyme in the pathway, IspF (=2*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase; EC 4.6.1.12; *Scheme 1*) [3].

Scheme 1. *Biosynthesis of the $C_5$ Precursors to Terpenes IPP* (**1**) *and DMAPP* (**2**), via *the Non-Mevalonate Pathway*[a])




[a]) DXS = 1-Deoxy-D-xylulose-5-phosphate synthase; CMP = cytosine 5′-monophosphate; MECDP = 2*C*-methyl-D-erythritol 2,4-cyclodiphosphate; IPP = isopentenyl diphosphate; DMAPP = dimethylallyl diphosphate.

While mammals use the mevalonate pathway for the biosynthesis of IPP (**1**) and DMAPP (**2**), many pathogenic bacteria, such as *Myobacterium tuberculosis*, as well as the protozoan *Plasmodium* parasites, exclusively use the non-mevalonate pathway. The antibiotic *Fosmidomycin* has recently been shown to be an efficient inhibitor of IspC (=1-deoxy-D-xylulose 5-phosphate reductoisomerase = 2*C*-methylerythritol-4-phosphate synthase; EC 1.1.1.267), the second enzyme in the non-mevalonate pathway, and has been submitted to clinical tests [4a–c]. Because of the discovery of the potent antimalarial activity of *Fosmidomycin*, the absence of the enzymes in humans, and the general fact that isoprenoids are essential for protozoa, the enzymes of the non-mevalonate pathway have been validated as attractive new drug targets [4].

Since these enzymes process phosphate- and diphosphate-based substrates, their active sites are highly polar. They feature only limited hydrophobic surfaces, so that the development of low-molecular-weight inhibitors appears quite challenging. Most of the

few inhibitors known to date, such as *Fosmidomycin*, indeed are phosphates or phosphonates [5][6].

Here, we describe the structure-based design, synthesis, and *in vitro* evaluation of cytosine derivatives and analogues **7**–**21** (*Fig. 1*), targeting the inhibition of IspF protein (for an illustration of our structure-based design approach for the development of new antimalarials, see [7]). We show how modeling-based variation of the spacer between cytosine or its replacements, and terminal aromatic rings led from inactive to the first weakly active non-phosphate inhibitors of IspF, exhibiting $IC_{50}$ values (concentration of inhibitor at which 50% maximal initial velocity is observed) in the upper micromolar range, *i.e.*, featuring higher affinities than previously described diphosphate-based ligands [6].

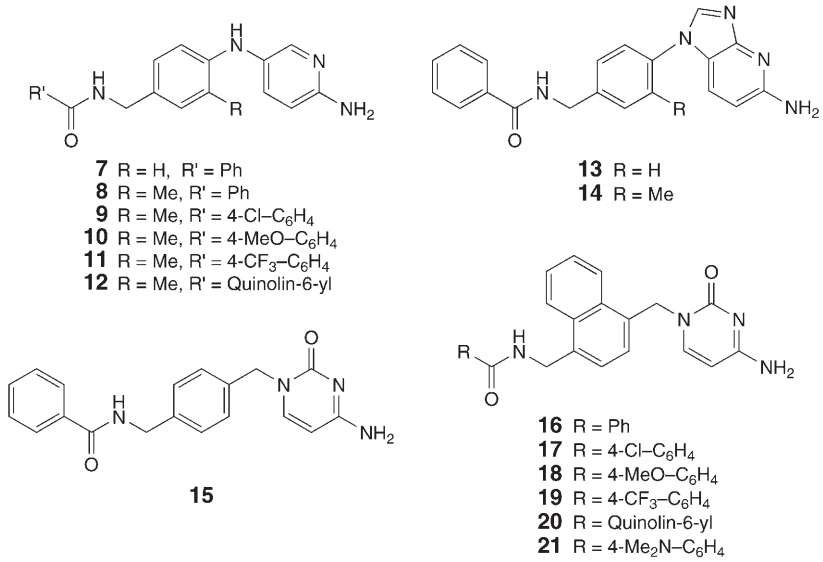



Fig. 1. *Cytosine derivatives and analogues prepared as potential inhibitors of IspF*

**2. Results and Discussion.** – 2.1. *Ligand Design*. Several X-ray crystal structures of IspF have been solved [6][8]. They show oligomeric IspF in most cases as a $C_3$-symmetric homotrimer, with active sites located at the interface of adjacent subunits. Each of the topologically equivalent active sites possesses two pockets. The rigid, well-conserved 'Pocket III' of one monomer binds the cytidine moiety of substrate **5**. The larger, more flexible 'Pocket II' in an adjacent monomer hosts the phosphate and erythritol moieties (for the protein residues lining these pockets, see *Figs. 2* and *3*,*a*). Additionally, 'Pocket II' also contains one or two divalent metal ions ($Mg^{2+}$ or $Mn^{2+}$, and $Zn^{2+}$) which participate in the binding of the diphosphate moiety of **5** as well as in catalysis.

Recently, we described the synthesis and biological activity of the first inhibitors for IspF [6]. These compounds closely resembled substrate **5**, featuring a cytosine diphosphate moiety attached to a fluorescent anthranilate (=2-aminobenzoate) or

dansylamide (= 5-(dimethylamino)naphthalene-1-sulfamoyl) residue to reach into the hydrophobic region of 'Pocket II'. These compounds were developed as fluorescent probes for assay development, and their binding mode was elucidated by X-ray crystal-structure analysis. To obtain more drug-like molecules, the new cytosine analogues and derivatives shown in *Fig. 1* were designed using the molecular modeling software MOLOC [9]. This new approach was based on two published X-ray crystal structures, one of IspF in complex with cytidine 5′-diphosphate (CDP), and $Zn^{2+}$ and $Mn^{2+}$ ions (Protein Data Bank (PDB) code: 1GX1 [8a]) and the other in complex with cytidine 5′-monophosphate (CMP), MECDP (**6**), and a $Zn^{2+}$ ion (PDB code: 1JY8 [8b]). Compared to the first-generation inhibitors, major structural changes were planned: *i*) modification of the cytosine nucleobase, *ii*) by-passing the ribose pocket lined with Asp56′ (see below), and *iii*) by-passing the highly polar phosphate binding site with the metal ion centers. In the modeling, the coordinates of the enzyme, as seen in the X-ray crystal structures, were left unchanged, while geometry and energy of the docked-in ligand were minimized.

Whereas a rich variety of adenine substitutes has been developed as part of the intense ongoing search for selective kinase inhibitors [10], cytosine analogues are much less known [11]. In our case, we chose 2,5-diaminopyridine and 5-amino-1*H*-imidazo[4,5-*b*]pyridine scaffolds as substitutes for cytosine.

The nucleobase in CMP bound to 'Pocket III' forms four H-bonds with the protein backbone, specifically with Leu106 (O···N 2.9 Å), Met105 (N···N 2.9 Å), Pro103 (N···O 3.1 Å), and Ala100 (N···O 3.0 Å) ( (PDB code: 1H48 [8g]; *Fig. 2*,*a*). In addition, the ribose moiety interacts with the side chain of Asp56′ (from the adjacent monomer). Replacing cytosine by the synthetically readily accessible 2,5-diaminopyridine moiety in **7**–**12** maintains three of the four H-bonds to the protein backbone (*Fig. 2*,*b*) while providing an exit vector to reach into the hydrophobic portion of 'Pocket II', by-passing both Asp56′ and the polar diphosphate binding site. A more complete, but synthetically more challenging cytosine substitute is the 5-amino-1*H*-imidazo[4,5-*b*]pyridine scaffold introduced into the potential ligands **13** and **14** (*Fig. 2*,*c*). While maintaining all four H-bonds to the protein backbone as seen for cytosine, this heterocycle also features an exit vector for reaching the hydrophobic portion of 'Pocket II', while avoiding the polar regions. Cytosine derivatives **15**–**21** should bind to 'Pocket III' in a similar fashion to CMP.

Examination of the active site of IspF protein by molecular modeling suggested that both cytosine and its substitutes bound to 'Pocket III' could be connected by relatively rigid linkers to the aromatic ring filling the hydrophobic portion of 'Pocket II', lined by Ala71′, Phe68′, Phe61′, and Leu76′, while by-passing both the polar ribose (Asp56′) and diphosphate binding sites. This is shown for ligand **11** in *Fig. 3*,*a*. In fact, all compounds depicted in *Fig. 1* could be docked in a similar fashion into the active site and energy-minimized, while avoiding any repulsive contacts with the enzyme. *Fig. 3*,*b* shows a superimposition of the proposed preferential binding mode for compounds **11** and **19**, which later were shown to be active inhibitors. It suggests that the site hosting the aromatic linker is quite large, allowing different, nearly orthogonal orientations of this ring.

2.2. *Ligand Synthesis.* – 2.2.1. *2,5-Diaminopyridine Derivatives.* The synthesis of **7** and **8** started from 4-nitrobenzyl alcohol (**22**) and 3-methyl-4-nitrobenzyl alcohol (**23**),

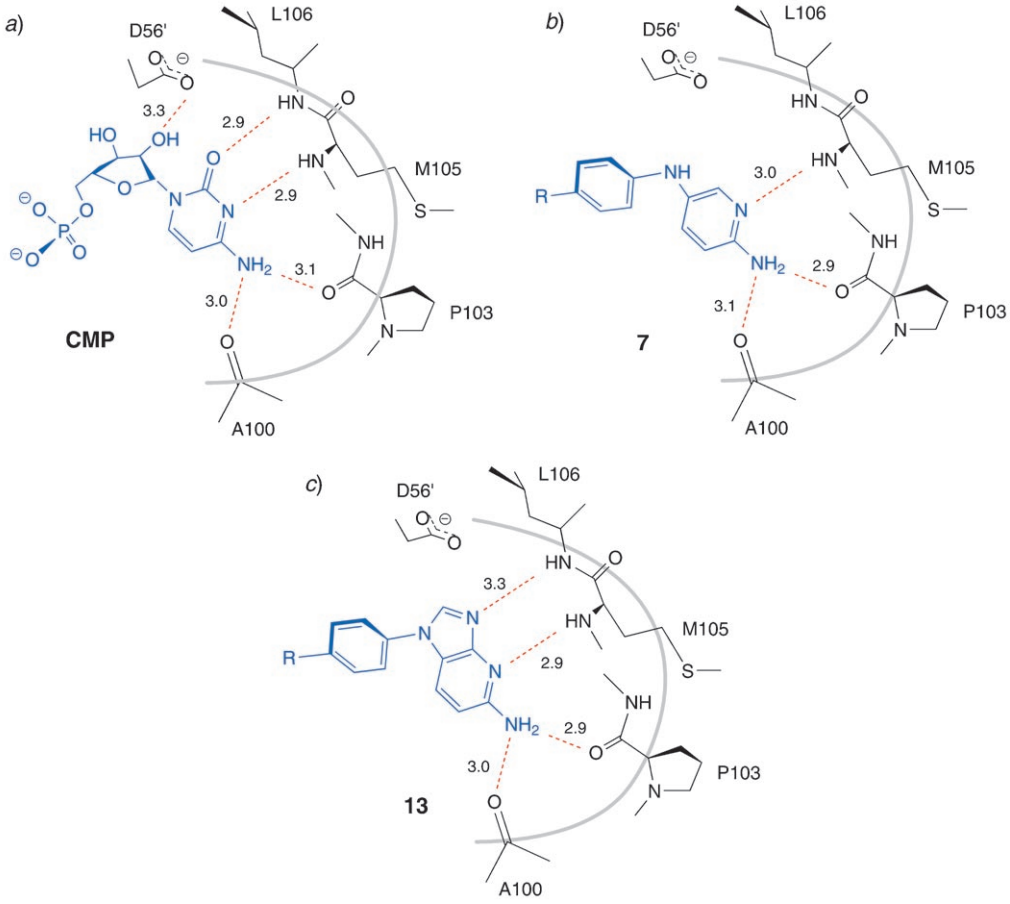



Fig. 2. *Schematic representation of CMP bound to 'Pocket III' of IspF* (*a*) (PDB code: 1H48 [8g]) *and proposed complexation of cytosine analogues* **7** (*b*) *and* **13** (*c*). Potential H-bonds are depicted in red.

respectively, which were converted into the corresponding phthalimides **24** and **25** *via* a *Mitsunobu* reaction (*Scheme 2*) [12]. Deprotection using $NH_2Me$ afforded the amines **26** and **27**, respectively. Amide coupling with PhCOOH, activated as the *N*-hydroxysuccinimide ester, provided the amides **28** and **29**, and Pd-catalyzed hydrogenation yielded amines **30** and **31**, respectively. *Buchwald–Hartwig* cross-coupling [13] with 5-bromo-2-nitropyridine, using $[Pd_2(dba)_3]$ as catalyst and (±)-BINAP as ligand, afforded **32** and **33**, which were converted into the desired target compounds **7** and **8**, respectively, by Pd-catalyzed hydrogenation. Methoxy derivative **10** was prepared in a similar fashion starting from 4-methoxybenzoic acid *via* **34** → **35** → **36** → **10**.

An alternative protocol to prepare the 2,5-diaminopyridine-based ligands is shown in *Scheme 3*. Alcohol **23** was silyl-protected (→ **37**) and then reduced to the aniline derivative **38**. *Buchwald–Hartwig* cross-coupling reaction with 5-bromo-2-nitropyr-

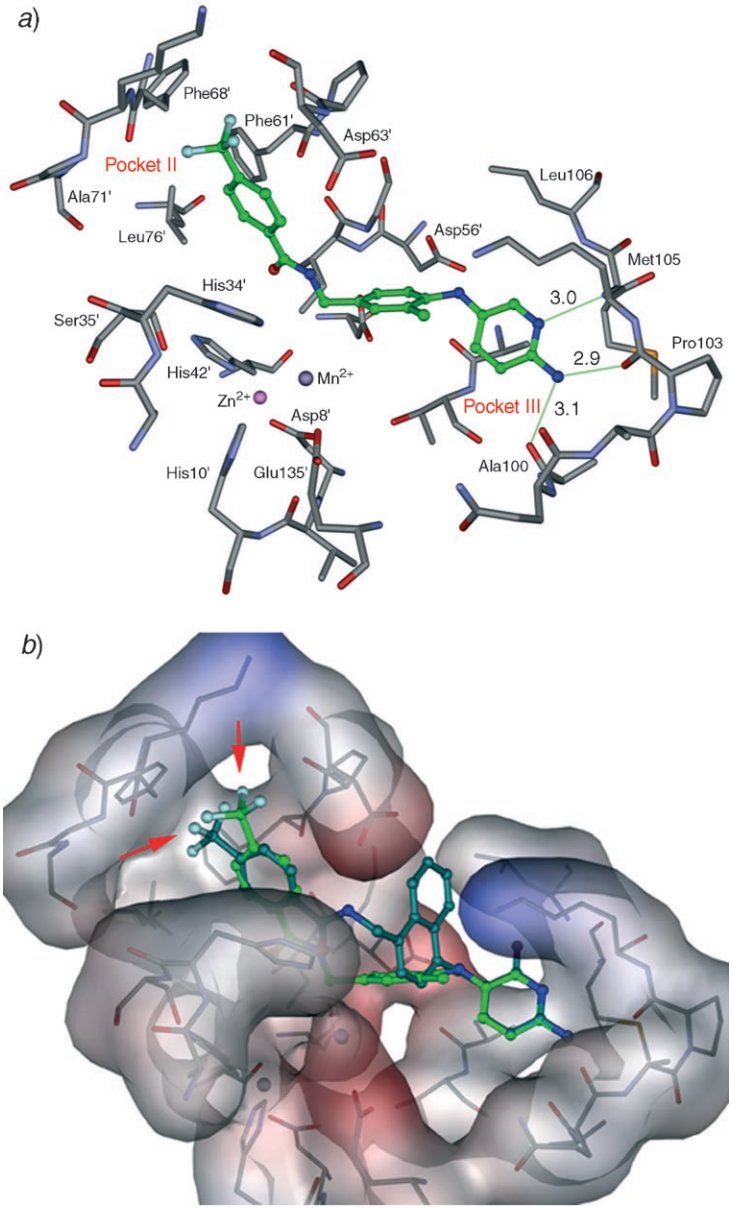
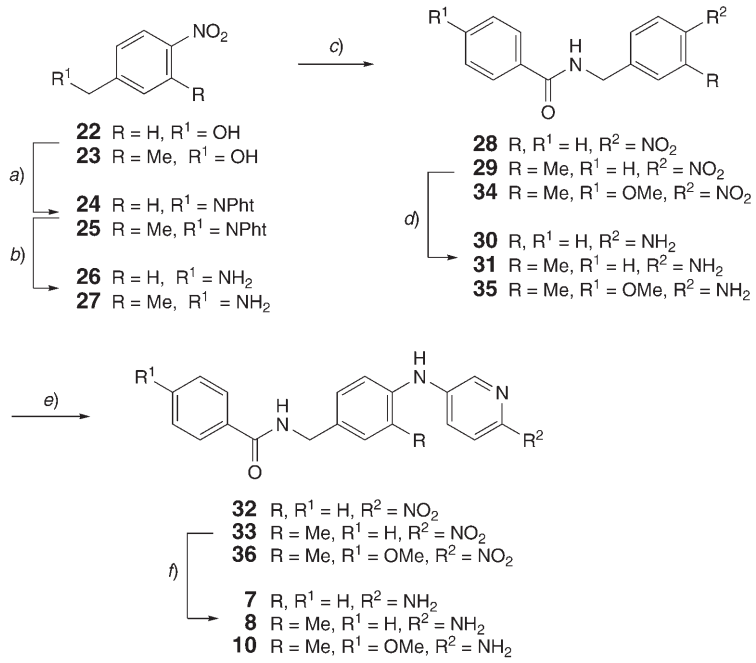



Fig. 3. a) *Computer model* (MOLOC) *of the proposed binding mode of* **11** *in the active site of IspF* (PDB code: 1GX1 [8a]). Potential H-bonds are depicted as thin green lines, and distances are given in Å. b) *Superimposition of the proposed binding modes for* **11** *and* **19**. Color code: C-skeleton of ligand **11**: *green*, C-skeleton of ligand **19**: dark *green*, C-skeleton of the protein: *grey*, N-atoms: *blue*, O-atoms: *red*, S-atoms: *yellow*.

Scheme 2. *Synthesis of the Pyridine-diamines* **7**, **8**, *and* **10**

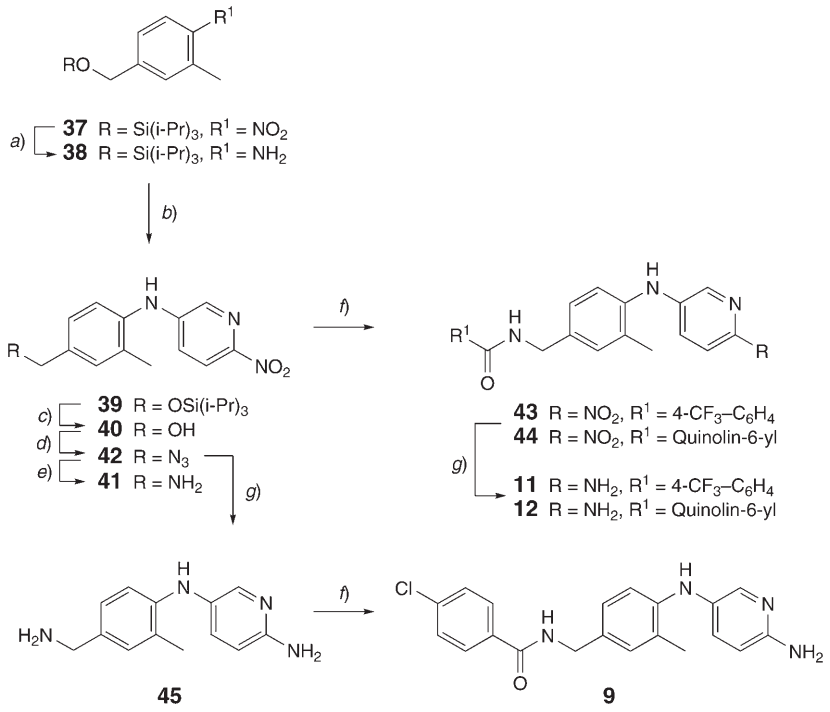



*a*) Phthalimide, $PPh_3$, DIAD, THF, 25°, 17 h; 88% (**24**); 99% (**25**). *b*) $NH_2Me$ (33% in EtOH), 25°, 20 h; quant. (**26**); 60% (**27**). *c*) 1. Benzoic acid or 4-methoxybenzoic acid, HO-Su, EDC·HCl, $CH_2Cl_2$, 25°, 2 h; 2. **26** or **27**, $Et_3N$, $CH_2Cl_2$, 25°, 20 h; 76% (**28**); 97% (**29**); 23% (**34**). *d*) Pd/C, $H_2$, MeOH/$CH_2Cl_2$, 25°, 3 h; 91% (**30**); 93% (**31**); 74% (**35**). *e*) 5-Bromo-2-nitropyridine, (±)-BINAP, $[Pd_2(dba)_3]$, $Cs_2CO_3$, DME, 110°, 20 h; 59% (**32**); 47% (**33**); 70% (**36**). *f*) Pd/C, $H_2$, MeOH/$CH_2Cl_2$, 25°, 3 h; 90% (**7**); 89% (**8**); 89% (**10**). DIAD = Diisopropyl azodicarboxylate; HO-Su = *N*-hydroxysuccinimide; NPht = *N*-phthalimido; EDC·HCl = (1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; dba = dibenzylideneacetone.

idine yielded **39**, which was deprotected to the alcohol **40**. Conversion of **40** into amine **41** was achieved *via* the azido derivative **42**. Amide couplings with the corresponding benzoic acids, activated as the *N*-hydroxysuccinimide esters, gave **43** and **44**, which were transformed by catalytic hydrogenation into the desired target molecules **11** and **12**, respectively. The potential ligand **9** was prepared by reducing both the $N_3$ and the $NO_2$ group in **42** to give **45**, followed by amide coupling. Performing the reduction of the $NO_2$ group by catalytic hydrogenation in the last step, as described for **11** and **12**, led to partial dechlorination under formation of an inseparable mixture.

2.2.2. *Imidazopyridine Derivatives.* The imidazopyridines **13** and **14** were synthesized starting from 2-amino-6-chloro-3-nitropyridine (**46**) (*Scheme 4*). Reduction of the $NO_2$ group afforded the corresponding diamine **47**. Cyclization with triethyl orthoformate yielded the chlorinated imidazopyridine **48**. A modified *Ullmann* coupling [14] with 4-iodobenzonitrile provided the desired compound **49** and by-product **50**. Similarly, **51** and **52** were obtained starting from 4-iodo-3-methylbenzoni-

Scheme 3. *Synthesis of the Pyridine-diamines* **9**, **11**, *and* **12**



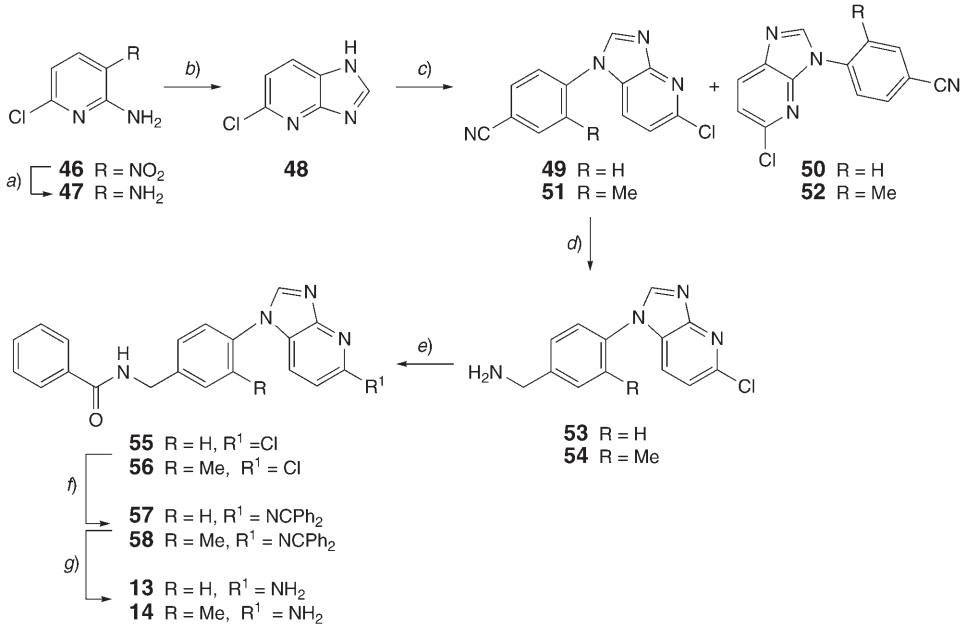

*a*) Pd/C, $H_2$, MeOH, 25°, 3 h; 55%. *b*) 5-Bromo-2-nitropyridine, (±)-BINAP, $[Pd_2(dba)_3]$, $Cs_2CO_3$, DME, 110°, 20 h; 39%. *c*) $Bu_4NF$, THF, 25°, 2 h; 88%. *d*) DPPA, DBU, THF, 0°, 2 h, 25°, 16 h; 98%. *e*) $PPh_3$, THF, $H_2O$, 25°, 20 h; 95%. *f*) 1. Benzoic acid derivative, HO-Su, EDC · HCl, $CH_2Cl_2$, 25°, 2 h; 2. **41** or **45**, $Et_3N$, $CH_2Cl_2$, 25°, 20 h; 61% (**43**); 34% (**44**); 47% (**9**). *g*) Pd/C, $H_2$, MeOH/$CH_2Cl_2$, 25°, 3 h; 82% (**45**); 78% (**11**); 72% (**12**). DME = 1,2-dimethoxyethane; DPPA = diphenylphosphoryl azide; DBU = 1,3-diazabicyclo[5.4.0]undecane.

trile. Reduction of the nitriles **49** and **51** to amines **53** and **54**, amide coupling to **55** and **56**, and *Buchwald–Hartwig* cross-coupling afforded imines **57** and **58**, respectively. Finally, cleavage of the imines under acidic conditions afforded the potential inhibitors **13** and **14**, respectively.

2.2.3. *Cytosine Derivatives.* The cytosine derivatives **16**–**21** were synthesized starting from naphthalene-1,4-dicarboxylic acid **59** (*Scheme 5*; the synthesis of cytosine derivative **15** (*cf Fig. 1*) is not described in this paper). Reduction afforded diol **60**, which, after mono-protection (→**61**), was transformed into bromide **62**, and reaction with Cbz-protected cytosine **63** provided **64**. Deprotection of the alcohol (→**65**), transformation *via* azido derivative **66** into amine **67**, and amide couplings yielded **68**–**73**. Finally, removal of the cytosine protecting group by catalytic hydrogenation afforded the desired inhibitors **16**–**21**.

2.3. *Biological Results.* The inhibitory affinity ($IC_{50}$ values) of the new potential ligands towards IspF protein was determined using a $^{13}$C-NMR assay [15]. This assay

Scheme 4. *Synthesis of the Imidazopyridines* **13** *and* **14**



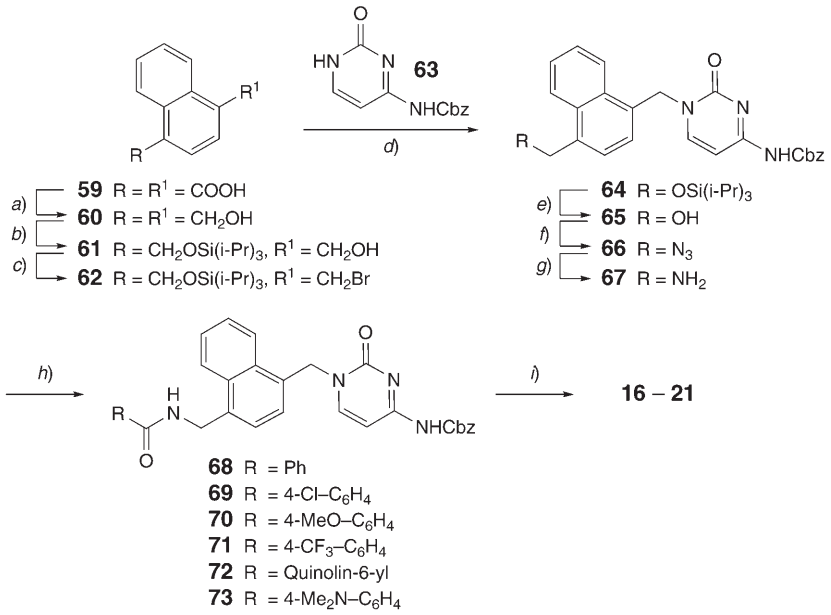

*a*) 1. $SnCl_2 \cdot 2\ H_2O$, AcOEt, *t*-BuOH, 60°, 1 h; 2. $NaBH_4$, 60°, 3 h; 66%. *b*) $HC(OEt)_3$, $TsOH \cdot H_2O$, toluene, 140°, 4 h; 95%. *c*) 4-Iodobenzonitrile or 4-iodo-3-methylbenzonitrile, 1,10-phenanthroline, CuI, $Cs_2CO_3$, DMF, 110°, 24 h; 33% (**49**) and 27% (**50**); 11% (**51**) and 20% (**52**). *d*) $CoCl_2 \cdot H_2O$, $NaBH_4$, MeOH, 50°, 24 h; 82% (**53**); 79% (**54**). *e*) 1. Benzoic acid, HO-Su, EDC·HCl, $CH_2Cl_2$, 25°, 2 h; 2. **53** or **54**, $Et_3N$, $CH_2Cl_2$, 25°, 20 h; 68% (**55**); 53% (**56**). *f*) Benzophenone imine, $[Pd_2(dba)_3]$, (±)-BINAP, $Cs_2CO_3$, DME, 110°, 20 h; 34% (**57**); 57% (**58**). *g*) HCl, THF, 25°, 2 h; 75% (**13**); 52% (**14**).

directly shows the conversion of $^{13}C$-labeled substrate to the product catalyzed by IspF. Activity was first checked in a single-point measurement at an inhibitor concentration of 1 mM. For ligands that displayed substantial activity at this concentration, the $IC_{50}$ value was determined by variation of the ligand concentration. In addition, the logarithmic partitioning coefficients clog*P* were calculated with the program ACD/Log*P* (*ACD/Labs*) to estimate the influence of lipophilicity (and partitioning) on binding.

Unexpectedly, the imidazopyridines **13** and **14** showed no detectable binding affinity, despite offering an array of three H-bond donor/acceptor sites similar to that of cytosine to bind to 'Pocket III' and the favorable accommodation into the active site suggested by the molecular modeling. Gratifyingly, several of the 2,5-diaminopyridine- and cytosine-based ligands showed activities (*Table*) that exceed, by one order of magnitude or more, the $IC_{50}$ values of the previously reported CDP-derived inhibitors, CDP, and CMP, determined under identical conditions [6]. All compounds shown in *Fig. 1* but excluded from the *Table* do not show measurable binding affinity.

It can be assumed that the new active ligands bind to 'Pocket III' in the way proposed in *Fig. 2.* This binding mode had been validated by X-ray crystallography for

Scheme 5. *Synthesis of the Cytosine Derivatives* **16**–**21**




*a*) $LiAlH_4$, THF, 70°, 20 h; 70%. *b*) $(i\text{-Pr})_3SiCl$, 1*H*-imidazole, THF, 0°, 2 h, 25°, 19 h; 46%. *c*) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0°, 3 h; 63%. *d*) 1. **63**, NaH, DMF, 25°, 1.5 h; 2. **62**, DMF 25°, 17 h; 79%. *e*) $Bu_4NF$, THF, 25°, 2 h; 90%. *f*) DPPA, DBU, THF, 0°, 2 h, 25°, 16 h; 93%. *g*) $PPh_3$, THF, $H_2O$, 25°, 20 h; 98%. *h*) 1. Benzoic acid derivative, HO-Su, EDC·HCl, $CH_2Cl_2$, 25°, 2 h; 2. **67**, $Et_3N$, $CH_2Cl_2$, 25°, 20 h; 81% (**68**); 74% (**69**); 22% (**70**); 42% (**71**); 78% (**72**); 31% (**73**). *i*) Pd/C, $H_2$, MeOH/$CH_2Cl_2$, 25°, 3 h; 76% (**16**); 65% (**17**); 54% (**18**); 59% (**19**); 40% (**20**); 72% (**21**).

Table. *Biological Activities* ($IC_{50}$ [mM][a])) *and clog*P *Values of the Inhibitors of IspF Protein*

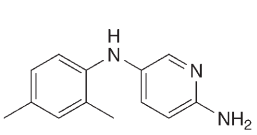
| Inhibitor | Inhibition at $c$(inhibitor) = 1 mM[a]) | $IC_{50}$ [mM] | clog*P* |
|---|---|---|---|
| **8** | 30% | n.d.[b]) | 2.7 ± 0.6 |
| **9** | 14% | n.d. | 3.5 ± 0.6 |
| **10** | 19% | n.d. | 2.9 ± 0.6 |
| **11** | 60% | 0.49 | 3.7 ± 0.6 |
| **12** | 5% | n.d. | 2.6 ± 0.6 |
| **16** | 59%[c]) | 0.45 | 2.3 ± 0.5 |
| **17** | 52%[c]) | 0.54 | 3.0 ± 0.5 |
| **18** | 0%[c]) | n.d. | 2.4 ± 0.5 |
| **19** | 35%[c]) | 0.65 | 3.2 ± 0.5 |
| **20** | 0%[c]) | n.d. | 2.2 ± 0.5 |
| **21** | 0%[c]) | n.d. | 2.7 ± 0.5 |
| CMP[d]) | | 15.0 | n.d. |
| CDP[d]) | | 7.3 | n.d. |

[a]) Uncertainties in $IC_{50}$ values: ± 2–10%. Values are determined from at least two experiments. [b]) Not determined. [c]) $c$(inhibitor) = 0.5 mM. [d]) Adopted from [6].

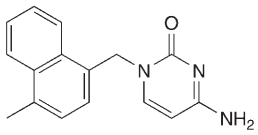
the weaker CDP-based ligands [6]. In agreement with the earlier results, filling the hydrophobic portion of 'Pocket II' does not seem to provide a large gain in binding free energy due to the very high flexibility of the surrounding protein. Although clear structure – activity relationships are not yet visible and currently also lack support by X-ray structural analysis, it seems that filling this pocket with a phenyl residue bearing electron-accepting substituents (*e.g.*, **11** ($CF_3$): $IC_{50} = 490$ μM; **17** (Cl): $IC_{50} = 540$ μM; **19** ($CF_3$): $IC_{50} = 650$ μM) is more favorable than filling it with a phenyl residue with an electron-donating group (*e.g.*, **10** and **18** (MeO), or **21** ($Me_2N$) with no or very weak measurable activity) or a larger residue (**12** and **20** with a quinolinyl residue). Partitioning, as estimated by the clog*P* values, also does not seem to greatly affect binding affinity, although the clog*P* values of the most active compounds are more on the positive side.

On the other hand, the investigation shows that it is possible to design 'drug-like' inhibitors, by-passing the ribose and diphosphate binding sites occupied by the natural substrate **5** and the previously reported CDP-based ligands [6]. In particular, the discovery of the sub-pocket that is filled by the 2-methyl-1,4-phenylene spacer in **11** and the naphthalene-1,4-diyl moiety in **16**, **17**, and **19** (*Fig. 3*) opens new perspectives for future lead developments.

Examination of the known crystal structures of IspF [8] revealed a preorganized, open sub-pocket in all co-crystals, except in the crystal of pure enzyme (PBD code: 1JN1, [8d]). It is lined by Pro62′, Asp63′, Gly58′, Asp56′, Ala131, Thr132, Thr133, Lys104, and Leu106. While most of the residues display highly conserved geometries in the various crystal structures, Pro62′, Asp63′, and Lys104 seem to be rather flexible. Overall, the sub-pocket is quite large, as suggested by the two different orientations of the aromatic spacers in the modeling experiments (*Fig. 3*, *b*); at present, it is clearly not optimally filled. We performed additional modeling studies with the truncated putative ligands **74** and **75**. We deliberately removed in these model compounds the vector reaching into the highly flexible hydrophobic part of 'Pocket II', since, in some structures, this region of the protein indeed arranges to give an open sub-pocket while some others show no sub-pocket at all. Compounds **74** and **75** could be docked in a strain-free way into all crystal structures featuring a preorganized open sub-pocket adjacent to the cytosine binding site. Further optimization of the occupancy of this pocket is currently under investigation.




**74**




**75**

**3. Conclusions.** – With its highly polar active site and the flexibility of the hydrophobic part of 'Pocket II' lined by Ala71′, Phe68′, Phe61′, and Leu76′, which limits the binding free enthalpy that can be gained through its occupancy, IspF presents itself as a rather 'tough target'. Nevertheless, the change from the first-generation inhibitors, highly polar, CDP-derived derivatives, to the new, much more 'drug-like'

ligands described in this paper has yielded an increase in efficacy of about one order of magnitude, as determined by $IC_{50}$ values. From the new data, the following conclusions can be drawn: *i*) It is possible to inhibit IspF without addressing the highly polar diphosphate binding site of the protein and the side chain of Asp56′. The latter was found to undergo ionic H-bonding with the OH residues of the ribose moieties in CMP [8b], CDP [8a], and analogues [6]. This contrasts our findings in the development of bisubstrate inhibitors of the enzyme catechol *O*-methyltransferase, which revealed a crucial role of the interaction between a ribose ring in the substrate and a glutamate side chain of the enzyme [16]. *ii*) Appropriate binding to the cytosine site in 'Pocket III' by 2,5-diaminopyridines and derivatives of the nucleobase presumably yields the largest part of the measured driving force for complexation. It still remains to be clarified, however, why the 5-amino-1*H*-imidazo[4,5-*b*]pyridine scaffold, which should undergo H-bonding interactions with the protein similar to cytosine, is not a suitable substitute of the nucleobase. *iii*) An appropriate residue for occupancy of the hydrophobic region of 'Pocket II', which makes a substantial contribution to the overall binding free enthalpy, has not yet been identified. This desirable objective remains difficult in view of the demonstrated large conformational flexibility in this region of the protein [6][8]. *iv*) We consider the identification of a new spacious sub-pocket, which presumably accommodates the aromatic spacers in our ligands between cytosine (and analogues) and the terminal ring for occupancy of 'Pocket III' as the most important finding of the present study. The occupation of this site (for the modeling, see *Fig. 3*) provides room for much optimization, which is the subject of ongoing research. Of course, we are well aware that the proposed binding mode of our inhibitors needs to be further validated by X-ray crystallography, and efforts in this direction are also pursued.

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## Experimental Part

*General*. Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: *6-chloropyridine-2,3-diamine* (**47**) [17], *(naphthalene-1,4-diyl)dimethanol* (**60**) [18], and *benzyl (1,2-dihydro-2-oxopyrimidin-4-yl)carbamate* (**63**) [19]. THF was freshly distilled from sodium benzophenone ketyl, $CH_2Cl_2$ from $CaH_2$. All products were dried under high vacuum ($10^{-2}$ Torr) before anal. characterization. Column chromatography (CC): $SiO_2$ *60* (40–63 μm) from *Fluka*, 0–0.3 bar pressure. TLC: $SiO_2$ *60* $F_{245}$ (on glass), *Merck*, visualization by UV light at 245 nm or staining with a soln. of $KMnO_4$ (3 g) and $K_2CO_3$ (20 g) in 5% aq. NaOH soln. (5 ml) and $H_2O$ (300 ml). M.p.: *Büchi B540* melting point apparatus; uncorrected. IR Spectra: *Perkin Elmer Spectrum BX FTIR System* spectrometer (ATR unit, Attenuated Total Reflection, Golden Gate); in $cm^{-1}$. NMR spectra ($^1H$, $^{13}C$, and $^{19}F$): *Varian Gemini-300* and *Bruker AMX-500*; spectra were recorded at 25°, with solvent peak as reference. High-resolution mass spectra (HR-MS): MALDI: *IonSpec Ultima* spectrometer, 2,5-dihydroxybenzoic acid (DHB) as matrix; EI: *VG TRIBRID* spectrometer at 70 eV. Elemental analyses were performed by the *Mikrolabor* at the Laboratorium für Organische Chemie, ETH Zürich. The nomenclature was generated with the computer program ACD-Name (*ACD/Labs*).

*General Procedure for the Synthesis of a Phthalimide by a* Mitsunobu *Reaction* (*GP A*). To a soln. of an alcohol (1.0 equiv.), phthalimide (1.2 equiv.), and $PPh_3$ (1.2 equiv.) in THF (4 ml per 1 mmol), DIAD (1.2 equiv.) was added. The mixture was stirred at 25° for 17 h, and the solvent was concentrated *in vacuo*.

*General Procedure for the Deprotection of a Phthalimide* (*GP B*). A soln. of a phthalimide (1.0 equiv.) in 33% $NH_2Me$ in EtOH (10 ml per 1 mmol) was stirred at 25° for 20 h. The solvent was concentrated *in vacuo*, and the resulting residue was taken up in 10% aq. AcOH soln. (15 ml per 1 mmol) and washed with $CH_2Cl_2$/i-PrOH 3 :1 (6 × 10 ml per 1 mmol). The aq. phase was treated with 1M aq. NaOH soln. until pH > 12 was reached and extracted with $CH_2Cl_2$/i-PrOH 3 :1 (6 × 10 ml per 1 mmol). The combined org. phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and dried.

*General Procedure for the Conversion of a Primary Amine to an Amide* (*GP C*). A soln. of a benzoic acid, *N*-hydroxysuccinimide, and EDC · HCl in $CH_2Cl_2$ was stirred at 25° for 2 h. The mixture was added to an amine. After the addition of $Et_3N$ and $CH_2Cl_2$, the soln. was stirred at 25° for 20 h. $CH_2Cl_2$ was added, and the org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*.

*General Procedure for the Reduction of an Aromatic $NO_2$ Group to an Amino Group or for the Deprotection of a Cbz-Protected Amine* (*GP D*). To a soln. of a nitrobenzene derivative or a Cbz-protected cytosine derivative (1.0 equiv.) in MeOH or $CH_2Cl_2$/MeOH, 10% Pd/C (*w*/*w*) was added under Ar. The flask was evacuated and refilled with $H_2$ (3 ×). The black suspension was stirred at 25° for 3 h under $H_2$. The mixture was filtered over *Celite*, and the *Celite* was washed with MeOH and $CH_2Cl_2$. The filtrate was concentrated *in vacuo*.

*General Procedure for a* Buchwald–Hartwig *Cross-Coupling Reaction* (*GP E*). [$Pd_2(dba)_3$] (5 mol-%), (±)-BINAP (10 mol-%), an aromatic halide (1.0 equiv.), and $Cs_2CO_3$ (2.5 equiv.) were added to an oven-dried sealed tube. The flask was evacuated and refilled with Ar. An aromatic amine or benzophenone imine (1.2 equiv.) and DME (2 ml per 1 mmol) were added, and the mixture was stirred at 110° for 20 h. The suspension was allowed to cool to 25° and taken up in $CH_2Cl_2$ (30 ml per 1 mmol). The org. phase was washed with sat. aq. NaCl soln. (30 ml per 1 mmol), dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*.

*General Procedure for the Deprotection of a (i-Pr)$_3$Si-Protected Alcohol* (*GP F*). To a soln. of a silyl ether (1.0 equiv.) in THF (15 ml per 1 mmol), $Bu_4NF$ (1M in THF, 1.2 equiv.) was added, and the mixture was stirred at 25° for 2 h. After addition of $H_2O$ (60 ml per 1 mmol), the aq. layer was extracted with $CH_2Cl_2$ (100 ml per 1 mmol). The org. phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo*.

*General Procedure for the Conversion of an Alcohol to an Azido Derivative* (*GP G*). A soln. of an alcohol (1.0 equiv.) and DPPA (1.4 equiv.) in THF (15 ml per 1 mmol) was stirred at 25° for 10 min, then cooled to 0°. DBU (1.4 equiv.) was added dropwise, and the mixture was stirred at 0° for 2 h and at 25° for 16 h. $CH_2Cl_2$ (60 ml per mmol) and $H_2O$ (50 ml per mmol) were added, and the phases were separated. The aq. layer was extracted with $CH_2Cl_2$ (30 ml per 1 mmol). The combined org. phases were washed with sat. aq. NaCl soln. (50 ml per 1 mmol), dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*.

*General Procedure for the* Staudinger *Reduction of an Azido Derivative to an Amine* (*GP H*). To a soln. of an azido derivative (1.0 equiv.) in THF (10 ml per 1 mmol) and $H_2O$ (0.4 ml per 1 mmol), $PPh_3$ (2.0 equiv.) was added, and the mixture was stirred at 25° for 20 h. AcOEt (40 ml per 1 mmol) was added, and the org. phase was extracted with 1M aq. HCl soln. (3 × 30 ml per 1 mmol). The aq. phase was treated with 4M aq. NaOH soln. until pH > 12 was reached and extracted with $CH_2Cl_2$ (2 × 30 ml per 1 mmol) and $CH_2Cl_2$/i-PrOH 3 :1 (2 × 40 ml per 1 mmol). The combined org. phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and dried.

*General Procedure for a modified* Ullmann *Coupling Reaction with an Imidazopyridine and an Aromatic Iodide* (*GP J*). CuI, an imidazopyridine, and $Cs_2CO_3$ or $K_2CO_3$ were added to an oven-dried sealed tube. The flask was evacuated and refilled with Ar. An aromatic iodide, 1,10-phenanthroline, and DMF were added, and the mixture was stirred at 110° for 24 h. The suspension was allowed to cool to 25° and taken up in AcOEt. The solvent was concentrated *in vacuo*.

*General Procedure for the Reduction of an Aromatic Nitrile to an Aromatic Amine* (*GP K*). To a suspension of a nitrile (1.0 equiv.) and $CoCl_2 \cdot 6\ H_2O$ (4.0 equiv.) in MeOH or $CH_2Cl_2$/MeOH 1:1, $NaBH_4$ (4.0 equiv.) was added, and the mixture was stirred at 50° for 24 h. The suspension was allowed to cool to 25°, taken up in 4M aq. HCl soln. (10 ml per 1 mmol) and $H_2O$ (40 ml per 1 mmol), and washed with $CH_2Cl_2$ ($3 \times 40$ ml per 1 mmol). The aq. phase was treated with 1M aq. NaOH soln. until pH > 12 was reached and extracted with $CH_2Cl_2$ ($2 \times 60$ ml per 1 mmol) and $CH_2Cl_2$/i-PrOH 3:1 ($3 \times 60$ ml per 1 mmol). The combined org. phases were washed with sat. aq. NaCl soln. (150 ml per 1 mmol), dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and dried.

*General Procedure for the Deprotection of an Aromatic Benzophenone Imine to an Aromatic Amine* (*GP L*). To a soln. of a benzophenone imine (1.0 equiv.) in THF (10 ml per mmol), 2M aq. HCl soln. (1 ml per 1 mmol) was added. The suspension was stirred at 25° for 2 h, 1M aq. HCl soln. (100 ml per 1 mmol) was added, and the aq. phase was washed with hexane/AcOEt 2:1 (150 ml per 1 mmol). The aq. phase was treated with 1M aq. NaOH soln. until pH > 12 was reached and extracted with $CH_2Cl_2$ ($3 \times 300$ ml per 1 mmol). The combined org. phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo*.

*2-(4-Nitrobenzyl)-1*H-*isoindole-1,3(2*H*)-dione* (**24**) [20]. *GP A* started from 4-nitrobenzyl alcohol (**22**) (5.01 g, 32.7 mmol), phthalimide (5.77 g, 39.2 mmol), $PPh_3$ (10.3 g, 39.2 mmol), THF (100 ml), and DIAD (7.8 ml, 39.2 mmol) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$), **24** (8.11 g, 88%). White solid. M.p. 173–174° ([20]: 171–174°). IR (neat): 3074*w*, 2931*w*, 2843*w*, 1767*m*, 1698*s*, 1598*m*, 1509*s*, 1466*m*, 1422*m*, 1392*s*, 1343*s*, 1327*s*, 1101*m*, 942*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 4.93 (*s*, 2 H); 7.58 (*d*, *J* = 8.4, 2 H); 7.73–7.76 (*m*, 2 H); 7.86–7.89 (*m*, 2 H); 8.18 (*d*, *J* = 8.7, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 41.0; 123.6; 123.9; 129.3; 131.8; 134.3; 143.2; 147.4; 167.6. HR-EI-MS: 282.0637 ($M^+$, $C_{15}H_{10}N_2O_4^+$; calc. 282.0641). Anal. calc. for $C_{15}H_{10}N_2O_4$ (282.25): C 63.83, H 3.57, N 9.92; found C 63.80, H 3.60, N 9.81.

*1-(4-Nitrophenyl)methanamine* (**26**) [21]. *GP B* started from **24** (4.0 g, 14.2 mmol) and 33% $NH_2Me$ in EtOH (150 ml) to yield **26** (2.17 g, quant.). Yellow oil. The crude product was used in the next step without further purification and was not fully characterized. $^1$H-NMR (300 MHz, $CDCl_3$): 4.01 (*s*, 2 H); 7.50 (*d*, *J* = 8.4, 2 H); 8.19 (*d*, *J* = 8.7, 2 H).

N-*(4-Nitrobenzyl)benzamide* (**28**) [22]. *GP C* started from PhCOOH (200 mg, 1.63 mmol), *N*-hydroxysuccinimide (244 mg, 2.12 mmol), EDC · HCl (469 mg, 2.45 mmol), $CH_2Cl_2$ (3 ml), **26** (372 mg, 2.45 mmol), $Et_3N$ (1.1 ml, 8.15 mmol), and $CH_2Cl_2$ (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 199:1 → 99:1), **28** (290 mg, 76%). Yellow solid. M.p. 155–156° ([22]: 155–156°). IR (neat): 3310*w*, 3076*w*, 2941*w*, 2850*w*, 1633*s*, 1603*m*, 1529*m*, 1512*s*, 1489*m*, 1346*s*, 1311*s*, 1290*s*, 1234*m*, 1106*m*, 854*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 4.76 (*d*, *J* = 6.2, 2 H); 6.61 (*s*, 1 H); 7.44–7.57 (*m*, 5 H); 7.81 (*d*, *J* = 8.1, 2 H); 8.20 (*d*, *J* = 8.7, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 43.4; 123.9; 126.9; 128.2; 128.7; 131.9; 133.6; 145.8; 147.2; 167.4. HR-EI-MS: 256.0845 ($M^+$, $C_{14}H_{12}N_2O_3^+$; calc. 256.0848). Anal. calc. for $C_{14}H_{12}N_2O_3$ (256.26): C 65.62, H 4.72, N 10.93; found C 65.34, H 4.80, N 10.80.

N-*(4-Aminobenzyl)benzamide* (**30**) [23]. *GP D* started from **28** (264 mg, 1.03 mmol), 10% Pd/C (27 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 2:1 (9 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **30** (211 mg, 91%). White solid. M.p. 142–143° ([23]: 142–143°). IR (neat): 3439*m*, 3338*m*, 3000*w*, 2926*w*, 1623*s*, 1610*s*, 1576*m*, 1530*s*, 1516*s*, 1486*s*, 1282*s*, 1077*m*, 841*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.30 (*d*, *J* = 5.9, 2 H); 4.94 (*s*, 2 H); 6.51 (*d*, *J* = 8.4, 2 H); 6.84 (*d*, *J* = 8.4, 2 H); 7.42–7.54 (*m*, 3 H); 7.87 (*d*, *J* = 8.4, 2 H); 8.84 (*t*, *J* = 5.6, 1 H). $^{13}$C-NMR (75 MHz, 60°, $(CD_3)_2SO$): 42.4; 113.7; 126.6; 127.0; 127.9; 128.0; 130.7; 134.6; 147.2; 165.7. HR-EI-MS: 226.1100 ($M^+$, $C_{14}H_{14}N_2O^+$; calc. 226.1106). Anal. calc. for $C_{14}H_{14}N_2O$ (226.28): C 74.31, H 6.24, N 12.38; found C 74.02, H 6.32, N 12.26.

N-*{4-[(6-Nitropyridin-3-yl)amino]benzyl}benzamide* (**32**). *GP E* started from $[Pd_2(dba)_3]$ (25 mg, 0.03 mmol, 5 mol-%), BINAP (34 mg, 0.06 mmol, 10 mol-%), 5-bromo-2-nitropyridine (114 mg, 0.56 mmol), $Cs_2CO_3$ (455 mg, 1.40 mmol), amine **30** (151 mg, 0.67 mmol), and DME (1.5 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **32** (124 mg, 59%). Orange solid. M.p. 198–200°. IR (neat): 3238*m*, 3066*w*, 2853*w*, 1633*s*, 1574*s*, 1500*s*, 1472*m*, 1444*m*, 1358*m*, 1332*s*, 1305*s*, 1290*s*, 1256*s*, 1105*s*, 1013*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.47 (*d*, *J* = 6.2, 2 H); 7.24 (*d*, *J* = 8.4, 2 H); 7.35 (*d*, *J* = 8.4, 2 H); 7.45–7.56 (*m*, 4 H); 7.90 (*d*, *J* = 8.4, 2 H); 8.15–8.18 (*m*, 2 H); 9.05 (*t*, *J* = 5.6, 1 H); 9.46 (*s*, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 42.2; 119.8; 120.4; 127.1; 128.1; 128.4; 131.1; 134.1; 134.6; 135.1; 137.9;

146.0; 147.2; 165.9 (one arom. signal missing due to overlap). HR-EI-MS: 348.1215 ($M^+$, $C_{19}H_{16}N_4O_3^+$; calc. 348.1222).

N-*{4-[(6-Aminopyridin-3-yl)amino]benzyl}benzamide* (**7**). *GP D* started from **32** (103 mg, 0.30 mmol), 10% Pd/C (10 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 2:1 (12 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 95:5), **7** (83 mg, 90%). Grey solid. M.p. 79–81°. IR (neat): 3297*m*, 3030*w*, 2922*w*, 1614*m*, 1575*m*, 1514*s*, 1494*s*, 1290*s*, 1178*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.33 (*d*, *J* = 5.9, 2 H); 5.62 (*s*, 2 H); 6.44 (*d*, *J* = 8.7, 1 H); 6.69 (*d*, *J* = 8.4, 2 H); 7.08 (*d*, *J* = 8.4, 2 H); 7.21 (*dd*, *J* = 8.7, 2.8, 1 H); 7.42–7.54 (*m*, 4 H); 7.72 (*d*, *J* = 2.8, 1 H); 7.87 (*d*, *J* = 8.4, 2 H); 8.89 (*t*, *J* = 5.3, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 42.2; 108.1; 113.4; 127.0; 128.1; 128.2; 128.3; 128.6; 130.9; 132.0; 134.3; 141.0; 145.2; 155.4; 165.6. HR-EI-MS: 318.1474 ($M^+$, $C_{19}H_{18}N_4O^+$; calc. 318.1481). Anal. calc. for $C_{19}H_{18}N_4O$ (318.37): C 71.68, H 5.70, N 17.60; found C 71.39, H 5.92, N 17.51.

*2-(3-Methyl-4-nitrobenzyl)-1*H*-isoindole-1,3(2*H*)-dione* (**25**). *GP A* started from 3-methyl-4-nitrobenzyl alcohol (**23**) (3.00 g, 17.9 mmol), phthalimide (3.17 g, 21.5 mmol), $PPh_3$ (5.65 g, 21.5 mmol), THF (60 ml), and DIAD (4.2 ml, 21.5 mmol) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$), **25** (5.27 g, 99%). Yellow solid. M.p. 154–156°. IR (neat): 3074*w*, 2988*w*, 1765*m*, 1710*s*, 1610*m*, 1588*m*, 1515*s*, 1464*m*, 1435*m*, 1395*s*, 1333*s*, 1319*s*, 1103*m*, 935*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.57 (*s*, 3 H); 4.86 (*s*, 2 H); 7.37–7.39 (*m*, 2 H); 7.72–7.77 (*m*, 2 H); 7.84–7.88 (*m*, 2 H); 7.93 (*d*, *J* = 8.7, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 20.7; 40.8; 123.5; 125.2; 126.8; 131.8; 132.6; 134.1; 134.2; 141.4; 148.4; 167.7. HR-EI-MS: 296.0790 ($M^+$, $C_{16}H_{12}N_2O_4^+$; calc. 296.0797). Anal. calc. for $C_{16}H_{12}N_2O_4$ (296.28): C 64.86, H 4.08, N 9.45; found C 64.82, H 4.13, N 9.71.

*1-(3-Methyl-4-nitrophenyl)methanamine* (**27**). *GP B* started from **25** (1.83 g, 6.19 mmol) and 33% $NH_2Me$ in EtOH (60 ml) to yield **27** (616 mg, 60%). Yellow oil. IR (neat): 3376*w*, 2930*w*, 2855*w*, 1610*m*, 1587*m*, 1509*s*, 1449*m*, 1337*s*, 1158*w*, 833*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.92 (*s*, 3 H); 3.94 (*s*, 2 H); 7.29 (*d*, *J* = 8.4, 1 H); 7.31 (*s*, 1 H); 7.97 (*d*, *J* = 8.1, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 20.6; 45.4; 125.0; 125.2; 131.1; 134.0; 147.7; 148.6. HR-EI-MS: 165.0659 ($[M-H]^+$, $C_8H_9N_2O_2^+$; calc. 165.0659).

N-*(3-Methyl-4-nitrobenzyl)benzamide* (**29**). *GP C* started from PhCOOH (801 mg, 6.56 mmol), *N*-hydroxysuccinimide (981 mg, 8.52 mmol), EDC·HCl (1.88 g, 9.81 mmol), $CH_2Cl_2$ (13 ml), **27** (1.64 g, 9.89 mmol), $Et_3N$ (4.5 ml, 32.5 mmol), and $CH_2Cl_2$ (9 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 199:1 → 99:1), **29** (1.72 g, 97%). Yellow solid. M.p. 127–128°. IR (neat): 3326*m*, 3058*w*, 1639*m*, 1578*m*, 1538*m*, 1511*s*, 1488*s*, 1335*s*, 1291*m*, 1237*m*, 986*m*, 835*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.59 (*s*, 3 H); 4.68 (*d*, *J* = 5.9, 2 H); 6.61 (*s*, 1 H); 7.29–7.31 (*m*, 2 H); 7.43–7.56 (*m*, 3 H); 7.80–7.82 (*m*, 2 H); 7.96 (*d*, *J* = 9.0, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 20.7; 43.2; 125.1; 125.7; 126.9; 128.6; 131.6; 131.8; 133.7; 134.1; 143.9; 148.1; 167.4. HR-EI-MS: 270.1000 ($M^+$, $C_{15}H_{14}N_2O_3^+$; calc. 270.1004). Anal. calc. for $C_{15}H_{14}N_2O_3$ (270.28): C 66.66, H 5.22, N 10.36; found C 66.47, H 5.05, N 10.31.

N-*(4-Amino-3-methylbenzyl)benzamide* (**31**). *GP D* started from **29** (1.50 g, 5.55 mmol), 10% Pd/C (150 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 2:1 (39 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **31** (1.24 g, 93%). Light pink solid. M.p. 113–114°. IR (neat): 3431*w*, 3308*m*, 3018*w*, 2920*w*, 2857*w*, 1629*s*, 1577*m*, 1532*s*, 1505*s*, 1487*m*, 1304*m*, 1277*s*, 1228*m*, 1148*m*, 832*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.02 (*s*, 3 H); 4.28 (*d*, *J* = 5.9, 2 H); 4.72 (*s*, 2 H); 6.54 (*d*, *J* = 7.8, 1 H); 6.83–6.88 (*m*, 2 H); 7.41–7.54 (*m*, 3 H); 7.85–7.89 (*m*, 2 H); 8.82 (*t*, *J* = 5.8, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 17.5; 42.4; 113.6; 120.6; 125.7; 126.7; 127.0; 128.1; 129.2; 130.9; 134.4; 145.2; 165.6. HR-EI-MS: 240.1260 ($M^+$, $C_{15}H_{16}N_2O^+$; calc. 240.1263). Anal. calc. for $C_{15}H_{16}N_2O$ (240.30): C 74.97, H 6.71, N 11.66; found C 74.85, H 6.74, N 11.57.

N-*{3-Methyl-4-[(6-nitropyridin-3-yl)amino]benzyl}benzamide* (**33**). *GP E* started from $[Pd_2(dba)_3]$ (58 mg, 0.06 mmol, 5 mol-%), BINAP (77 mg, 0.12 mmol, 10 mol-%), 5-bromo-2-nitropyridine (249 mg, 1.21 mmol), $Cs_2CO_3$ (987 mg, 3.03 mmol), **31** (350 mg, 1.46 mmol), and DME (3.5 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **33** (207 mg, 47%). Orange solid. M.p. 206–208°. IR (neat): 3300*m*, 2872*w*, 1633*s*, 1574*s*, 1512*s*, 1469*s*, 1325*s*, 1280*s*, 1260*s*, 1218*s*, 1104*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.19 (*s*, 3 H); 4.47 (*d*, *J* = 5.9, 2 H); 7.04 (*dd*, *J* = 9.0, 2.8, 1 H); 7.20–7.29 (*m*, 3 H); 7.46–7.57 (*m*, 3 H); 7.90–7.92 (*m*, 2 H); 8.03 (*d*, *J* = 2.8, 1 H); 8.13 (*d*, *J* = 9.0, 1 H); 9.04 (*s*, 1 H); 9.05 (*t*, *J* = 5.8, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 17.7; 42.2; 119.0; 120.5; 124.2; 125.8; 127.1; 128.1; 130.0; 131.1; 132.7; 133.8; 134.1; 135.7; 137.2; 146.8; 147.6; 165.9. HR-MALDI-MS: 385.1268 ($[M + Na]^+$ $C_{20}H_{18}N_4NaO_3^+$; calc. 385.1271).

N-*{4-[(6-Aminopyridin-3-yl)amino]-3-methylbenzyl}benzamide* (**8**). *GP D* started from **33** (109 mg, 0.30 mmol), 10% Pd/C (11 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:2 (18 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 95:5), **8** (89 mg, 89%). Grey solid. M.p. > 220° (dec.). IR (neat): 3464*w*, 3370*m*, 3288*m*, 3032*w*, 2929*w*, 1624*m*, 1542*m*, 1497*s*, 1424*m*, 1316*s*, 1293*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.17 (*s*, 3 H); 4.33 (*d*, *J* = 5.9, 2 H); 5.59 (*s*, 2 H); 6.43 (*d*, *J* = 8.4, 1 H); 6.60 (*d*, *J* = 8.1, 1 H); 6.65 (*s*, 1 H); 6.93 (*d*, *J* = 8.4, 1 H); 7.03 (*s*, 1 H); 7.15 (*dd*, *J* = 8.7, 2.8, 1 H); 7.42–7.54 (*m*, 3 H); 7.70 (*d*, *J* = 2.5, 1 H); 7.86–7.88 (*m*, 2 H); 8.88 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 18.0; 42.2; 108.0; 112.7; 123.9; 125.6; 127.0; 128.1; 129.0; 129.2; 129.7; 130.9; 132.5; 134.3; 141.6; 143.5; 155.5; 165.6. HR-EI-MS: 332.1634 ($M^+$, $C_{20}H_{20}N_4O^+$; calc. 332.1632).

*4-Methoxy*-N-*(3-methyl-4-nitrobenzyl)benzamide* (**34**). *GP C* started from 4-methoxybenzoic acid (367 mg, 2.41 mmol), *N*-hydroxysuccinimide (360 mg, 3.13 mmol), EDC·HCl (692 mg, 3.61 mmol), $CH_2Cl_2$ (5 ml), **27** (592 mg, 3.56 mmol), $Et_3N$ (1.7 ml, 12.2 mmol), and $CH_2Cl_2$ (5 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 199:1), **34** (1.67 g, 23%). Grey solid. M.p. 145–147°. IR (neat): 3375*w*, 2941*m*, 2864*m*, 1626*m*, 1509*s*, 1462*m*, 1367*w*, 1280*m*, 1158*m*, 1145*m*, 1092*m*, 1063*s*, 1012*m*, 882*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.60 (*s*, 3 H); 3.86 (*s*, 3 H); 4.67 (*d*, *J* = 6.1, 2 H); 6.42 (br. *s*, 1 H); 6.95 (*d*, *J* = 9.0, 2 H); 7.29–7.33 (*m*, 2 H); 7.78 (*d*, *J* = 8.7, 2 H); 7.97 (*d*, *J* = 8.7, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 20.8; 43.3; 55.6; 114.1; 125.4; 126.0; 126.2; 129.0; 132.0; 134.4; 144.5; 148.4; 162.7; 167.2. HR-MALDI-MS: 301.1186 ($[M+H]^+$, $C_{16}H_{17}N_2O_4^+$; calc. 301.1183). Anal. calc. for $C_{16}H_{16}N_2O_4$ (300.31): C 63.99, H 5.37, N 9.33; found C 63.91, H 5.53, N 9.28.

N-*(4-Amino-3-methylbenzyl)-4-methoxybenzamid*e (**35**). *GP D* started from **34** (497 mg, 1.65 mmol), 10% Pd/C (50 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 2:1 (12 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 99:1 → 98:2), **35** (332 mg, 74%). White solid. M.p. 134–136°. IR (neat): 3301*w*, 2920*w*, 1625*s*, 1574*m*, 1540*m*, 1503*s*, 1445*m*, 1360*m*, 1300*m*, 1283*s*, 1257*s*, 1226*s*, 1177*s*, 1107*m*, 1026*s*, 970*m*, 846*s*, 825*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.16 (*s*, 3 H); 3.61 (br. *s*, 2 H); 3.84 (*s*, 3 H); 4.49 (*d*, *J* = 5.3, 2 H); 6.16 (br. *s*, 1 H); 6.65 (*d*, *J* = 8.1, 1 H); 6.91 (*d*, *J* = 8.7, 2 H); 7.02–7.05 (*m*, 2 H); 7.74 (*d*, *J* = 9.0, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 17.2; 43.8; 55.3; 113.6; 114.9; 122.5; 126.8; 128.0; 128.6; 130.4; 144.0; 162.0; 166.5 (one arom. signal missing due to overlap). HR-EI-MS: 270.1361 ($M^+$, $C_{16}H_{18}N_2O_2^+$; calc. 270.1363). Anal. calc. for $C_{16}H_{18}N_2O_2$ (270.33): C 71.09, H 6.71, N 10.36; found C 70.93, H 6.72, N 10.26.

*4-Methoxy*-N-*{3-methyl-4-[(6-nitropyridin-3-yl)amino]benzyl}benzamide* (**36**). *GP E* started from $[Pd_2(dba)_3]$ (35 mg, 0.04 mmol, 5 mol-%), BINAP (48 mg, 0.08 mmol, 10 mol-%), 5-bromo-2-nitropyridine (155 mg, 0.77 mmol), $Cs_2CO_3$ (631 mg, 1.93 mmol), **35** (250 mg, 0.92 mmol), and DME (3 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 99:1 → 98:2), **36** (212 mg, 70%). Orange solid. M.p. 186–188°. IR (neat): 3277*w*, 2924*w*, 1634*w*, 1605*m*, 1573*m*, 1503*s*, 1385*w*, 1286*s*, 1251*s*, 1177*m*, 1104*m*, 1027*m*, 1006*m*, 841*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.18 (*s*, 3 H); 3.81 (*s*, 3 H); 4.45 (*d*, *J* = 5.9, 2 H); 7.01 (*d*, *J* = 8.7, 2 H); 7.08 (*dd*, *J* = 9.0, 2.8, 1 H); 7.18–7.27 (*m*, 3 H); 7.89 (*d*, *J* = 9.0, 2 H); 8.02 (*d*, *J* = 2.8, 1 H); 8.13 (*d*, *J* = 9.0, 1 H); 8.90 (*t*, *J* = 6.1, 1 H); 8.99 (*s*, 1 H). $^{13}$C-NMR (125 MHz, $(CD_3)_2SO$): 18.4; 42.8; 56.0; 114.2; 119.9; 121.3; 125.1; 126.6; 127.2; 129.8; 130.9; 133.5; 134.6; 136.6; 138.3; 147.7; 148.5; 162.3; 166.3. HR-MALDI-MS: 415.1384 ($[M + Na]^+$, $C_{21}H_{20}N_4NaO_4^+$; calc. 415.1377).

N-*{4-[(6-Aminopyridin-3-yl)amino]-3-methylbenzyl}-4-methoxybenzamide* (**10**). *GP D* started from **36** (160 mg, 0.41 mmol), 10% Pd/C (16 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 2:1 (21 ml) to yield, after purification by CC ($SiO_2$; AcOEt/pentane/MeOH 8:1:0.1), **10** (132 mg, 89%). Light grey solid. M.p. 206–208°. IR (neat): 3318*w*, 2926*w*, 1605*m*, 1573*w*, 1542*w*, 1493*s*, 1381*w*, 1291*m*, 1250*s*, 1177*m*, 1118*w*, 1027*m*, 843*m*, 814*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.16 (*s*, 3 H); 3.80 (*s*, 3 H); 4.30 (*d*, *J* = 5.9, 2 H); 5.59 (br. *s*, 2 H); 6.43 (*d*, *J* = 8.4, 1 H); 6.59 (*d*, *J* = 8.1, 1 H); 6.65 (*s*, 1 H); 6.91 (*d*, *J* = 8.1, 1 H); 6.98 (*d*, *J* = 9.0, 2 H); 7.00 (br. *s*, 1 H); 7.15 (*dd*, *J* = 8.7, 2.8, 1 H); 7.69 (*d*, *J* = 2.5, 1 H); 7.85 (*d*, *J* = 9.0, 2 H); 8.72 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 18.0; 42.2; 55.3; 108.2; 113.0; 113.5; 124.2; 125.8; 126.8; 129.1; 129.5; 129.9; 132.7; 141.8; 143.7; 155.7; 161.5; 165.4 (one arom. signal missing due to overlap). HR-MALDI-MS: 362.1722 ($[M + Na]^+$, $C_{21}H_{22}N_4NaO_2^+$; calc. 362.1737).

*Triisopropyl[(3-methyl-4-nitrobenzyl)oxy]silane* (**37**). To a soln. of 3-methyl-4-nitrobenzyl alcohol (**23**) (10.0 g, 59.8 mmol) in THF (100 ml), (i-Pr)$_3$SiCl (15.4 ml, 71.8 mmol) and 1*H*-imidazole (4.89 g, 71.8 mmol) were added at 0°. The mixture was stirred at 0° for 2 h and at 25° for 21 h. After addition of $CH_2Cl_2$ (200 ml), the mixture was washed with sat. aq. $NaHCO_3$ soln. (3 × 200 ml) and sat. aq. NaCl soln.

(200 ml). The org. phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by CC ($SiO_2$, $CH_2Cl_2$) to yield **37** (17.5 g, 90%). Yellow oil. IR (neat): 2943*m*, 2866*m*, 1614*w*, 1591*w*, 1519*s*, 1462*m*, 1340*s*, 1164*m*, 1107*s*, 1070*m*, 881*s*, 836*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.07–1.25 (*m*, 21 H); 2.62 (*s*, 3 H); 4.87 (*s*, 2 H); 7.31 (*s*, 1 H); 7.32 (*d*, $J$ = 8.1, 1 H); 7.99 (*d*, $J$ = 8.4, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 12.1; 18.1; 21.0; 64.1; 123.7; 124.8; 129.5; 133.7; 147.3; 147.6. HR-EI-MS: 280.1364 ($[M - C_3H_7]^+$, $C_{14}H_{22}NO_3Si^+$; calc. 280.1364). Anal. calc. for $C_{17}H_{29}NO_3Si$ (323.51): C 63.12, H 9.04, N 4.33; found C 63.11, H 8.79, N 4.41.

*2-Methyl-4-{[(triisopropylsilyl)oxy]methyl}aniline* (**38**). *GP D* started from **37** (4.21 g, 13.0 mmol), 10% Pd/C (420 mg, 10% (*w*/*w*)), and MeOH (40 ml) to yield, after purification by CC ($SiO_2$; AcOEt/pentane/$Et_2O$ 9:1 → 5:1), **38** (2.08 g, 55%). Red oil. IR (neat): 3319*m*, 2928*w*, 1633*s*, 1605*s*, 1549*s*, 1523*s*, 1505*s*, 1439*m*, 1354*s*, 1343*s*, 1296*s*, 1247*s*, 1186*s*, 1110*m*, 1024*s*, 834*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.08–1.17 (*m*, 21 H); 2.17 (*s*, 3 H); 3.57 (br. *s*, 2 H); 4.70 (*s*, 2 H); 6.65 (*d*, $J$ = 8.7, 1 H); 7.02–7.04 (*m*, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 12.0; 17.4; 18.0; 64.9; 114.7; 122.0; 124.8; 128.4; 131.8; 143.3. HR-EI-MS: 293.2171 ($M^+$, $C_{17}H_{31}NOSi^+$; calc. 293.2170). Anal. calc. for $C_{17}H_{31}NOSi$ (293.52): C 69.56, H 10.64, N 4.77; found C 69.38, H 10.60, N 4.85.

N-*(2-Methyl-4-{[(triisopropylsilyl)oxy]methyl}phenyl)-6-nitropyridin-3-amine* (**39**). *GP E* started from $[Pd_2(dba)_3]$ (196 mg, 0.21 mmol, 5 mol-%), BINAP (270 mg, 0.43 mmol, 10 mol-%), 5-bromo-2-nitropyridine (864 mg, 4.26 mmol), $Cs_2CO_3$ (3.47 g, 10.7 mmol), **38** (1.49 g, 5.08 mmol), and DME (9 ml) to yield, after purification by CC ($SiO_2$; pentane/AcOEt 5:1), **39** (691 mg, 39%). Orange solid. M.p. 106–108°. IR (neat): 3246*m*, 3120*w*, 3060*w*, 2880*w*, 1570*m*, 1544*m*, 1505*s*, 1474*m*, 1387*m*, 1326*s*, 1288*s*, 1269*s*, 1156*m*, 1110*s*, 1045*m*, 1000*s*, 827*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.09–1.23 (*m*, 21 H); 2.25 (*s*, 3 H); 4.83 (*s*, 2 H); 6.05 (br. *s*, 1 H); 7.05 (*dd*, $J$ = 9.0, 3.1, 1 H); 7.20–7.30 (*m*, 3 H); 8.04 (*d*, $J$ = 2.8, 1 H); 8.12 (*d*, $J$ = 8.7, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 12.2; 18.2; 64.6; 119.8; 120.2; 124.7; 124.7; 128.9; 133.3; 134.4; 134.9; 140.4; 146.9; 148.3 (one aliph. signal missing due to overlap). HR-MALDI-MS: 416.2362 ($[M + H]^+$, $C_{22}H_{34}N_3O_3Si^+$; calc. 416.2364).

*{3-Methyl-4-[(6-nitropyridin-3-yl)amino]phenyl}methanol* (**40**). *GP F* started from **39** (600 mg, 1.44 mmol), THF (20 ml), and $Bu_4NF$ (1M in THF, 1.7 ml, 1.73 mmol) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 97:3), **40** (331 mg, 88%). Orange solid. M.p. 176–178°. IR (neat): 3252*w*, 2942*m*, 2864*m*, 1574*s*, 1506*s*, 1471*m*, 1354*m*, 1329*s*, 1262*s*, 1214*m*, 1155*m*, 1105*s*, 1009*m*, 882*m*, 811*s*. $^1$H-NMR (300 MHz, $CDCl_3$/$CD_3OD$ 6:1): 2.11 (*s*, 3 H); 4.49 (*s*, 2 H); 6.91 (*dd*, $J$ = 9.1, 3.0, 1 H); 7.05–7.11 (*m*, 2 H); 7.17 (*s*, 1 H); 7.85 (*d*, $J$ = 3.0, 1 H); 7.96 (*d*, $J$ = 9.1, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$/$CD_3OD$ 6:1): 17.3; 63.6; 119.0; 120.2; 124.6; 125.5; 129.9; 133.5; 134.0; 135.8; 139.3; 147.0; 147.9. HR-EI-MS: 259.0955 ($M^+$, $C_{13}H_{13}N_3O_3^+$; calc. 259.0952). Anal. calc. for $C_{13}H_{13}N_3O_3$ (259.26): C 60.23, H 5.05, N 16.21; found C 60.02, H 5.14, N 15.93.

N-*[4-(Azidomethyl)-2-methylphenyl]-6-nitropyridin-3-amine* (**42**). *GP G* started from **40** (310 mg, 1.20 mmol), DPPA (0.36 ml, 1.68 mmol), THF (30 ml), and DBU (0.25 ml, 1.68 mmol) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 99:1), **42** (332 mg, 98%). Orange oil. IR (neat): 3294*w*, 3054*w*, 2921*w*, 2092*s*, 1570*s*, 1502*s*, 1470*m*, 1385*m*, 1328*s*, 1285*s*, 1260*s*, 1158*m*, 1104*s*, 1007*m*, 832*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.28 (*s*, 3 H); 4.35 (*s*, 2 H); 6.17 (br. *s*, 1 H); 7.13 (*dd*, $J$ = 9.1, 3.1, 1 H); 7.20–7.42 (*m*, 3 H); 8.08 (*d*, $J$ = 3.1, 1 H); 8.14 (*d*, $J$ = 9.1, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 18.1; 54.5; 120.4; 120.7; 124.6; 127.4; 130.3; 131.8; 133.7; 135.1; 137.1; 146.7; 149.0. HR-MALDI-MS: 285.1100 ($[M + H]^+$, $C_{13}H_{13}N_6O_2^+$; calc. 285.1095).

N-*[4-(Aminomethyl)-2-methylphenyl]-6-nitropyridin-3-amine* (**41**). *GP H* started from **42** (325 mg, 1.14 mmol), $PPh_3$ (0.60 g, 2.28 mmol), THF (14 ml), and $H_2O$ (0.6 ml) to yield **41** (280 mg, 95%). Yellow solid. M.p. 96–98°. IR (neat): 2840*w*, 1569*s*, 1503*s*, 1340*m*, 1381*m*, 1327*s*, 1265*s*, 1218*m*, 1159*m*, 1105*s*, 1000*m*, 897*m*, 835*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.25 (*s*, 3 H); 3.88 (*s*, 2 H); 6.06 (br. *s*, 1 H); 7.05 (*dd*, $J$ = 9.0, 2.5, 1 H); 7.21–7.23 (*m*, 2 H); 7.29 (*s*, 1 H); 8.05 (*d*, $J$ = 2.5, 1 H); 8.12 (*d*, $J$ = 9.0, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 18.1; 46.1; 120.2; 120.4; 125.1; 126.4; 130.7; 132.3; 133.8; 134.8; 135.4; 142.2; 147.1. HR-EI-MS: 258.1105 ($M^+$, $C_{13}H_{14}N_4O_2^+$; calc. 258.1117).

N-*{3-Methyl-4-[(6-nitropyridin-3-yl)amino]benzyl}-4-(trifluoromethyl)benzamide* (**43**). *GP C* started from α,α,α-trifluoro-4-toluic acid (148 mg, 0.78 mmol), *N*-hydroxysuccinimide (115 mg, 0.99 mmol), EDC·HCl (218 mg, 1.14 mmol), $CH_2Cl_2$ (5 ml), **41** (135 mg, 0.52 mmol), $Et_3N$ (0.5 ml, 2.60 mmol), and $CH_2Cl_2$ (5 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **43** (137 mg, 61%). Yellow

solid. M.p. 158–160°. IR (neat): 3232*w*, 2925*w*, 1638*m*, 1572*m*, 1535*m*, 1499*s*, 1470*m*, 1322*s*, 1264*s*, 1222*m*, 1158*m*, 1125*s*, 1106*s*, 1067*m*, 1004*m*, 837*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.19 (*s*, 3 H); 4.49 (*d*, *J* = 5.6, 2 H); 7.09 (*dd*, *J* = 9.0, 3.0, 1 H); 7.21–7.30 (*m*, 3 H); 7.87 (*d*, *J* = 8.1, 2 H); 8.03 (*d*, *J* = 2.5, 1 H); 8.11 (*d*, *J* = 8.1, 2 H); 8.13 (*d*, *J* = 8.7, 1 H); 9.00 (*s*, 1 H); 9.29 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 17.7; 42.4; 119.0; 120.5; 124.2; 125.2; 125.8; 128.0; 130.1; 132.7; 133.8; 135.8; 136.7; 137.8; 146.8; 147.6; 164.8 ($CF_3$ signal missing, one arom. signal missing due to overlap). $^{19}$F-NMR (282 MHz, $(CD_3)_2SO$): −60.3. HR-EI-MS: 430.1249 ($M^+$, $C_{21}H_{17}F_3N_4O_3^+$; calc. 430.1248).

N-*{4-[(6-Aminopyridin-3-yl)amino]-3-methylbenzyl}-4-(trifluoromethyl)benzamide* (**11**). *GP D* started from **43** (110 mg, 0.26 mmol), 10% Pd/C (11 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:2 (15 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2 → 95:5), **11** (80 mg, 78%). Light grey solid. M.p. 208–210°. IR (neat): 3467*w*, 3370*w*, 3267*w*, 1627*m*, 1549*m*, 1499*s*, 1425*m*, 1326*s*, 1314*s*, 1293*s*, 1176*m*, 1129*s*, 1068*s*, 1019*s*, 861*s*, 808*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.17 (*s*, 3 H); 4.34 (*d*, *J* = 5.9, 2 H); 5.60 (br. *s*, 2 H); 6.43 (*d*, *J* = 8.4, 1 H); 6.59 (*d*, *J* = 8.4, 1 H); 6.66 (*s*, 1 H); 6.93 (*dd*, *J* = 8.4, 1.8, 1 H); 7.03 (*d*, *J* = 1.8, 1 H); 7.15 (*dd*, *J* = 8.7, 2.8, 1 H); 7.70 (*d*, *J* = 2.5, 1 H); 7.84 (*d*, *J* = 8.1, 2 H); 8.06 (*d*, *J* = 8.4, 2 H); 9.12 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 18.0; 42.4; 108.0; 112.7; 123.9; 125.1 (*d*, $^3J$(C,F) = 3.7); 125.6; 128.0; 128.5; 129.1; 129.8; 130.8 (*q*, $^2J$(C,F) = 31.0); 132.6; 138.1; 141.7; 143.7; 155.5; 164.5 ($CF_3$ signal missing). $^{19}$F-NMR (282 MHz, $(CD_3)_2SO$): −60.9. HR-MALDI-MS: 401.1577 ($[M + H]^+$, $C_{21}H_{20}F_3N_4O^+$; calc. 401.1584). Anal. calc. for $C_{21}H_{19}F_3N_4O$ (400.40): C 62.99, H 4.78, N 13.99; found C 62.89, H 4.70, N 13.76.

N-*{3-Methyl-4-[(6-nitropyridin-3-yl)amino]benzyl}quinoline-6-carboxamide* (**44**). *GP C* started from quinoline-6-carboxylic acid (140 mg, 0.81 mmol), *N*-hydroxysuccinimide (115 mg, 0.99 mmol), EDC·HCl (218 mg, 1.14 mmol), $CH_2Cl_2$ (5 ml), **41** (135 mg, 0.52 mmol), $Et_3N$ (0.5 ml, 2.60 mmol), and $CH_2Cl_2$ (5 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **44** (73 mg, 34%). Orange solid. M.p. 127–129°. IR (neat): 3266*w*, 2921*w*, 1643*m*, 1573*s*, 1496*s*, 1383*w*, 1326*s*, 1285*s*, 1262*s*, 1158*m*, 1104*s*, 1006*m*, 842*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.20 (*s*, 3 H); 4.54 (*d*, *J* = 5.9, 2 H); 7.09 (*dd*, *J* = 9.0, 2.9, 1 H); 7.27–7.34 (*m*, 3 H); 7.62 (*dd*, *J* = 8.3, 4.2, 1 H); 8.03 (*d*, *J* = 2.7, 1 H); 8.10 (*d*, *J* = 9.0, 1 H); 8.13 (*d*, *J* = 9.2, 1 H); 8.24 (*dd*, *J* = 8.8, 2.0, 1 H); 8.49 (*dd*, *J* = 8.5, 1.1, 1 H); 8.58 (*d*, *J* = 1.9, 1 H); 8.96–9.07 (*m*, 2 H); 9.29 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 17.7; 42.4; 119.2; 120.6; 122.1; 124.4; 126.0; 127.1; 127.7; 128.0; 129.0; 130.3; 132.1; 132.9; 133.9; 136.0; 137.1; 137.1; 147.0; 147.8; 148.6; 152.0; 165.7. HR-MALDI-MS: 414.1555 ($[M + H]^+$, $C_{23}H_{20}N_5O_3^+$; calc. 414.1561).

N-*{4-[(6-Aminopyridin-3-yl)amino]-3-methylbenzyl}quinoline-6-carboxamide* (**12**). *GP D* started from **44** (60 mg, 0.15 mmol), 10% Pd/C (6 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:2 (9 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 92:8), **12** (40 mg, 72%). Light grey solid. M.p. > 198° (dec.). IR (neat): 3466*w*, 3371*m*, 3283*w*, 2925*w*, 1622*s*, 1538*m*, 1496*s*, 1424*m*, 1379*m*, 1332*m*, 1293*s*, 1137*w*, 1118*w*, 841*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.18 (*s*, 3 H); 4.39 (*d*, *J* = 5.6, 2 H); 5.60 (*s*, 2 H); 6.43 (*d*, *J* = 8.4, 1 H); 6.61 (*d*, *J* = 8.4, 1 H); 6.67 (*s*, 1 H); 6.98 (*dd*, *J* = 9.0, 2.1, 1 H); 7.07 (*d*, *J* = 1.8, 1 H); 7.16 (*dd*, *J* = 8.4, 2.5, 1 H); 7.60 (*dd*, *J* = 8.3, 4.2, 1 H); 7.70 (*d*, *J* = 2.5, 1 H); 8.07 (*d*, *J* = 8.7, 1 H); 8.20 (*dd*, *J* = 8.7, 2.2, 1 H); 8.47 (*dd*, *J* = 8.1, 1.6, 1 H); 8.53 (*d*, *J* = 1.6, 1 H); 8.98 (*dd*, *J* = 4.2, 1.8, 1 H); 9.12 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (125 MHz, $(CD_3)_2SO$): 18.6; 43.2; 108.9; 113.7; 122.8; 124.9; 126.6; 127.8; 128.5; 128.6; 129.6; 129.7; 130.1; 130.7; 133.1; 133.4; 137.7; 142.5; 144.5; 149.3; 152.7; 156.4; 166.2. HR-MALDI-MS: 384.1813 ($[M + H]^+$, $C_{23}H_{22}N_5O^+$; calc. 384.1819).

*5-{[4-(Aminomethyl)-2-methylphenyl]amino}pyridin-2-amine* (**45**). *GP D* started from **42** (106 mg, 0.37 mmol), 10% Pd/C (11 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:2 (6 ml) to yield **45** (70 mg, 82%). Yellow oil. The crude product was used in the next step without further purification and was not fully characterized. $^1$H-NMR (300 MHz, $CDCl_3$): 2.16 (*s*, 3 H); 3.62 (*s*, 2 H); 6.45 (*d*, *J* = 8.7, 1 H); 6.65 (*d*, *J* = 8.1, 1 H); 6.87 (br. *d*, *J* = 7.5, 1 H); 6.97 (br. *s*, 1 H); 7.19 (*dd*, *J* = 8.7, 2.4, 1 H); 7.67 (*d*, *J* = 2.7, 1 H). HR-EI-MS: 228.1363 ($M^+$, $C_{13}H_{16}N_4^+$; calc. 228.1369).

N-*{4-[(6-Aminopyridin-3-yl)amino]-3-methylbenzyl}-4-chlorobenzamide* (**9**). *GP C* started from 4-chlorobenzoic acid (67 mg, 0.43 mmol), *N*-hydroxysuccinimide (62 mg, 0.53 mmol), EDC·HCl (119 mg, 0.62 mmol), $CH_2Cl_2$ (2 ml), **45** (65 mg, 0.28 mmol), $Et_3N$ (0.2 ml, 1.35 mmol), and $CH_2Cl_2$ (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 95:5), **9** (48 mg, 47%). Light grey solid. M.p. > 175° (dec.). IR (neat): 3468*w*, 3310*w*, 2927*w*, 1624*s*, 1598*m*, 1543*m*, 1497*s*, 1417*m*, 1381*m*, 1278*s*, 1118*w*, 1090*m*, 1016*m*, 807*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.17 (*s*, 3 H); 4.31 (*d*, *J* = 5.6, 2 H); 5.60 (br. *s*, 2 H); 6.43

(*d*, *J* = 8.7, 1 H); 6.59 (*d*, *J* = 8.1, 1 H); 6.66 (*s*, 1 H); 6.92 (br. *d*, *J* = 8.1, 1 H); 7.02 (br. *s*, 1 H); 7.15 (*dd*, *J* = 9.0, 2.5, 1 H); 7.53 (*d*, *J* = 8.4, 2 H); 7.69 (*d*, *J* = 2.5, 1 H); 7.89 (*d*, *J* = 8.7, 2 H); 8.96 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 18.0; 42.4; 108.2; 112.9; 124.2; 125.8; 128.4; 129.0; 129.2; 129.4; 130.0; 132.8; 133.3; 136.0; 141.9; 143.9; 155.8; 164.9. HR-MALDI-MS: 367.1325 ($[M + H]^+$, $C_{20}H_{20}ClN_4O^+$; calc. 367.1320).

*5-Chloro-1*H-*imidazo[4,5-*b*]pyridine* (**48**) [24]. A soln. of **47** (2.86 g, 19.9 mmol), $TsOH \cdot H_2O$ (379 mg, 2.00 mmol), and $HC(OEt)_3$ (6.6 ml, 39.8 mmol) in toluene (60 ml) was stirred under reflux for 4 h. The solvent was concentrated *in vacuo*, and the crude product was purified by CC ($SiO_2$, 98 : 2 → 95 : 5) to yield **48** (2.89 g, 95%). Light brown solid. M.p: 230–232°. IR (neat): 3068*w*, 3039*w*, 2959*w*, 2896*w*, 2824*m*, 1620*w*, 1568*m*, 1488*w*, 1450*m*, 1385*s*, 1342*s*, 1266*m*, 1205*m*, 1110*s*, 920*s*, 804*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 7.29 (*d*, *J* = 8.4, 1 H); 8.06 (*d*, *J* = 8.1, 1 H); 8.49 (*s*, 1 H). $^{13}$C-NMR (125 MHz, $(CD_3)_2SO$): 117.6; 126.1; 128.5; 143.7; 145.1; 151.4. HR-EI-MS: 153.0090 ($M^+$, $C_6H_4ClN_3^+$; calc. 153.0089). Anal. calc. for $C_6H_4ClN_3$ (153.57): C 46.93, H 2.63, N 27.36; found C 46.89, H 2.66, N 27.33.

*4-(5-Chloro-1*H-*imidazo[4,5-*b*]pyridin-1-yl)benzonitrile* (**49**) *and 4-(5-Chloro-3*H-*imidazo[4,5-*b*]pyridin-3-yl)benzonitrile* (**50**). *GP J* started from CuI (114 mg, 0.60 mmol, 10 mol-%), **48** (1.10 g, 7.16 mmol), $Cs_2CO_3$ (4.08 g, 12.5 mmol), 4-iodobenzonitrile (1.37 g, 5.97 mmol), 1,10-phenanthroline (215 mg, 1.19 mmol, 20 mol-%), and DMF (5 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2/Et_2O$ 9 : 1 → 5 : 1 → 1 : 1), **49** (509 mg, 33%) and **50** (407 mg, 27%).

*Data of* **49**: Violet solid. M.p. 313–315°. IR (neat): 3358*w*, 3099*w*, 2227*m*, 1600*m*, 1507*s*, 1480*m*, 1413*s*, 1364*m*, 1317*m*, 1244*m*, 1203*m*, 1178*m*, 1157*m*, 1128*m*, 1102*m*, 976*m*, 922*m*, 805*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 7.49 (*d*, *J* = 8.7, 1 H); 7.99 (*d*, *J* = 9.0, 2 H); 8.15 (*d*, *J* = 9.0, 2 H); 8.27 (*d*, *J* = 8.4, 1 H); 9.05 (*s*, 1 H). $^{13}$C-NMR (125 MHz, $(CD_3)_2SO$): 111.3; 118.9; 119.8; 123.5; 124.8; 134.1; 135.0; 139.6; 145.5; 147.2; 156.4. HR-EI-MS: 254.0356 ($M^+$, $C_{13}H_7ClN_4^+$; calc. 254.0354).

*Data of* **50**: White solid. M.p. 247–249°. IR (neat): 3080*w*, 2228*m*, 1595*m*, 1518*s*, 1488*m*, 1450*m*, 1408*m*, 1361*m*, 1299*m*, 1288*m*, 1242*m*, 1167*s*, 1105*m*, 921*m*, 838*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 7.52 (*d*, *J* = 8.4, 1 H); 8.15 (*d*, *J* = 9.0, 2 H); 8.22 (*d*, *J* = 9.0, 2 H); 8.32 (*d*, *J* = 8.4, 1 H); 9.08 (*s*, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 109.9; 118.3; 119.5; 123.1; 131.3; 133.9; 135.0; 138.4; 144.6; 144.8; 145.2. HR-EI-MS: 254.0354 ($M^+$, $C_{13}H_7ClN_4^+$; calc. 254.0354). Anal. calc. for $C_{13}H_7ClN_4$ (254.68): C 61.31, H 2.77, N 22.00; found C 61.09, H 2.78, N 21.84.

*1-[4-(5-Chloro-1*H-*imidazo[4,5-*b*]pyridin-1-yl)phenyl]methanamine* (**53**). *GP K* started from **49** (300 mg, 1.18 mmol), $CoCl_2 \cdot 6\,H_2O$ (1.12 g, 4.71 mmol), $NaBH_4$ (178 mg, 4.71 mmol), and MeOH (100 ml) to yield **53** (250 mg, 82%). Brown solid. The crude product was used in the next step without further purification and was not fully characterized. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 3.82 (*s*, 2 H); 7.43 (*d*, *J* = 8.4, 1 H); 7.59 (*d*, *J* = 8.1, 2 H); 7.65 (*d*, *J* = 8.7, 2 H); 8.12 (*d*, *J* = 8.7, 1 H); 8.89 (*s*, 1 H).

N-*[4-(5-Chloro-1*H-*imidazo[4,5-*b*]pyridin-1-yl)benzyl]benzamide* (**55**). *GP C* started from PhCOOH (61 mg, 0.50 mmol), *N*-hydroxysuccinimide (75 mg, 0.65 mmol), $EDC \cdot HCl$ (144 mg, 0.75 mmol), $CH_2Cl_2$ (2 ml), **53** (155 mg, 0.60 mmol), $Et_3N$ (0.35 ml, 2.50 mmol), and $CH_2Cl_2$ (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98 : 2), **55** (123 mg, 68%). Yellow solid. M.p. 165–167°. IR (neat): 3436*w*, 3348*w*, 3045*w*, 2923*w*, 1651*s*, 1602*m*, 1515*s*, 1481*s*, 1410*s*, 1368*m*, 1328*m*, 1290*m*, 1237*s*, 1209*m*, 1159*m*, 1097*s*, 1076*m*, 976*m*, 922*s*, 798*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 4.77 (*d*, *J* = 5.9, 2 H); 6.74 (br. *s*, 1 H); 7.30 (*d*, *J* = 8.4, 1 H); 7.43–7.62 (*m*, 7 H); 7.78 (*d*, *J* = 8.4, 1 H); 7.83–7.86 (*m*, 2 H); 8.28 (*s*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 43.6; 119.6; 121.3; 124.3; 125.3; 127.2; 128.9; 129.9; 132.1; 134.1; 134.7; 139.9; 145.1; 146.8; 156.0; 167.8. HR-EI-MS: 362.0932 ($M^+$, $C_{20}H_{15}ClN_4O^+$; calc. 362.0929).

N-*(4-[5-[(Diphenylmethylidene)amino]-1*H-*imidazo[4,5-*b*]pyridin-1-yl]benzyl)benzamide* (**57**). *GP E* started from $[Pd_2(dba)_3]$ (14 mg, 0.02 mmol, 5 mol-%), BINAP (20 mg, 0.03 mmol, 10 mol-%), **55** (107 mg, 0.29 mmol), $Cs_2CO_3$ (245 mg, 0.78 mmol), benzophenone imine (0.06 ml, 0.36 mmol), and DME (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98 : 2 → 97 : 3 → 95 : 5), **57** (50 mg, 34%). Yellow solid. M.p. > 115° (dec.). IR (neat): 3284*w*, 3055*w*, 1733*w*, 1639*m*, 1599*m*, 1575*s*, 1515*s*, 1481*m*, 1404*m*, 1292*m*, 1236*m*, 977*m*, 693*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 4.73 (*d*, *J* = 6.2, 2 H); 6.58 (*d*, *J* = 8.7, 1 H); 6.78 (br. *s*, 1 H); 7.22 (*s*, 4 H); 7.37–7.54 (*m*, 11 H); 7.56 (*d*, *J* = 8.4, 1 H); 7.81–7.86 (*m*, 4 H); 8.13 (*s*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 43.5; 112.2; 120.2; 122.5; 123.8; 127.3; 128.1; 128.3; 128.8; 128.9; 129.6; 129.7; 129.9; 130.3; 131.4; 131.9; 134.3; 135.2; 136.5; 139.2; 143.5; 155.6; 160.4; 167.7; 170.7. HR-MALDI-MS: 508.2145 ($[M + H]^+$, $C_{33}H_{26}N_5O^+$; calc. 508.2132).

N-*[4-(5-Amino-1*H-*imidazo[4,5-*b*]pyridin-1-yl)benzyl]benzamide* (**13**). *GP L* started from **57** (43 mg, 0.09 mmol), THF (1.0 ml), and 2M aq. HCl soln. (0.1 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 95:5 → 9:1), **13** (22 mg, 75%). Yellow solid. M.p. 112–114°. IR (neat): 3393*w*, 3326*m*, 3198*m*, 2927*w*, 1636*m*, 1600*m*, 1576*s*, 1517*s*, 1490*s*, 1410*s*, 1283*m*, 1248*s*, 1114*m*, 979*m*, 803*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.55 (*d*, *J* = 6.2, 2 H); 5.83 (*s*, 2 H); 6.48 (*d*, *J* = 8.7, 1 H); 7.47–7.61 (*m*, 7 H); 7.71 (*d*, *J* = 8.7, 1 H); 7.92 (*d*, *J* = 6.9, 2 H); 8.40 (*s*, 1 H); 9.15 (*t*, *J* = 5.6, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 42.2; 105.5; 117.7; 120.9; 122.5; 127.1; 128.2; 128.6; 131.2; 134.0; 134.5; 138.8; 141.7; 155.0; 156.9; 166.0. HR-MALDI-MS: 344.1512 ($[M + H]^+$, $C_{20}H_{18}N_5O^+$; calc. 344.1506).

*4-(5-Chloro-1*H-*imidazo[4,5-*b*]pyridin-1-yl)-3-methylbenzonitrile* (**51**) *and 4-(5-Chloro-3*H-*imidazo[4,5-*b*]pyridin-3-yl)-3-methylbenzonitrile* (**52**). *GP J* started from CuI (124 mg, 0.65 mmol, 20 mol-%), **48** (501 mg, 3.26 mmol), $K_2CO_3$ (1.35 g, 9.77 mmol), 4-iodo-3-methylbenzonitrile (1.19 g, 4.89 mmol), 1,10-phenanthroline (235 mg, 1.30 mmol, 40 mol-%), and DMF (8 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/$Et_2O$ 9:1 → 5:1 → 1:1), **51** (99 mg, 11%) and **52** (171 mg, 20%).

*Data of* **51**: Yellow solid. M.p. 198–200°. IR (neat): 3072*w*, 3040*w*, 2923*w*, 2236*m*, 1727*w*, 1667*w*, 1603*m*, 1504*s*, 1484*s*, 1435*m*, 1410*s*, 1313*m*, 1285*m*, 1246*m*, 1206*m*, 1174*m*, 1118*m*, 1100*m*, 978*m*, 917*m*, 895*m*, 829*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.20 (*s*, 3 H); 7.32 (*d*, *J* = 8.4, 1 H); 7.46 (*d*, *J* = 8.4, 1 H); 7.46 (*d*, *J* = 8.4, 1 H); 7.73 (*dd*, *J* = 8.3, 1.8, 1 H); 7.78 (br. *s*, 1 H); 8.19 (*s*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 17.9; 114.4; 117.6; 120.0; 121.0; 128.5; 131.2; 131.6; 135.8; 136.8; 137.9; 145.3; 147.2; 155.5. HR-EI-MS: 268.0510 ($M^+$, $C_{14}H_9ClN_4^+$; calc. 268.0511). Anal. calc. for $C_{14}H_9ClN_4$ (268.70): C 62.58, H 3.38, N 20.85; found C 62.37, H 3.20, N 20.79.

*Data of* **52**: White solid. M.p. 238–240°. IR (neat): 3100*w*, 3036*w*, 2923*w*, 2228*m*, 1596*m*, 1581*m*, 1506*s*, 1486*m*, 1449*m*, 1409*s*, 1355*m*, 1312*m*, 1292*m*, 1225*s*, 1167*s*, 1123*m*, 1102*m*, 1040*m*, 985*m*, 891*m*, 845*s*, 816*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.25 (*s*, 3 H); 7.36 (*d*, *J* = 8.4, 1 H); 7.47 (*d*, *J* = 8.1, 1 H); 7.70 (*d*, *J* = 8.4, 1 H); 7.75 (br. *s*, 1 H); 8.09 (*s*, 1 H); 8.13 (*d*, *J* = 8.4, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 18.5; 113.9; 118.0; 120.0; 128.8; 131.1; 131.2; 134.2; 135.5; 137.2; 137.3; 143.8; 145.3; 147.1. HR-EI-MS: 268.0512 ($M^+$, $C_{14}H_9ClN_4^+$; calc. 268.0511). Anal. calc. for $C_{14}H_9ClN_4$ (268.70): C 62.58, H 3.38, N 20.85; found C 62.32, H 3.21, N 20.56.

*1-[4-(5-Chloro-1*H-*imidazo[4,5-*b*]pyridin-1-yl)-3-methylphenyl]methanamine* (**54**). *GP K* started from **51** (129 mg, 0.48 mmol), $CoCl_2 \cdot 6\ H_2O$ (460 mg, 1.94 mmol), $NaBH_4$ (37 mg, 1.94 mmol), and $CH_2Cl_2$/MeOH 1:1 (50 ml) to yield **54** (103 mg, 79%). Yellow oil. The crude product was used in the next step without further purification and was not fully characterized. $^1$H-NMR (300 MHz, $CDCl_3$): 2.08 (*s*, 3 H); 3.98 (*s*, 2 H); 7.25–7.46 (*m*, 5 H); 8.16 (*s*, 1 H). HR-EI-MS: 271.0745 ($[M - H]^+$, $C_{14}H_{12}ClN_4^+$; calc. 271.0745).

N-*[4-(5-Chloro-1*H-*imidazo[4,5-*b*]pyridin-1-yl)-3-methylbenzyl]benzamide* (**56**). *GP C* started from PhCOOH (59 mg, 0.39 mmol), *N*-hydroxysuccinimide (57 mg, 0.49 mmol), EDC · HCl (110 mg, 0.57 mmol), $CH_2Cl_2$ (2 ml), **54** (71 mg, 0.26 mmol), $Et_3N$ (0.2 ml, 1.30 mmol), and $CH_2Cl_2$ (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **56** (52 mg, 53%). Yellow solid. M.p. 78–80°. IR (neat): 3328*w*, 3065*w*, 2924*w*, 1640*m*, 1602*m*, 1531*m*, 1505*s*, 1476*s*, 1401*s*, 1358*m*, 1306*m*, 1244*m*, 1226*s*, 1170*s*, 1113*m*, 1098*m*, 978*m*, 920*s*, 806*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.09 (*s*, 3 H); 4.74 (*d*, *J* = 5.9, 2 H); 6.58 (br. *s*, 1 H); 7.26–7.29 (*m*, 2 H); 7.38–7.55 (*m*, 6 H); 7.84 (*d*, *J* = 8.1, 2 H); 8.15 (*s*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 17.8; 43.6; 119.5; 121.3; 126.2; 127.0; 127.2; 127.8; 128.9; 131.3; 132.0; 133.1; 134.2; 135.6; 141.0; 146.0; 146.6; 155.4; 167.7. HR-MALDI-MS: 377.1156 ($[M + H]^+$, $C_{21}H_{18}ClN_4O^+$; calc. 377.1164).

N-*(4-{5-[(Diphenylmethylidene)amino]-1*H-*imidazo[4,5-*b*]pyridin-1-yl}-3-methylbenzyl)benzamide* (**58**). *GP E* started from $[Pd_2(dba)_3]$ (9 mg, 0.01 mmol, 10 mol-%), BINAP (12 mg, 0.02 mmol, 20 mol-%), **56** (37 mg, 0.10 mmol), $Cs_2CO_3$ (160 mg, 0.49 mmol), benzophenone imine (0.02 ml, 0.12 mmol), and DME (1 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2 → 97:3 → 95:5), **58** (29 mg, 57%). Yellow solid. M.p. 118–120°. IR (neat): 3276*w*, 3057*w*, 2922*w*, 2852*w*, 1634*m*, 1599*m*, 1575*m*, 1532*m*, 1505*s*, 1479*s*, 1446*m*, 1401*s*, 1361*m*, 1292*s*, 1249*m*, 1194*m*, 1142*m*, 1101*m*, 1075*w*, 1028*w*, 978*s*, 821*m*, 693*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 2.05 (*s*, 3 H); 4.71 (*d*, *J* = 6.0, 2 H); 6.53 (*d*, *J* = 8.6, 1 H); 6.57 (*t*, *J* = 6.0, 1 H); 7.18–7.56 (*m*, 15 H); 7.81–7.84 (*m*, 4 H); 8.01 (*s*, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 17.8; 43.7; 112.1; 120.1; 123.6; 126.7; 127.2; 128.0; 128.0; 128.3; 128.9; 129.7; 130.0; 131.2; 131.3;

132.0; 133.9; 134.3; 135.7; 136.6; 139.3; 140.3; 144.6; 155.1; 160.3; 167.7; 170.6 (one arom. signal missing due to overlap). HR-MALDI-MS: 520.2130 ($[M-H]^+$, $C_{34}H_{26}N_5O^+$; calc. 520.2132).

N-*[4-(5-Amino-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-3-methylbenzyl]benzamide* (**14**). *GP L* started from **58** (28 mg, 0.05 mmol), THF (1.0 ml), and 2M aq. HCl soln. (0.1 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 95:5 → 9:1), **14** (10 mg, 52%). Grey solid. M.p. 176–178°. IR (neat): 3202*w*, 2924*w*, 1601*s*, 1575*m*, 1538*m*, 1505*s*, 1489*s*, 1411*s*, 1349*w*, 1306*s*, 1248*m*, 1229*m*, 1168*w*, 1105*w*, 1027*w*, 983*w*, 806*m*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.05 (*s*, 3 H); 4.54 (*d*, *J* = 5.9, 2 H); 5.78 (*s*, 2 H); 6.42 (*d*, *J* = 8.4, 1 H); 7.25 (*d*, *J* = 8.7, 1 H); 7.33 (br. *s*, 2 H); 7.41 (*s*, 1 H); 7.46–7.55 (*m*, 3 H); 7.92 (*d*, *J* = 8.4, 2 H); 8.17 (*s*, 1 H); 9.15 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 17.3; 42.2; 105.5; 119.2; 120.4; 125.8; 127.0; 127.1; 128.2; 129.9; 131.2; 133.0; 133.9; 134.0; 140.4; 142.8; 154.2; 156.8; 166.0. HR-EI-MS: 357.1586 ($M^+$, $C_{21}H_{19}N_5O^+$; calc. 357.1585).

*{4-[(Triisopropylsilyl)oxy)methyl]naphthalen-1-yl}methanol* (**61**). To a soln. of **60** (500 mg, 2.66 mmol) in THF (10 ml), (i-Pr)$_3$SiCl (0.6 ml, 2.66 mmol) and 1*H*-imidazole (181 mg, 2.66 mmol) were added at 0°. The mixture was stirred at 0° for 2 h and at 25° for 19 h. After addition of $CH_2Cl_2$ (50 ml), the mixture was washed with sat. aq. $NaHCO_3$ soln. (3 × 50 ml) and sat. aq. NaCl soln. (50 ml). The org. phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by CC ($SiO_2$, $CH_2Cl_2$) to yield **61** (418 mg, 46%). White solid. M.p. 88–90°. IR (neat): 3256*w*, 2937*m*, 2862*m*, 1718*w*, 1516*w*, 1461*m*, 1391*m*, 1270*m*, 1243*m*, 1117*s*, 1006*s*, 880*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.11–1.30 (*m*, 21 H); 1.69 (*t*, *J* = 5.9, 1 H); 5.15 (*d*, *J* = 5.9, 2 H); 5.30 (*s*, 2 H); 7.50–7.59 (*m*, 3 H); 7.65 (*d*, *J* = 7.5, 1 H); 8.00 (*dd*, *J* = 7.2, 2.5, 1 H); 8.19 (*dd*, *J* = 7.2, 2.5, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 12.3; 18.3; 63.5; 64.1; 123.0; 123.9; 124.6; 125.5; 126.0; 126.2; 131.1; 131.4; 135.6; 137.6. HR-EI-MS: 301.1619 ($[M-C_3H_7]^+$, $C_{18}H_{25}O_2Si^+$; calc. 301.1619).

*{[4-(Bromomethyl)naphthalen-1-yl]methoxy}triisopropylsilane* (**62**). To a soln. of **61** (1.48 g, 4.30 mmol) in $CH_2Cl_2$ (30 ml), $PPh_3$ (1.24 g, 4.73 mmol) was added at 0°, and the mixture was stirred for 10 min. $CBr_4$ (1.57 g, 4.73 mmol) was added portionwise, and the mixture was stirred for 3 h at 0°. The solvent was concentrated *in vacuo*, and the crude product was purified by CC ($SiO_2$, pentane → pentane/$CH_2Cl_2$ 10:1) to yield **62** (1.11 g, 63%). Yellow oil. IR (neat): 2940*m*, 2863*m*, 1517*w*, 1461*m*, 1388*w*, 1245*m*, 1206*m*, 1164*m*, 1112*s*, 880*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.18–1.27 (*m*, 21 H); 4.98 (*s*, 2 H); 5.29 (*s*, 2 H); 7.49–7.64 (*m*, 4 H); 7.98 (*d*, *J* = 7.2, 1 H); 8.19 (*d*, *J* = 8.4, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 12.3; 18.3; 63.4; 63.7; 122.9; 123.9; 124.6; 126.3; 126.4; 127.8; 131.2; 132.5; 136.1; 139.0. HR-EI-MS: 363.0777 ($[M-C_3H_7]^+$, $C_{18}H_{24}BrOSi^+$; calc. 363.0775).

*Benzyl {1,2-Dihydro-2-oxo-1-[(4-{[(triisopropylsilyl)oxy]methyl}naphthalen-1-yl)methyl]pyrimidin-4-yl}carbamate* (**64**). To a suspension of **63** (708 mg, 2.89 mmol) and NaH (115 mg, 2.89 mmol, as a 60% dispersion in mineral oil) in anh. DMF stirred at 25° for 1.5 h, **62** (1.07 g, 2.62 mmol) in anh. DMF was added slowly. The mixture was stirred at 25° for 17 h. MeOH was added, the solvent was concentrated *in vacuo*, and the crude product was purified by CC ($SiO_2$, $CH_2Cl_2$/MeOH 99:1 → 98:2) to yield **64** (1.18 g, 79%). White solid. M.p. 67–69°. IR (neat): 2940*m*, 2863*m*, 1743*m*, 1661*s*, 1627*s*, 1553*m*, 1495*s*, 1455*m*, 1366*s*, 1207*s*, 1050*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.12–1.31 (*m*, 21 H); 5.17 (*s*, 2 H); 5.31 (*s*, 2 H); 5.50 (*s*, 2 H); 7.13 (*d*, *J* = 7.2, 1 H); 7.30–7.35 (*m*, 6 H); 7.45 (*d*, *J* = 7.2, 1 H); 7.50–7.57 (*m*, 2 H); 7.71 (*d*, *J* = 7.2, 1 H); 7.76 (br. *s*, 1 H); 7.90–8.02 (*m*, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 12.2; 18.3; 50.5; 63.1; 67.9; 95.0; 122.6; 123.7; 124.0; 126.4; 127.0; 128.3; 128.6; 129.1; 130.0; 131.0; 134.9; 138.9; 146.8; 152.1; 155.8; 161.8 (two arom. signals missing due to overlap). HR-MALDI-MS: 572.2930 ($[M+H]^+$, $C_{33}H_{42}N_3O_4Si^+$; calc. 572.2939). Anal. calc. for $C_{33}H_{41}N_3O_4Si$ (571.78): C 69.32, H 7.23, N 7.35; found C 69.04, H 7.29, N 7.45.

*Benzyl (1,2-Dihydro-1-{[4-(hydroxymethyl)naphthalen-1-yl]methyl}-2-oxopyrimidin-4-yl)carbamate* (**65**). *GP F* started from **64** (182 mg, 0.32 mmol), THF (5 ml), and $Bu_4NF$ (1M in THF, 0.38 ml, 0.38 mmol) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **65** (120 mg, 90%). White solid. M.p. > 90° (dec.). IR (neat): 3264*w*, 2930*w*, 1742*m*, 1646*s*, 1626*s*, 1553*m*, 1494*s*, 1455*m*, 1366*s*, 1191*s*, 1058*m*, 998*m*, 744*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 1.84 (br. *s*, 1 H); 5.18 (*s*, 2 H); 5.20 (*s*, 2 H); 5.52 (*s*, 2 H); 7.04 (*d*, *J* = 7.2, 1 H); 7.30–7.43 (*m*, 7 H); 7.55–7.60 (*m*, 3 H); 7.92–7.95 (*m*, 1 H); 8.15–8.18 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 50.2; 63.0; 67.8; 95.0; 123.7; 124.2; 124.5; 126.7; 127.1; 127.9; 128.2; 128.6; 130.1; 131.2; 131.6; 134.8; 138.3; 146.9; 152.1; 155.9; 161.9 (one arom. signal missing due to overlap). HR-MALDI-MS: 416.1602 ($[M+H]^+$, $C_{24}H_{22}N_3O_4^+$; calc. 416.1605).

*Benzyl (1-{[4-(Azidomethyl)naphthalen-1-yl]methyl}-1,2-dihydro-2-oxopyrimidin-4-yl)carbamate* (**66**). *GP G* started from **65** (1.13 g, 2.73 mmol), DPPA (0.82 ml, 3.82 mmol), THF (15 ml), and DBU (0.57 ml, 3.82 mmol) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 99:1 → 98:2), **66** (1.12 g, 93%). White solid. M.p. > 65° (dec.). IR (neat): 3030*w*, 2094*m*, 1738*m*, 1657*m*, 1626*m*, 1548*m*, 1494*s*, 1454*m*, 1365*s*, 1190*s*, 1055*m*, 995*m*, 743*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 5.18 (*s*, 2 H); 5.30 (*s*, 2 H); 5.54 (*s*, 2 H); 7.08 (*d*, *J* = 7.5, 1 H); 7.33–7.41 (*m*, 7 H); 7.48 (*s*, 1 H); 7.49 (*d*, *J* = 7.2, 1 H); 7.57–7.66 (*m*, 2 H); 7.97–8.00 (*m*, 1 H); 8.07–8.10 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 50.3; 52.9; 68.0; 95.1; 124.0; 124.3; 126.4; 127.2; 127.6; 128.3; 128.6; 131.4; 131.5; 131.7; 132.8; 134.7; 146.8; 151.9; 155.6; 161.7 (two arom. signals missing due to overlap). HR-MALDI-MS: 441.1664 ($[M + H]^+$, $C_{24}H_{21}N_6O_3^+$; calc. 441.1670). Anal. calc. for $C_{24}H_{20}N_6O_3$ (440.46): C 65.45, H 4.58, N 19.08; found C 65.49, H 4.59, N 18.79.

*Benzyl (1-{[4-(Aminomethyl)naphthalen-1-yl]methyl}-1,2-dihydro-2-oxopyrimidin-4-yl)carbamate* (**67**). *GP H* started from **66** (1.12 g, 2.54 mmol), $PPh_3$ (1.33 g, 5.08 mmol), THF (20 ml), and $H_2O$ (0.8 ml) to yield **67** (1.03 g, 98%). White solid. M.p. 156–157°. IR (neat): 3352*w*, 3287*w*, 2917*w*, 1732*m*, 1652*s*, 1584*s*, 1507*s*, 1454*m*, 1422*m*, 1364*s*, 1222*s*, 1189*s*, 1066*s*, 934*s*, 745*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 3.65 (*s*, 2 H); 4.38 (*s*, 2 H); 5.17 (*s*, 2 H); 5.51 (*s*, 2 H); 7.03 (*d*, *J* = 7.2, 1 H); 7.29–7.43 (*m*, 7 H); 7.51–7.62 (*m*, 4 H); 7.91–7.94 (*m*, 1 H); 8.13–8.16 (*m*, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 44.1; 50.6; 68.2; 95.2; 124.1; 124.4; 127.0; 127.4; 128.6; 128.8; 128.9; 131.8; 132.1; 132.3; 132.4; 133.9; 134.0; 141.1; 147.0; 152.4; 156.2; 162.1. HR-MALDI-MS: 415.1758 ($[M + H]^+$, $C_{24}H_{23}N_4O_3^+$; calc. 415.1765).

*Benzyl [1-({4-[(Benzoylamino)methyl]naphthalen-1-yl}methyl)-1,2-dihydro-2-oxopyrimidin-4-yl]-carbamate* (**68**). *GP C* started from PhCOOH (49 mg, 0.40 mmol), *N*-hydroxysuccinimide (60 mg, 0.52 mmol), EDC·HCl (116 mg, 0.60 mmol), $CH_2Cl_2$ (3 ml), **67** (200 mg, 0.48 mmol), $Et_3N$ (0.3 ml, 2.01 mmol), and $CH_2Cl_2$ (3 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2 → 97:3), **68** (168 mg, 81%). White solid. M.p. 208–210°. IR (neat): 3157*w*, 3066*w*, 2961*w*, 1720*m*, 1641*s*, 1613*s*, 1536*s*, 1487*s*, 1456*m*, 1424*s*, 1384*s*, 1361*s*, 1287*s*, 1249*s*, 1200*s*, 1029*s*, 998*s*, 751*s*, 695*s*. $^1$H-NMR (300 MHz, $CDCl_3$/$CD_3OD$ 6:1): 4.95 (*d*, *J* = 5.6, 2 H); 5.04 (*s*, 2 H); 5.37 (*s*, 2 H); 7.01 (*d*, *J* = 7.0, 1 H); 7.18–7.23 (*m*, 5 H); 7.28–7.32 (*m*, 3 H); 7.34–7.50 (*m*, 4 H); 7.66–7.72 (*m*, 3 H); 7.77–7.81 (*m*, 1 H); 8.03–8.06 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$/$CD_3OD$ 6:1): 41.9; 50.5; 67.7; 96.3; 123.8; 124.4; 125.5; 127.1; 127.2; 127.3; 127.6; 128.2; 128.6; 128.6; 130.3; 131.4; 131.8; 132.0; 134.0; 135.2; 135.5; 147.1; 153.1; 157.0; 163.1; 168.4 (one arom. signal missing due to overlap). HR-MALDI-MS: 519.2019 ($[M + H]^+$, $C_{31}H_{27}N_4O_4^+$; calc. 519.2027). Anal. calc. for $C_{31}H_{26}N_4O_4$ (518.57): C 71.80, H 5.05, N 10.80; found C 71.79, H 5.06, N 10.73.

N-*({4-[(4-Amino-2-oxopyrimidin-1(2H)-yl)methyl]naphthalen-1-yl}methyl)benzamide* (**16**). *GP D* started from **68** (150 mg, 0.29 mmol), 10% Pd/C (15 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:1 (15 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 9:1), **16** (85 mg, 76%). White solid. M.p. 305–306°. IR (neat): 3352*m*, 3072*m*, 1641*s*, 1615*s*, 1519*s*, 1484*s*, 1423*s*, 1381*s*, 1341*m*, 1296*s*, 1278*s*, 1207*m*, 786*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.93 (*d*, *J* = 5.6, 2 H); 5.34 (*s*, 2 H); 5.66 (*d*, *J* = 7.2, 1 H); 7.04 (br. *s*, 1 H); 7.11 (br. *s*, 1 H); 7.21 (*d*, *J* = 7.2, 1 H); 7.43–7.55 (*m*, 5 H); 7.57–7.64 (*m*, 2 H); 7.89 (*d*, *J* = 8.4, 2 H); 8.14–8.17 (*m*, 1 H); 8.22–8.25 (*m*, 1 H); 9.06 (*t*, *J* = 5.6, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 40.8; 48.5; 94.0; 124.1; 124.3; 124.9; 125.2; 126.4; 127.4; 128.3; 130.9; 131.2; 131.3; 132.8; 134.3; 134.8; 145.3; 155.9; 165.9; 166.3 (one arom. signal missing due to overlap). HR-MALDI-MS: 407.1473 ($[M + Na]^+$, $C_{23}H_{20}N_4NaO_2^+$; calc. 407.1479). Anal. calc. for $C_{23}H_{20}N_4O_2$ (384.44): C 71.86, H 5.24, N 14.57; found C 71.58, H 5.24, N 14.41.

*Benzyl {1-[(4-{[(4-Chlorobenzoyl)amino]methyl}naphthalen-1-yl)methyl]-1,2-dihydro-2-oxopyrimidin-4-yl}carbamate* (**69**). *GP C* started from 4-chlorobenzoic acid (63 mg, 0.41 mmol), *N*-hydroxysuccinimide (59 mg, 0.51 mmol), EDC·HCl (114 mg, 0.59 mmol), $CH_2Cl_2$ (4 ml), **67** (112 mg, 0.27 mmol), $Et_3N$ (0.2 ml, 1.35 mmol), and $CH_2Cl_2$ (4 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **69** (110 mg, 74%). White solid. M.p. 184–186°. IR (neat): 3200*w*, 3060*w*, 2924*w*, 1749*m*, 1647*s*, 1542*m*, 1488*s*, 1437*m*, 1420*m*, 1365*s*, 1320*m*, 1191*s*, 1119*s*, 1095*s*, 1060*m*, 997*s*, 805*s*, 786*s*, 752*s*, 720*s*, 694*s*. $^1$H-NMR (300 MHz, $CDCl_3$/$CD_3OD$ 6:1): 4.92 (br. *s*, 2 H); 5.04 (*s*, 2 H); 5.36 (*s*, 2 H); 7.01 (*d*, *J* = 7.2, 1 H); 7.19–7.49 (*m*, 12 H); 7.64 (*d*, *J* = 8.4, 2 H); 7.77–7.80 (*m*, 1 H); 8.01–8.05 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$/$CD_3OD$ 6:1): 41.7; 50.4; 67.6; 96.1; 123.5; 124.1; 125.2; 126.8; 127.0; 127.2; 127.9; 128.3; 128.5; 128.6; 130.0; 130.4; 131.1; 131.6; 134.9; 135.1; 137.6; 146.9; 152.8; 156.7; 162.8; 167.0 (one arom. signal missing due to overlap). HR-MALDI-MS: 575.1451 ($[M + Na]^+$, $C_{31}H_{25}ClN_4NaO_4^+$; calc. 575.1457).

N-*({4-[(4-Amino-2-oxopyrimidin-1(2*H*)-yl)methyl]naphthalen-1-yl}methyl)-4-chlorobenzamide* (**17**). *GP D* started from **69** (120 mg, 0.22 mmol), 10% Pd/C (12 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:1 (20 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 9:1), **17** (60 mg, 65%). White solid. M.p. 301–303°. IR (neat): 3349*m*, 3074*m*, 1660*s*, 1616*s*, 1519*s*, 1377*s*, 1309*m*, 1280*s*, 1206*m*, 1130*m*, 1094*m*, 1016*m*, 848*m*, 786*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.92 (*d*, *J* = 5.9, 2 H); 5.34 (*s*, 2 H); 5.66 (*d*, *J* = 7.2, 1 H); 7.05 (br. *s*, 1 H); 7.10 (br. *s*, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 7.45 (*d*, *J* = 7.2, 1 H); 7.49 (*d*, *J* = 7.2, 1 H); 7.54 (*d*, *J* = 8.4, 2 H); 7.59–7.64 (*m*, 2 H); 7.92 (*d*, *J* = 8.4, 2 H); 8.15–8.18 (*m*, 1 H); 8.21–8.24 (*m*, 1 H); 9.14 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 40.9; 48.5; 94.0; 124.1; 124.3; 125.1; 126.4; 127.4; 128.4; 129.3; 130.9; 132.2; 132.9; 133.1; 134.5; 136.1; 145.4; 155.6; 165.2; 165.9 (one arom. signal missing due to overlap). HR-MALDI-MS: 419.1260 ($[M + H]^+$, $C_{23}H_{20}ClN_4O_2^+$; calc. 419.1269).

*Benzyl {1,2-Dihydro-1-[(4-{[(4-methoxybenzoyl)amino]methyl}naphthalen-1-yl)methyl]-2-oxopyrimidin-4-yl}carbamate* (**70**). *GP C* started from 4-methoxybenzoic acid (61 mg, 0.40 mmol), *N*-hydroxysuccinimide (60 mg, 0.52 mmol), EDC·HCl (116 mg, 0.60 mmol), $CH_2Cl_2$ (2 ml), **67** (250 mg, 0.60 mmol), $Et_3N$ (0.3 ml, 2.01 mmol), and $CH_2Cl_2$ (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **70** (48 mg, 22%). White solid. M.p. 192–194°. IR (neat): 3140*w*, 3076*w*, 2967*w*, 1749*m*, 1652*s*, 1604*s*, 1549*s*, 1494*s*, 1418*m*, 1364*s*, 1323*m*, 1256*s*, 1204*s*, 1180*s*, 1057*s*, 1028*m*, 997*s*, 786*s*, 738*s*. $^1$H-NMR (300 MHz, $CDCl_3/CD_3OD$ 6:1): 3.70 (*s*, 3 H); 4.92 (*d*, *J* = 5.7, 2 H); 5.04 (*s*, 2 H); 5.36 (*s*, 2 H); 6.78 (*d*, *J* = 9.0, 2 H); 7.00 (*d*, *J* = 6.9, 1 H); 7.19–7.30 (*m*, 6 H); 7.36–7.49 (*m*, 4 H); 7.65 (*d*, *J* = 9.0, 2 H); 7.76–7.80 (*m*, 1 H); 8.02–8.04 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3/CD_3OD$ 6:1): 41.8; 50.4; 55.3; 67.7; 96.3; 113.7; 123.7; 124.4; 125.4; 126.2; 127.1; 127.3; 127.6; 128.1; 128.6; 128.8; 129.0; 130.1; 131.9; 132.0; 132.5; 135.7; 147.1; 155.0; 157.0; 162.4; 163.1; 168.0. HR-MALDI-MS: 571.1943 ($[M + Na]^+$, $C_{32}H_{28}N_4NaO_5^+$; calc. 571.1952).

N-*({4-[(4-Amino-2-oxopyrimidin-1(2*H*)-yl)methyl]naphthalen-1-yl}methyl)-4-methoxybenzamide* (**18**). *GP D* started from **70** (48 mg, 0.09 mmol), 10% Pd/C (5 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:1 (10 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 9:1), **18** (20 mg, 54%). White solid. M.p. 302–304°. IR (neat): 3349*m*, 3076*w*, 1660*m*, 1619*s*, 1575*m*, 1522*m*, 1503*s*, 1485*s*, 1418*m*, 1398*m*, 1381*s*, 1298*s*, 1279*m*, 1252*s*, 1180*s*, 1129*m*, 1108*m*, 1022*m*, 846*m*, 786*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 3.80 (*s*, 3 H); 4.91 (*d*, *J* = 5.3, 2 H); 5.34 (*s*, 2 H); 5.66 (*d*, *J* = 7.2, 1 H); 6.99 (*d*, *J* = 9.0, 2 H); 7.04 (br. *s*, 1 H); 7.10 (br. *s*, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 7.44 (*d*, *J* = 7.2, 1 H); 7.48 (*d*, *J* = 7.5, 1 H); 7.58–7.62 (*m*, 2 H); 7.88 (*d*, *J* = 8.7, 2 H); 8.14–8.17 (*m*, 1 H); 8.22–8.25 (*m*, 1 H); 8.90 (*t*, *J* = 5.6, 1 H). HR-MALDI-MS: 437.1583 ($[M + Na]^+$, $C_{24}H_{22}N_4NaO_3^+$; calc. 437.1584). Anal. calc. for $C_{24}H_{22}N_4O_3$ (414.46): C 69.55, H 5.35, N 13.52; found C 69.62, H 5.54, N 13.30.

*Benzyl (1,2-Dihydro-2-oxo-1-{[4-({[4-(trifluoromethyl)benzoyl]amino}methyl)naphthalen-1-yl]methyl}pyrimidin-4-yl)carbamate* (**71**). *GP C* started from α,α,α-trifluoro-*p*-toluic acid (44 mg, 0.23 mmol), *N*-hydroxysuccinimide (35 mg, 0.30 mmol), EDC·HCl (67 mg, 0.35 mmol), $CH_2Cl_2$ (2 ml), **67** (144 mg, 0.35 mmol), $Et_3N$ (0.2 ml, 1.16 mmol), and $CH_2Cl_2$ (2 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **71** (56 mg, 42%). White solid. M.p. 247–249°. IR (neat): 3240*w*, 3150*w*, 2973*m*, 1752*m*, 1651*s*, 1629*m*, 1616*m*, 1552*m*, 1493*s*, 1454*m*, 1419*m*, 1362*s*, 1319*s*, 1260*m*, 1165*s*, 1123*s*, 1061*s*, 997*s*, 855*s*, 803*s*, 745*s*, 693*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.96 (*d*, *J* = 5.6, 2 H); 5.18 (*s*, 2 H); 5.50 (*s*, 2 H); 7.02 (*d*, *J* = 7.2, 1 H); 7.21 (*d*, *J* = 7.2, 1 H); 7.33–7.40 (*m*, 5 H); 7.48 (*d*, *J* = 7.2, 1 H); 7.62–7.65 (*m*, 2 H); 7.85 (*d*, *J* = 8.4, 2 H); 8.03 (*d*, *J* = 7.5, 1 H); 8.09 (*d*, *J* = 8.1, 2 H); 8.15–8.17 (*m*, 1 H); 8.23–8.26 (*m*, 1 H); 9.30 (*t*, *J* = 5.6, 1 H); 10.82 (*s*, 1 H). $^{13}$C-NMR (125 MHz, $(CD_3)_2SO$): 40.9; 49.3; 66.4; 94.6; 123.7; 123.8 (*q*, $^1J$(C, F) = 270.8, $CF_3$); 124.2; 125.0; 125.2 (*d*, $^3J$(C, F) = 3.8); 126.3; 126.4; 127.8; 128.0; 128.2; 128.4; 130.6; 131.1 (*q*, $^2J$(C, F) = 31.2); 131.1; 131.7; 134.5; 135.8; 137.9; 149.4; 153.0; 155.0; 162.8; 165.0 (one arom. signal missing due to overlap). $^{19}$F-NMR (282 MHz, $(CD_3)_2SO$): −60.9. HR-MALDI-MS: 587.1892 ($[M + H]^+$, $C_{32}H_{26}F_3N_4O_4^+$; calc. 587.1901).

N-*({4-[(4-Amino-2-oxopyrimidin-1(2*H*)-yl)methyl]naphthalen-1-yl}methyl)-4-(trifluoromethyl)benzamide* (**19**). *GP D* started from **71** (37 mg, 0.06 mmol), 10% Pd/C (4 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:1 (6 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 9:1), **19** (16 mg, 59%). White solid. M.p. > 308° (dec.) IR (neat): 3355*m*, 3076*w*, 1660*m*, 1643*s*, 1617*s*, 1539*m*, 1521*m*, 1486*s*, 1425*m*, 1381*m*, 1325*s*, 1279*m*, 1180*s*, 1134*s*, 1109*s*, 1071*s*, 1020*m*, 860*m*, 784*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 4.95 (*d*, *J* = 5.6, 2 H); 5.35 (*s*, 2 H); 5.66 (*d*, *J* = 7.5, 1 H); 7.04 (br. *s*, 1 H); 7.10 (br. *s*, 1 H); 7.20 (*d*, *J* = 7.2, 1 H); 7.47 (*d*, *J* = 6.9, 1 H); 7.49 (*d*, *J* = 7.2, 1 H); 7.58–7.63 (*m*, 2 H); 7.85 (*d*, *J* = 8.1, 2 H); 8.08 (*d*, *J* =

8.1, 2 H); 8.15–8.18 (*m*, 1 H); 8.21–8.24 (*m*, 1 H); 9.30 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 41.0; 48.5; 93.8; 123.9; 124.0; 124.8; 124.9; 125.2 (*d*, $^3J$(C, F) = 3.8); 126.2; 126.2; 128.1; 130.7; 131.0; 132.8; 134.1; 137.8; 145.1; 155.6; 164.8; 165.0 ($CF_3$ signal missing, one arom. signal missing due to overlap). $^{19}$F-NMR (282 MHz, $(CD_3)_2SO$): −60.9. HR-MALDI-MS: 453.1524 ($[M + H]^+$, $C_{24}H_{20}F_3N_4O_2^+$; calc. 453.1533). Anal. calc. for $C_{24}H_{19}F_3N_4O_2$ (452.43): C 63.71, H 4.23, N 12.38; found C 63.43, H 4.42, N 12.08.

*Benzyl (1,2-Dihydro-2-oxo-1-{[4-({[(4-quinolin-6-yl)carbonyl]amino}methyl)naphthalen-1-yl]methyl}pyrimidin-4-yl)carbamate* (**72**). *GP C* started from quinoline-6-carboxylic acid (125 mg, 0.72 mmol), *N*-hydroxysuccinimide (106 mg, 0.92 mmol), EDC · HCl (204 mg, 1.06 mmol), $CH_2Cl_2$ (6 ml), **67** (200 mg, 0.48 mmol), $Et_3N$ (0.3 ml, 2.41 mmol), and $CH_2Cl_2$ (6 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2 → 95:5), **72** (212 mg, 78%). White solid. M.p. > 153° (dec.). IR (neat): 3200*w*, 3062*w*, 1746*m*, 1646*s*, 1616*s*, 1548*s*, 1494*s*, 1418*m*, 1366*s*, 1300*m*, 1255*m*, 1202*s*, 1056*m*, 1000*m*, 846*m*, 785*s*, 747*s*, 696*s*. $^1$H-NMR (300 MHz, $CDCl_3/CD_3OD$ 6:1): 5.01 (*d*, *J* = 5.6, 2 H); 5.05 (*s*, 2 H); 5.38 (*s*, 2 H); 7.03 (*d*, *J* = 7.2, 1 H); 7.21–7.23 (*m*, 5 H); 7.31 (*d*, *J* = 7.5, 1 H); 7.39 (*dd*, *J* = 8.4, 4.4, 1 H); 7.43 (*d*, *J* = 7.4, 1 H); 7.47–7.52 (*m*, 3 H); 7.79–7.82 (*m*, 1 H); 7.96 (*d*, *J* = 9.0, 1 H); 8.03 (*dd*, *J* = 8.7, 1.9, 1 H); 8.08–8.12 (*m*, 1 H); 8.18–8.21 (*m*, 2 H); 8.29 (*d*, *J* = 1.6, 1 H); 8.78 (*dd*, *J* = 4.4, 1.6, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3/CD_3OD$ 6:1): 42.0; 50.5; 67.7; 96.3; 122.0; 123.8; 124.4; 125.6; 127.1; 127.3; 127.4; 127.8; 127.9; 128.2; 128.6; 128.6; 128.9; 130.4; 131.4; 132.0; 132.3; 135.2; 135.4; 138.0; 147.2; 148.7; 151.6; 153.1; 157.0; 163.1; 167.5 (one arom. signal missing due to overlap). HR-MALDI-MS: 570.2127 ($[M + H]^+$, $C_{34}H_{28}N_5O_4^+$; calc. 570.2136).

N-*({4-[(4-Amino-2-oxopyrimidin-1(2*H*)-yl)methyl]naphthalen-1-yl}methyl)quinoline-6-carboxamide* (**20**). *GP D* started from **72** (177 mg, 0.31 mmol), 10% Pd/C (18 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:1 (40 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 9:1), **20** (54 mg, 40%). White solid. M.p. > 260° (dec.). IR (neat): 3351*w*, 3105*w*, 1659*m*, 1616*s*, 1519*m*, 1484*s*, 1420*m*, 1377*m*, 1326*m*, 1280*m*, 1204*m*, 1130*m*, 1032*w*, 785*s*, 649*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 5.00 (*d*, *J* = 5.9, 2 H); 5.35 (*s*, 2 H); 5.66 (*d*, *J* = 7.2, 1 H); 7.04 (br. *s*, 1 H); 7.11 (br. *s*, 1 H); 7.22 (*d*, *J* = 7.8, 1 H); 7.50 (*d*, *J* = 7.2, 1 H); 7.52 (*d*, *J* = 7.2, 1 H); 7.58–7.65 (*m*, 3 H); 8.08 (*d*, *J* = 8.7, 1 H); 8.16–8.29 (*m*, 3 H); 8.45–8.74 (*m*, 1 H); 8.55 (*d*, *J* = 1.6, 1 H); 8.98 (*dd*, *J* = 4.4, 1.6, 1 H); 9.30 (*t*, *J* = 5.9, 1 H). $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$): 41.0; 48.5; 94.0; 122.2; 124.1; 124.3; 125.1; 126.4; 127.2; 127.9; 128.1; 129.0; 130.9; 131.3; 132.2; 133.0; 134.6; 137.2; 145.4; 148.7; 152.1; 155.9; 165.9; 165.9 (two arom. signals missing due to overlap). HR-MALDI-MS: 458.1588 ($[M + Na]^+$, $C_{26}H_{21}N_5NaO_2^+$; calc. 458.1588).

*Benzyl (1-{[4-({[4-(Dimethylamino)benzoyl]amino}methyl)naphthalen-1-yl]methyl}-1,2-dihydro-2-oxopyrimidin-4-yl)carbamate* (**73**). *GP C* started from 4-(dimethylamino)benzoic acid (66 mg, 0.40 mmol), *N*-hydroxysuccinimide (60 mg, 0.52 mmol), EDC · HCl (116 mg, 0.60 mmol), $CH_2Cl_2$ (3 ml), **67** (200 mg, 0.48 mmol), $Et_3N$ (0.3 ml, 2.01 mmol), and $CH_2Cl_2$ (3 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2), **73** (70 mg, 31%). White solid. M.p. 176–178°. IR (neat): 3187*w*, 3070*w*, 2925*w*, 1751*m*, 1734*m*, 1653*s*, 1604*s*, 1558*s*, 1488*s*, 1443*m*, 1418*m*, 1368*s*, 1278*s*, 1253*s*, 1205*s*, 1065*s*, 1042*s*, 1008*s*, 804*s*, 787*s*, 753*s*. $^1$H-NMR (300 MHz, $CDCl_3/CD_3OD$ 6:1): 3.88 (*s*, 6 H); 4.94 (*s*, 2 H); 5.06 (*s*, 2 H); 5.38 (*s*, 2 H); 6.55 (*d*, *J* = 9.0, 2 H); 7.02 (*d*, *J* = 6.5, 1 H); 7.22–7.30 (*m*, 5 H); 7.38–7.50 (*m*, 5 H); 7.58 (*d*, *J* = 9.0, 2 H); 7.78–7.81 (*m*, 1 H); 8.03–8.06 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3/CD_3OD$ 6:1): 40.0; 41.8; 50.5; 67.8; 96.3; 111.2; 123.8; 124.5; 125.5; 127.1; 127.3; 127.8; 128.2; 128.6; 128.6; 128.7; 130.1; 131.4; 132.0; 135.2; 136.0; 147.1; 152.8; 163.1; 168.3 (one arom. signal missing due to overlap, no resonance for two C=O groups). HR-MALDI-MS: 584.2259 ($[M + Na]^+$, $C_{33}H_{31}N_5NaO_4^+$; calc. 584.2268).

N-*({4-[(4-Amino-2-oxopyrimidin-1(2*H*)-yl)methyl]naphthalen-1-yl}methyl)-4-(dimethylamino)-benzamide* (**21**). *GP D* started from **73** (60 mg, 0.11 mmol), 10% Pd/C (6 mg, 10% (*w*/*w*)), and $CH_2Cl_2$/MeOH 1:1 (15 ml) to yield, after purification by CC ($SiO_2$; $CH_2Cl_2$/MeOH 9:1), **21** (34 mg, 72%). White solid. M.p. 294–296°. IR (neat): 3355*m*, 3104*s*, 1659*m*, 1610*s*, 1512*s*, 1484*s*, 1420*m*, 1380*m*, 1299*s*, 1277*m*, 1205*m*, 785*s*. $^1$H-NMR (300 MHz, $(CD_3)_2SO$): 2.96 (*s*, 6 H); 4.89 (*d*, *J* = 5.6, 2 H); 5.33 (*s*, 2 H); 5.65 (*d*, *J* = 7.5, 1 H); 6.69 (*d*, *J* = 8.7, 2 H); 7.03 (br. *s*, 1 H); 7.09 (br. *s*, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 7.41 (*d*, *J* = 7.5, 1 H); 7.46 (*d*, *J* = 7.2, 1 H); 7.57–7.60 (*m*, 2 H); 7.77 (*d*, *J* = 8.7, 2 H); 8.13–8.16 (*m*, 1 H); 8.22–8.25 (*m*, 1 H); 8.67 (*t*, *J* = 5.6, 1 H). HR-MALDI-MS: 450.1895 ($[M + Na]^+$, $C_{25}H_{25}N_5NaO_2^+$; calc. 450.1901).

*Biological Assay. Materials.* [1,3,4-$^{13}C_3$]-**5** was prepared as described in [15]. IspF *E. coli* was prepared according to the procedure reported in [6].

*Inhibition of the Reaction Catalyzed by IspF Monitored* via *$^{13}$C-NMR Spectroscopy.* Assay mixtures contained 100 mM *Tris*·HCl, pH 8.0, 10 mM $MgCl_2$, 2 mM dithiothreitol, 1 mM [1,3,4-$^{13}C_3$]-**5**, and 12 μg IspF protein. Inhibitory substances to final concentrations of 0, 0.5, or 1 mM and additional $Me_2SO$ (final concentration of 5% (*v*/*v*)) were added to a total volume of 515 μl. The mixtures were incubated at 37° for 40 min, and the reaction was terminated by the addition of EDTA to a final concentration of 25 mM. $D_2O$ was added to a final concentration of 10% (*v*/*v*). The soln. was analyzed by $^{13}$C-NMR spectroscopy on a *Bruker DRX-500* (125 MHz) NMR spectrometer. The dependence of the intensity of the $^{13}$C-signals of the substrate and the product (measured by integration) on the concentration of a given inhibitor was used to determine a % inhibition. Substrate/product ratios were obtained from the signals of C(1) of [1,3,4-$^{13}C_3$]-**5** and C-1 of [1,3,4-$^{13}C_3$]-**6** [15].

*Determination of* $IC_{50}$ *Values* via *$^{13}$C-NMR Spectroscopy.* The same assay mixture as described above was used. Inhibitory substances were added at various concentrations. $IC_{50}$ Values were calculated by non-linear least-squares regression fit (GraphPad Prism 4 Software, San Diego, CA, 2003).

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