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Synthesis and biological evaluation of pyrimidine analogs of antimycobacterial purines

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ABSTRACT

Pyrimidine analogs of antimycobacterial 6-aryl-9-benzylpurines have been synthesized and screened for antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ in vitro. Several active compounds were identified and the best results were observed for 5-formamidopyrimidines. These compounds generally displayed IC_{90} values ≤ 1 μg/mL, and they exhibited low toxicity towards mammalian cells. Imidazolylpyrimidines, which may be regarded as fleximer analogs of the parent purines, were also synthesized and one of them was found to be quite a potent inhibitor of *M. tuberculosis* (IC_{90} 14 μg/mL).

1. Introduction

We have previously studied 6-aryl-9-benzylpurines as antimycobacterial agents.[1] A general structure **I** of purines with profound antimycobacterial activity as well as a summary of structure–activity relationship (SAR) knowledge are shown in Figure 1. Our antibacterial purines display several properties which make them highly interesting as potential drugs against tuberculosis, such as high selectivity towards *Mycobacterium tuberculosis* (*Mtb*) compared to other microorganisms, activity against several drug-resistant strains of *Mtb*, generally low toxicity towards mammalian cells, and ability to affect *Mtb* inside macrophages. Though the mode of action for this class of antimycobacterials has not yet been established, our findings points towards a novel target. Tuberculosis (TB) still claims ca. two millions deaths per year worldwide and resistance to existing drugs is a growing problem.[2] Thus there is an urgent need for novel drugs for the treatment of TB.

After exploring SAR of intact purines,[1] we decided to study non-purine analogs of the compounds described above[3] for instance pyrimidines **II** and imidazoles **III** (Fig. 1). Relatively simple 4-substituted 1-methoxybenzylimidazoles **III**, were only moderately active against *Mtb* in vitro.[3c] As reported in a preliminary communication, we have observed profound and selective antimycobacterial activity in vitro for certain 5-formylaminopyrimidines,

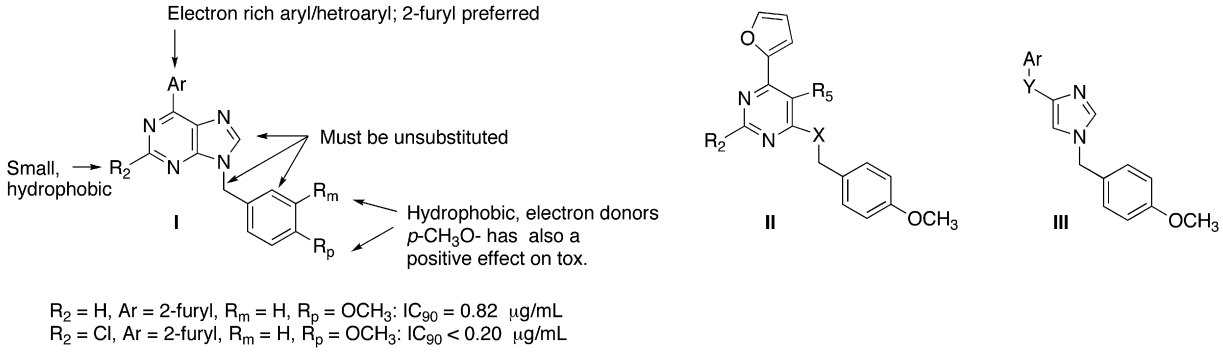

Figure 1. General structure of potent antimycobacterial purines **I**, pyrimidine analogs **II** and imidazole analogs **III**, and summary of SAR knowledge for the purines **I**.

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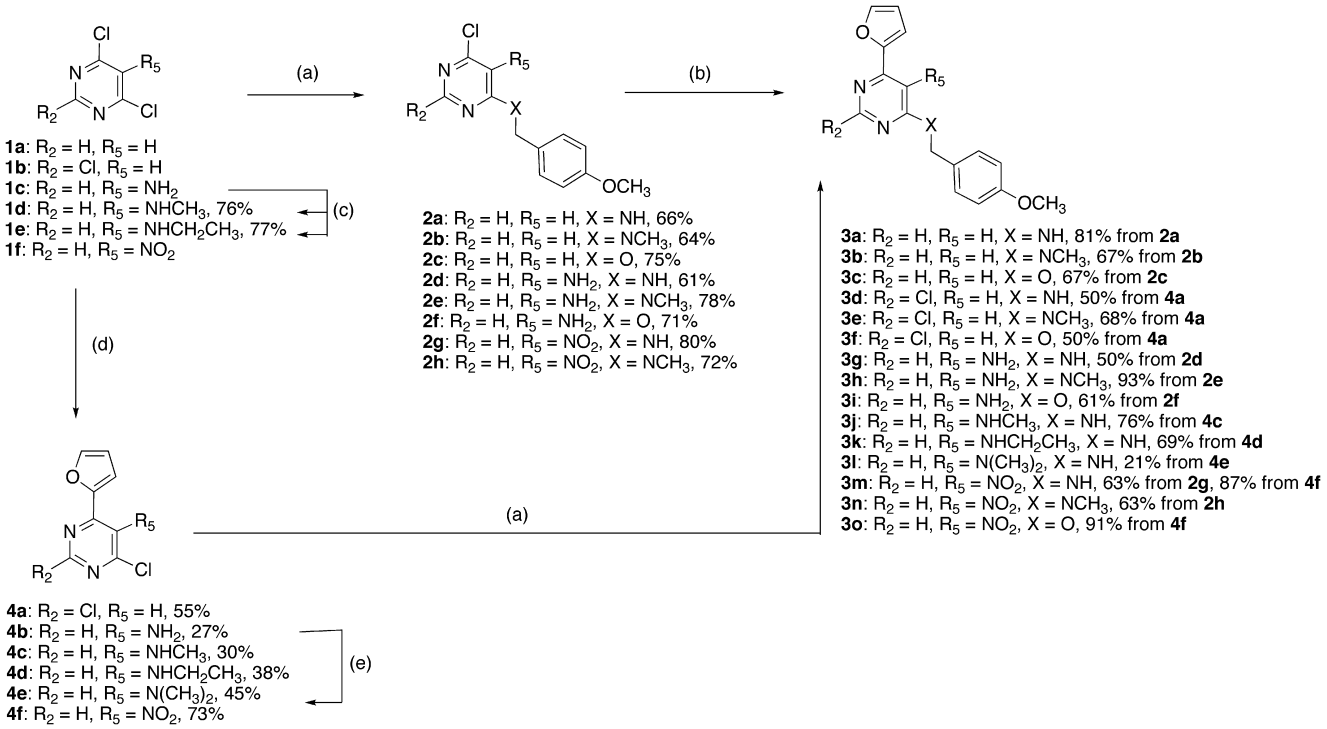
otherwise structurally related to the above-mentioned purines.[3b] We herein report synthesis and antimycobacterial activity for a variety of pyrimidine analogs **II** and also imidazolylpyrimidines which may be regarded as fleximer analogs of the parent purines. Toxicity towards mammalian cells was determined for the most active compounds. In the purine series, the presence of the benzyl subsistent is extremely important for antimycobacterial activity,[1] and, not surprisingly, 2-chloro-4-(2-furyl)pyrimidine[4] (structure not shown) was essentially inactive against *M. tuberculosis* (*Mtb*). Hence, we decided to synthesize a focused library of pyrimidines carrying both the 2-furyl and the benzyl group (general structure **II**, Fig. 1).

2. Chemistry

Target compounds **3** were synthesized from commercially available 4,6-dichloropyrimidines **1a**, **1b**, **1c** or **1e** as shown in Scheme 1. The benzylic amino or benzyloxy groups were introduced by nucleophilic substitution and the furyl substituent by Stille coupling. In some cases controlling mono- versus disubstitution required quite a lot of fine-tuning of reaction conditions when the dichloropyrimidines **1** were reacted with amines or alcohols. For the trichloropyrimidine **1b**, regioselectivity was also an issue. Furthermore, some compounds **2** carrying amino or alkoxy groups, also displayed a low reactivity in Stille couplings. Hence, the Stille coupling was performed prior to the nucleophilic substitution in the syntheses of some targets **3**, since it turned out to be easier to fine tune the reaction conditions leading to mono-substitution and desired regiochemistry in the cross-coupling reaction compared to the nucleophilic substitution.

As mentioned in a preliminary communication,[3b] 5-formamidopyrimidines **6** can be synthesized by a ring-opening reaction of the corresponding purines **5** (Scheme 2). Compounds **5** carrying electron withdrawing substituents in the purine 2-position, participated readily in the ring-opening reaction and >90% conversion was generally seen after 1 h. The yields for less activated purines were more modest. Formamidopyrimidines carrying a secondary benzylamino group or a benzyloxy group at C-6 were also synthesized (Scheme 2). Compounds **6i** and **6j** were available from the formamidopyrimidine **1g** following the same route as for several other pyrimidines **3** (see Scheme 1 above). Alternatively compound **6i** could be synthesized in moderate yields by N-formylation of the aminopyrimidine **3h**. N-Formylation the corresponding ether **3i** under the same set of reaction conditions failed. Instead the unexpected oxopyrimidine **7**, where the *p*-methoxybenzyl group had migrated from O to N, was formed. No attempt to elucidate the detailed mechanism of this reaction has been made as this point. In the formylation of compound **3h**, NMR of the crude product indicated that a rearranged compound was formed in very small amounts.

Due to restricted rotation around the amide bond in the 5-formylaminopyrimidines **6**, two rotamers were generally observed in the NMR spectra, with the s-*cis* rotamer as the major form in DMSO-d_6 at ambient temperature. NH–CHO coupling constants were in the area of 11–12 Hz for the s-*trans* rotamer and ca. 1 Hz, for the s-*cis* rotamers. These values are in good agreement with coupling constants found for other 5-formylaminopyrimidines.[5] The CHO ^{1}H NMR signal for the minor rotamer (s-*trans*) in compound **6i** was very broad and no *J* value could be determined at ambient temperature. The s-*cis*:s-*trans* ratios were ca. 8:2 with only minor variations in the ratio depending on the pyrimidine 2-substituent. For all 4-furylformamidopyrimidines reported herein, ^{1}H NMR spectroscopy shows the CHO-proton in the s-*cis* rotamer is more deshielded than in the s-*trans* rotamer. The same trend is reported for other 4,6-diamino-5-formamidopyrimidines,[5] and it is believed that in these cases the amide group is rotated about the C5–NH bond to a position more or less perpendicular to the pyrimidine plane due to sterical effects of the 4- and 6-substituents, even though an approximately planar conformation may be stabilized by a H-bond interaction between the amide oxygen and benzylamine NH in the s-*cis* rotamer of compounds **6a**–**6h**.[5b]

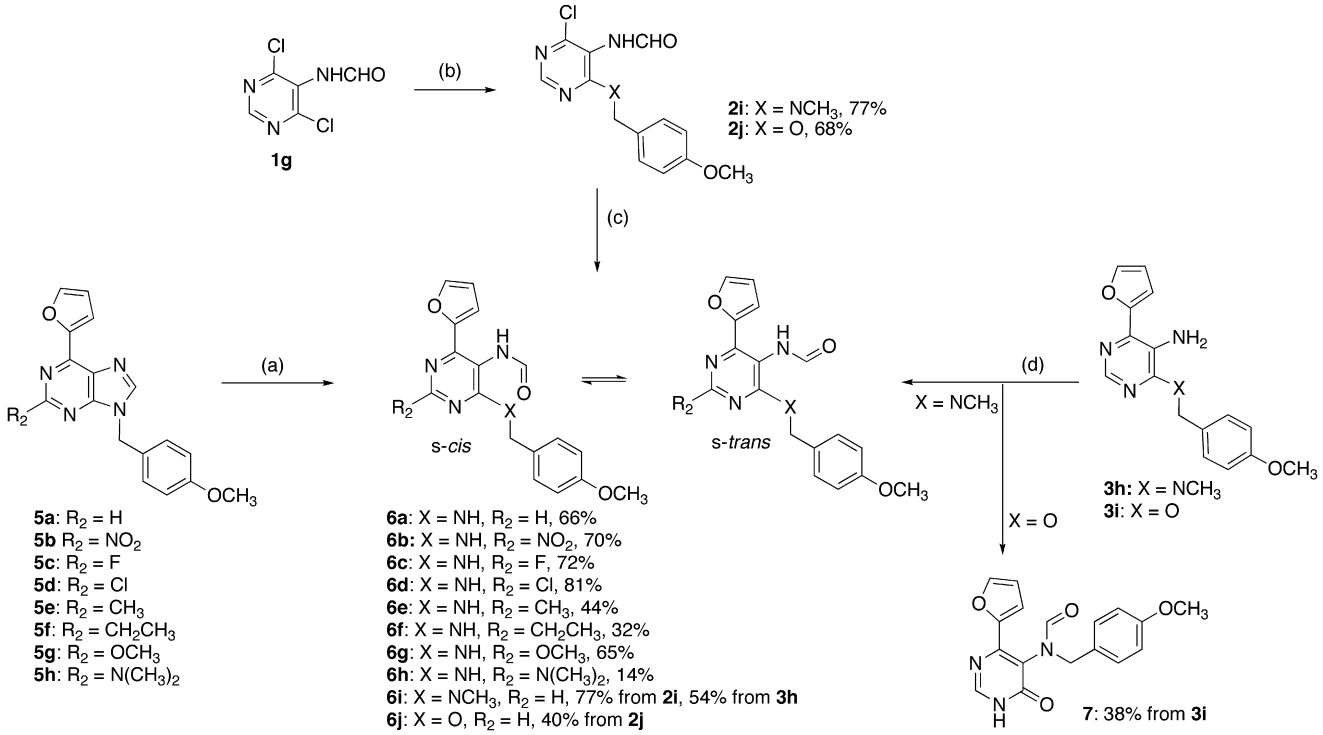


Scheme 1. Reagents and conditions: (a) $HXCH_2C_6H_4$-*p*-OCH_3, base; (b) (2-furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (c) RX, Bu_4NBr, THF; (d) (2-furyl)$SnBu_3$, $Pd_2(dba)_3$, $(2\text{-Fur})_3P$, DMF; (e) CH_3I, Bu_4NBr, THF.

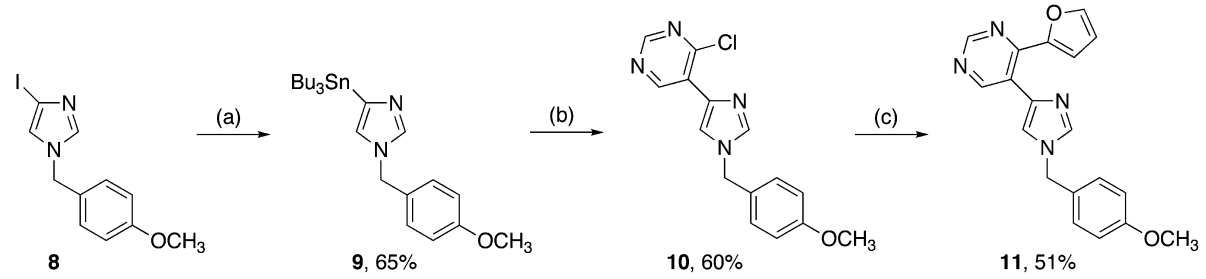
Many binding sites in biomolecules appears to be more flexible than previously believed, and can adjust to fit a wide variety of substrates. Substrates that are designed based on crystal structures of biomolecular targets, may not be the most potent ligands. Hence, pyrimidinylimidazole nucleosides have been synthesized and studied, as more flexible analogs of purine nucleosides.[6] Thus we designed the pyrimidinylimidazoles **11** and **17** as fleximer analogs of previously reported purines. The syntheses of these compounds are shown in Schemes 3 and 4.

5-(Imidazol-4-yl)pyrimidines have been synthesized by an imidazol-constructing reaction of a 5-acetylpyrimidine,[7] or by a Pd-catalyzed coupling between a (5-pyrimidinyl)boronic acid and a 4-iodoimidazole.[6d] This strategy failed in an attempt to prepare an inosine fleximer, and this target was synthesized from a 4-cyanomethylimidazole by a Diels–Alder—retro-Diels–Alder reaction on 1,3,5-triazine.[6e] We found, however, that our target 5-(imidazol-4-yl)pyrimidine **11** was easily available by two consecutive Stille couplings on 6-chloro-5-iodopyrimidine (Scheme 3). Whereas several attempts to metallate another 4-iodoimidazole derivative have failed,[6d] we were able to synthesize the stannylimidazole **9** when the iodide **8** first was reacted with methylmagnesium iodide followed by a transmetallation with tributylstannyl chloride. The stannylimidazole **9** was reacted with 6-chloro-5-iodopyrimidine in a completely regioselective Stille coupling to give the imidazolylpyrimidine **10**, when the reaction was carried out in toluene at 120 °C in a sealed tube. A second Stille coupling gave the target 4-furylpyrimidine **11**.

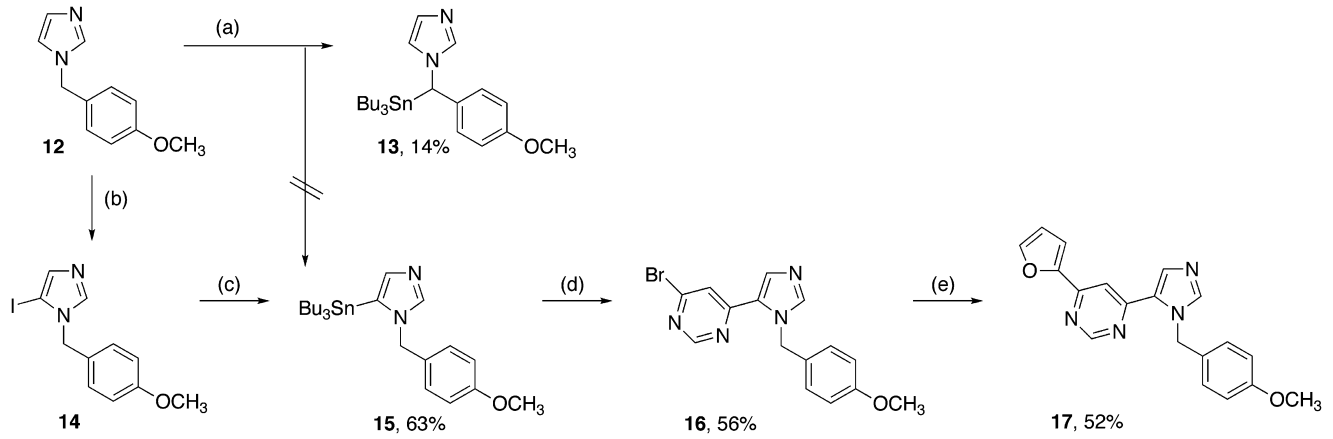
Previous syntheses of 6-(imidazol-5-yl)pyrimidine fleximers have included a rather tedious construction of a tricyclic nucleoside containing a thiophene spacer ring, followed by a reductive thiophene ring opening employing Raney nickel.[6a,b] We decided to employ principally the same simple strategy as used for the synthesis of the fleximer **17** (Scheme 4), as described for compound **11** above; two consecutive Stille couplings this time on a 4,6-dihalopyrimidine. 1-Methylimidazole have been dilitiated in the 2- and 5-position and quenched with 2 equiv of tributyltin chloride to give, after aqueous work-up, the 5-stannylated derivative.[8] However, when this protocol was applied to 1-(4-methoxybenzyl)imidazole **12**, the only product isolated was compound **13**, were stannylation had taken place in the benzylic position. This unexpected product was isolated in 14% yield after chromatography together with 49% recovered starting material. Instead we synthesized the required stannane **15** from the 5-iodoimidazole **14** employing the same set of reaction conditions as for the synthe-



Scheme 2. Reagents and conditions: (a) Bu_4NOH, THF, H_2O; (b) $HXCH_2C_6H_4$-*p*-OCH_3, base; (c) (2-furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (d) Ac_2O, HCO_2H, 0 °C.



Scheme 3. Reagents and conditions: (a) (1) CH_3MgI, (2) Bu_3SnCl, CH_2Cl_2; (b) 4-chloro-5-iodopyrimidine, $[(2\text{-Fur})_3P]_4Pd$, toluene 120 °C, sealed tube; (c) (2-furyl)$SnBu_3$, $Pd_2(dba)_3$, $(2\text{-Fur})_3P$, toluene–DMF, 110 °C.



Scheme 4. Reagents and conditions: (a) (1) TMEDA, *n*-BuLi, THF–hexane, −20 °C–rt; (2) Bu_3SnCl, THF–hexane, −20 °C–rt; (3) H_2O; (b) see Ref. 3c; (c) (1) CH_3MgI; (2) Bu_3SnCl, CH_2Cl_2; (d) 4,6-dibromopyrimidine, $Pd_2(dba)_3$, $(2\text{-Fur})_3P$, toluene 120 °C, sealed tube; (e) (2-furyl)$SnBu_3$, $Pd_2(dba)_3$, $(2\text{-Fur})_3P$, toluene, Δ.

sis of the isomer **9** above. Further synthesis of the target **17** from 4,6-dibromopyrimidine followed the same strategy as for the fleximer **11** described above.

3. Antimycobacterial activity

The furylpyrimidines **3**, **6**, **7**, **11** and **17** were screened for antibacterial activity against *M. tuberculosis* $H_{37}Rv$ in vitro and the results are presented in Table 1. All synthetic intermediates **2** and **4** were essentially inactive against *Mtb* at 6.25 μg/mL concn (data not shown).

None of the 6-benzyloxypyrimidines (compounds **3c**, **3f**, **3i**, **3o** or **6j**) displayed any inhibitory activity in the concentration range studied. For the pyrimidines **3**, it seems like an *N*-methylbenzylamino group (X = NCH_3 in Table 1 and Fig. 1) results in better activity compared with a benzylamino group (X = NH), but the positive effect of the extra methyl group is best seen for the pyrimidines not substituted at C-5. A nitro group (compound **3m**) or a methylamino group (compound **3j**), in the pyrimidine 5-position increases the activity of the 6-benzylamino (X = NH) pyrimidines. The most active compounds **3** identified were the *N*-methylbenzylaminopyrimidines **3b** and **3e** (IC_{90} 7.1 and 3.0 μg/mL,

Table 1
Activity against *M. tuberculosis* for pyrimidines **3**, **6**, **7**, **11** and **17**[a]

Compd	R_2	R_5	X	IC_{90} *M. tuberculosis* $H_{37}Rv$[b] (μg/mL)	IC_{50} *M. tuberculosis* $H_{37}Rv$[b] (μg/mL)	IC_{50} VERO cells[c] (μg/mL)
3a	H	H	NH	n.d.[d,e]	n.d.	n.d.
3b	H	H	NCH_3	7.1	5.5	n.d.
3c	H	H	O	>100	>100	n.d.
3d	Cl	H	NH	>100	>100	n.d.
3e	Cl	H	NCH_3	3.0	1.4	22
3f	Cl	H	O	>100	>100	n.d.
3g	H	NH_2	NH	n.d.[e]	n.d.	n.d.
3h	H	NH_2	NCH_3	17	9.4	n.d.
3i	H	NH_2	O	>100	>100	n.d.
3j	H	$NHCH_3$	NH	15	9.0	n.d.
3k	H	$NHCH_2CH_3$	NH	46	36	n.d.
3l	H	$N(CH_3)_2$	NH	>100	17	n.d.
3m	H	NO_2	NH	21	13	n.d.
3n	H	NO_2	NCH_3	13	5.7	n.d.
3o	H	NO_2	O	>50	>50	n.d.
6a	H	NHCHO	NH	0.56	0.22	>40
6b	NO_2	NHCHO	NH	1.1	0.59	>40
6c	F	NHCHO	NH	<0.20	<0.20	>40
6d	Cl	NHCHO	NH	0.20	<0.20	>40
6e	CH_3	NHCHO	NH	0.33	<0.20	>40
6f	CH_2CH_3	NHCHO	NH	0.53	0.26	>40
6g	OCH_3	NHCHO	NH	1.5	0.53	>40
6h	$N(CH_3)_2$	NHCHO	NH	26	11	n.d.
6i	H	NHCHO	NCH_3	>100	>100	n.d.
6j	H	NHCHO	O	>100	>100	n.d.
7	H	$N(CHO)CH_2C_6H_4$-*p*-OCH_3	OH[f]	92	68	n.d.
11	H	1-($CH_2C_6H_4$-*p*-OCH_3)-imidazol-5-yl	H	82	62	n.d.
17	N	H	1-($CH_2C_6H_4$-*p*-OCH_3)-imidazol-6-yl	14	9.8	n.d.

[a] A general structure of pyrimidines **3** and **6** is shown in Figure 1. The structures of compounds **7**, **11** and **17** can be found in Schemes 2–4, respectively.
[b] IC_{90} amicain 0.13 and IC_{50} amicain 0.07 μg/mL.
[c] EC_{50} hyamine 0.01 μg/mL.
[d] n.d. = not determined.
[e] 0% Inhibition at 6.25 μg/mL concn.
[f] ^1H NMR indicate an oxo tautomer, see also Scheme 2.

respectively). These were significantly better inhibitors than any compound studied in the imidazole series (compounds **II**, Fig. 1),[3c] but less active than the parent purine (see Fig. 1, IC_{90} 0.82 μg/mL).[3b]

However, when a formamido group was introduced in the pyrimidine 5-position (compounds **6**) excellent inhibitory activities were generally seen. Compound **6a** (IC_{90} 0.56 μg/mL) is more potent than the parent purine (IC_{90} 0.82 μg/mL),[3b] and chloride, fluoride or small alkyl substituents in the pyrimidine 2-position increased the inhibitory activity even more. The same substituents are found to be beneficial for activity also in the purine series.[1f] Antimycobacterial data for some compounds **6** have been communicated before.[3c] Now we can also report that these compounds are of very low toxicity towards mammalian cells (IC_{50} VERO cells >40 μg/mL). As discussed above for pyrimidines **3**, an *N*-methylbenzylamino group at C-6 results in better activity compared with a benzylamino group, but the positive effect of the *N*-methyl group is less for some C-5 substituted pyrimidines. In the 5-formamidopyrimidine series, the extra *N*-methyl group is not tolerated at all; compound **6i** was inactive in the concentration range studied.

Since the formamidopyrimidines (**6a**–**6h**) displayed profound inhibitory activity against *M. tuberculosis*, their chemical stability was of great interest. We could not completely exclude that cyclization back to the antimycobacterial parent purine **5** may have occurred in the bioassay. In this respect it is also worth noting that the formamidopyrimidines **6i** and **6j**, which are not capable of cyclization, were found to be inactive. Hence, any bioactivity observed from formamidopyrimidines may actually (in part) be caused by the corresponding purine **5**. Therefore, we chose to examine by ^{1}H NMR spectroscopy, the ability of the formamidopyrimidines **6a** and **6c**–**6h** to ring-close in different solvents. Unfortunately, solubility problems precluded studies in pure D_2O or D_2O containing minor amounts of DMSO-d_6. Hence, reactions in DMSO-d_6–D_2O (1:1) and CD_3OD were studied. The solubility of the nitro compound **3b** was too low also in these solvent systems. The results are summarized in Table 2.

No cyclization could be observed for the fluoropyrimidine **6c** in any of the solvent combinations studied. Also the chloride **6d**, methoxy compound **6g**, and amine **6h** were inert in DMSO-d_6–D_2O, but some cyclization took place with these compounds in CD_3OD; ca. 12–13% of the corresponding purines were present after 25 days. Compound **6a**, without any substituent in the 2-position, and the 2-alkylpyrimidines **6e** and **6f**, on the other hand, were more prone to cyclization. In CD_3OD quantitative (**6e** and **6f**) or 90% (**6a**) conversion to the corresponding purine were seen after 25 days. In DMSO-d_6, 40–60% purines were formed after 25 days. The cyclization reaction is favored in CD_3OD compared to the DMSO-d_6–D_2O mixture, and hardly any cyclization was seen for any of the compounds studied in pure DMSO-d_6 (data not shown). Electron withdrawing substituents in the 2-position, may lower the nucleophilicity of the amine in the ring-closing reaction, and the reactivity of the pyrimidine, was generally reduced when the σ_I-values[9] of the R_2-substituent was decreased (Table 2). It is worth noting that the most active antimycobacterial formamidopyrimidines are those with less tendencies to undergo the ring-closing reaction. Hence, we strongly believe that the formamidopyrimidines themselves are the compounds responsible for the bacterial growth inhibition.

There were profound differences between the inhibitory activities (Table 1) found for the fleximers **11** (Scheme 3) and **17** (Scheme 4). When the pyrimidine C-5 was connected to the imidazole C-4 (compound **11**) only a very weak activity was observed (IC_{90} 82 μg/mL), whereas the isomeric fleximer **17** displayed an IC_{90} value of 14 μg/mL; an activity similar to some of the simple 6-benzylaminopyrimidines (e.g., **3h**, **3j** and **3n**), but not comparable to the parent purine[3b] (see also Fig. 1) or the most active compound identified in the pyrimidine series (compound **3e**).

The potent antimycobacterial pyrimidines described herein displays essentially no toxicity towards mammalian cells. We have previously reported that some of them are inactive towards other bacteria. For the parent purines **I**, we have previously reported virtually no cross resistance against a panel of drug-resistant *Mtb* strains.[1b] We assume that the closely related structures reported herein act by the same, currently unknown, mechanism of action as the purine. Hence, we believe that cross resistance will not be an issue for the antimycobacterial compounds described herein.

4. Experimental

The ^{1}H NMR spectra were recorded at 600 MHz with a Bruker AV 600 instrument, at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument, or at 200 MHz with a Bruker Avance DPX 200 instrument or a Varian Gemini 200 instrument. The ^{1}H decoupled ^{13}C NMR spectra were recorded at 150, 125, 75 or 50 MHz using instruments mentioned above. Mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing voltage with a VG Prospec instrument, and are presented as *m*/*z* (% rel. int.). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany or School of Chemistry, University of Birmingham, UK. Melting points were determined with a C. Reichert melting point apparatus or a Büchi Melting Point B-545 apparatus and are uncorrected. DMF was distilled from BaO and stored over 4 Å mol sieve, CH_2Cl_2 and Et_3N were distilled from CaH_2, and THF and toluene from Na/benzophenone. Alternatively, DMF, THF and CH_2Cl_2 were dried by a solvent purification system, MB SPS-800 from MBraun. Antimycobacterial activity was deter-

Table 2
Ring-closing of selected formamidopyrimidines **6** in DMSO-d_6–D_2O (1:1) and CD_3OD

Starting material	R_2	Range σ_I values[a]	Ratio **6**:**5**							
			DMSO-d_6–D_2O (1:1)				CD_3OD			
			3 days	7 days	14 days	25 days	3 days	7 days	14 days	25 days
6a	H	0.00	88:12	79:21	74:26	63:37	70:30	52:48	31:69	10:90
6c	F	0.46–0.57	100:0	100:0	100:0	100:0	100:0	100:0	100:0	100:0
6d	Cl	0.42–0.47	100:0	100:0	100:0	100:0	96:4	94:6	92:8	88:12
6e	CH_3	−0.01–0.01	87:13	81:19	71:29	51:49	48:52	25:75	7:93	0:100[b]
6f	CH_2CH_3	−0.01–0.06	79:21	74:26	58:42	41:59	53:47	31:69	11:89	0:100[c]
6g	OCH_3	0.29–0.31	100:0	100:0	100:0	100:0	97:3	96:4	93:7	87:13
6h	$N(CH_3)_2$	0.15–0.17	100:0	100:0	100:0	100:0	98:2	96:4	92:8	87:13

[a] Values taken from Ref. 9.
[b] Determined after 21 days.
[c] Determined after 23 days.

mined as previously reported.[1,2] The following compounds were prepared according to literature procedures: 2-chloro-4-(2-furyl)pyrimidine,[4] 6-chloro-5-iodopyrimidine,[10] 4,6-dibromopyrimidine,[11] **1g**,[12] **5a**,[1d] **5b–5c**,[15] **5d**,[1d] and **5e–5h**,[1f] **6a–6h**,[3b] **8**,[3c] **12**,[13] **14**.[3c]

4.1. Antimycobacterial data

The purines were screened for antimycobacterial activities as described before.[1g] Compounds were tested in 10 twofold dilutions, from 100 μg/mL to 0.19 μg/mL, against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA). The IC_{90} and IC_{50} values are determined from the dose–response curve as the IC_{90} using the curve fitting program XLFIT, formula 205.

4.2. Activity against VERO cells

The compounds were screened for mammalian cell cytotoxicity to VERO cells essentially as described before;[1g] After 72 h exposure, viability is assessed using the CellTiter 96® Non-Radioactive Cell Proliferation Assay (MTT) reagent from Promega. Cytotoxicity is determined from the dose–response curve as the EC_{50} using the curve fitting program XLFIT, formula 205.

4.3. 4,6-Dichloro-*N*-methylpyrimidine-5-amine (1d)

A solution of 4,6-dichloropyrimidine-5-amine **1c** (980 mg, 6.00 mmol) in THF (15 mL) was treated with NaH (260 mg, ca. 65% in oil, ca. 7.00 mmol) in THF (10 mL) at 0 °C under N_2-atm, before the mixture was allowed to warm to ambient temperature and stirred for 20 min. MeI (1.00 g, 7.00 mmol) and *n*-Bu_4NBr (2.25 g, 7.00 mmol) were added. The mixture was stirred for 2 h at ambient temperature, concentrated in vacuo and purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:8); yield 808 mg (76%), mp 81.9–82.0 °C, (Lit.[14] mp 78–79 °C), colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.14 (s, 3H, CH_3), 4.05 (br s, 1H, NH), 8.18 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.1 (CH_3), 139.1 (C-5), 147.2 (C-2), 147.8 (C-4 and C-6); MS EI *m/z* (rel. %): 181/179/177 (10/64/100, M^+), 140 (27), 100 (7), 79 (12); HRMS: found 176.9854, calcd for $C_5H_5Cl_2N_3$ 176.9861.

4.4. 4,6-Dichloro-*N*-ethylpyrimidine-5-amine (1e)

The title compound was prepared from 4,6-dichloropyrimidine-5-amine **1c** (820 mg, 5.00 mmol) and EtI (936 mg, 6.00 mmol) as described for the synthesis of compound **1d** above. EtOAc–hexane (3:17) was used as eluent for flash chromatography; yield 740 mg (77%), mp 53–54 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 t, J = 7.2 Hz, 3H, CH_3), 3.55 (q, J = 7.2 Hz, 2H, CH_2), 4.04 (br s, 1H, NH), 8.26 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7 (CH_3), 41.8 (CH_2), 138.3 (C-5), 147.6 (C-2), 148.8 (C-4 and C-6); MS EI *m/z* (rel. %): 195/193/191 (3/17/26, M^+), 176 (100); HRMS: found 191.0021, calcd for $C_6H_7Cl_2N_3$ 191.0017. Spectral data were in good agreement with those reported before.[15]

4.5. 6-Chloro-*N*-(4-methoxybenzyl)pyrimidine-4-amine (2a)

A mixture of 4,6-dichloropyrimidine **1a** (590 mg, 4.00 mmol), 4-methoxybenzylamine (550 mg, 4.00 mmol), and Et_3N (0.59 mg, 4.20 mmol) in *n*-BuOH (10 mL) was heated at reflux for 24 h N_2-atm, cooled and evaporated. The residue was dissolved in CH_2Cl_2 (150 mL) and the solution was washed with water (2 × 50 mL), dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:3), followed by EtOAc–hexane (1:2); yield 660 mg (66%), mp 118–120 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 4.43 (br d, J = 4.8 Hz, 2H, CH_2), 5.61 (br s, 1H, NH), 6.32 (s, 1H, H-5), 6.87 (d, J = 8.4 Hz, 2H, Ar), 7.22 (d, J = 8.4 Hz, 2H, Ar), 8.28 (s, 1H, H-2); MS EI *m/z* (rel. %): 251/249 (16/50, M^+), 234 (4), 218 (5), 136 (16), 121 (100). The ^{1}H NMR data were in good agreement with those reported before.[16]

4.6. 6-Chloro-*N*-(4-methoxybenzyl)-*N*-methylpyrimidine-4-amine (2b)

The title compound was synthesized from 4,6-dichloropyrimidine **1a** (590 mg, 4.00 mmol) and *N*-methyl-4-methoxybenzylamine (600 mg, 4.00 mmol), as described for **2a** above. EtOAc–hexane (1:3) was used as eluent for flash chromatography; yield 680 mg (64%), mp 71–73 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.99 (br s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 4.73 (br s, 2H, CH_2), 6.41 (s, 1H, H-5), 6.84 (d, J = 8.6 Hz, 2H, Ar), 7.11 (d, J = 8.6 Hz, 2H, Ar), 8.39 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.3 (NCH_3), 52.0 (CH_2), 55.3 (OCH_3), 101.0 (C-5), 114.1 (CH in Ar), 128.2 (C-1 in Ar), 128.4 (CH in Ar), 157.9 (C-2), 159.0 (C-4 in Ar), 159.8 (C-4 or C-6), 162. 7 (C-4 or C-6); MS EI *m/z* (rel. %): 265/263 (13/39, M^+), 250 (8), 248 (25), 150 (7), 142 (6), 140 (4), 121 (100); HRMS: found 263.0832, calcd for $C_{13}H_{14}ClN_3O$ 263.0825.

4.7. 4-Chloro-6-(4-methoxybenzyloxy)pyrimidine (2c)

A solution of 4-methoxybenzyl alcohol (276 mg, 2.00 mmol) in THF (1.0 mL) was added over 5 min to a stirring suspension of NaH (131 mg, ca. 55% in oil, ca. 3 mmol) in THF (3.0 mL) under N_2-atm. The mixture was stirred at ambient temperature for 40 min and cooled to 0 °C before 4,6-dichloropyrimidine **1** (298 mg, 2.00 mmol) in THF (2.5 mL) was added over 15 min. The resulting mixture was stirred at 0 °C for 1.5 h and at ambient temperature for 15 h. Satd aq NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:8); yield 376 mg (75%), colorless wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.80 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.76 (s, 1H, H-5), 6.89 (d, J = 8.8 Hz, 2H, Ar), 7.35 (d, J = 8.8 Hz, 2H, Ar), 8.57 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.2 (OCH_3), 68.8 (CH_2), 108.0 (C-5), 113.9 (CH in Ar), 127.4 (C-1 in Ar), 130.1 (CH in Ar), 158.0 (C-2), 159.7 (C-4 in Ar), 160.6 (C-4), 169.9 (C-6); MS EI *m/z* (rel. %): 252/250 (11/33, M^+), 137 (57), 122 (13), 121 (100); HRMS: found 250.0502, calcd for $C_{12}H_{11}ClN_2O_2$ 250.0509.

4.8. 6-Chloro-N^4-(4-methoxybenzyl)pyrimidine-4,5-diamine (2d)

The title compound was synthesized from 4,6-dichloropyrimidine-5-amine **1c** (1.03 g, 6.30 mmol) and 4-methoxybenzylamine (864 mg, 6.30 mmol), as described for **2a** above. EtOAc–hexane (1:2), followed by EtOAc were used as eluents for flash chromatography; yield 1.02 g (61%), mp 185–187 °C (Lit.[17] mp 186–188 °C), off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.34 (br s, 2H, NH_2), 3.79 (s, 3H, CH_3), 4.59 (d, J = 5.2 Hz, 2H, CH_2), 5.01 (br s, 1H, NH), 6.86 (d, J = 8.4 Hz, 2H, Ar), 7.26 (d, J = 8.4 Hz, 2H, Ar), 8.09 (s, 1H, H-2); MS EI *m/z* (rel. %): 266/264 (5/15, M^+), 136 (2), 122 (9), 121 (100).

4.9. 6-Chloro-N^4-(4-methoxybenzyl)-N^4-methylpyrimidine-4,5-diamine (2e)

The title compound was synthesized from 4,6-dichloropyrimidine-5-amine **1c** (650 mg, 4.00 mmol) and *N*-methyl-4-methoxy-

benzylamine (600 mg, 4.00 mmol), as described for **2a** above. EtOAc–hexane (1:3) was used as eluent for flash chromatography; yield 870 mg (78%), mp 88–89 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.89 (br s, 3H, NCH_3), 3.79 (br s, 5H, NH_2 and OCH_3), 4.45 (br s, 2H, CH_2), 6.87 (d, J = 8.6 Hz, 2H, Ar), 7.20 (d, J = 8.6 Hz, 2H, Ar), 8.12 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.2 (NCH_3), 54.2 (CH_2), 55.3 (OCH_3), 114.1 (CH in Ar), 127.5 (C-1 in Ar or C-5), 128.6 (CH in Ar), 129.3 (C-1 in Ar or C-5), 143.3 (C-6), 147.0 (C-2), 156.4 (C-4), 158.9 (C-4 in Ar); MS EI m/z (rel. %): 280/278 (5/16, M^+), 263 (5), 150 (5), 122 (13), 121 (100); HRMS: found 278.0934, calcd for $C_{13}H_{15}ClN_4O$ 278.0934.

4.10. 4-Chloro-6-(4-methoxybenzyloxy)pyrimidine-5-amine (2f)

The title compound was synthesized from 4,6-dichloropyrimidine-5-amine **1c** (325 mg, 2.00 mmol) and 4-methoxybenzyl alcohol (276 mg, 2.00 mmol) as described for **2c** above. EtOAc–hexane (1:3) was used as eluent for flash chromatography; yield 379 mg (71%), mp 85–86 °C, off-white powdery crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.80 (s, 3H, CH_3), 4.02 (br s, 2H, NH_2), 5.38 (s, 2H, CH_2), 6.89 (d, J = 8.6 Hz, 2H, Ar), 7.37 (d, J = 8.6 Hz, 2H, Ar), 8.03 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.2 (CH_3), 68.9 (CH_2), 113.9 (CH in Ar), 126.3 (H-5), 127.7 (C-1 in Ar), 130.2 (CH in Ar), 140.4 (C-4), 145.2 (C-2), 157.3 (C-6), 159.7 (C-4 in Ar); MS EI m/z (rel. %): 267/265 (4/11, M^+), 122 (17), 121 (100); HRMS: found 265.0616, calcd for $C_{12}H_{12}ClN_3O_2$ 265.0618.

4.11. 6-Chloro-*N*-(4-methoxybenzyl)-5-nitropyrimidine-4-amine (2g)

A mixture of 4,6-dichloro-5-nitropyrimidine **1f** (291 mg, 1.50 mmol), 4-methoxybenzylamine (0.13 mL, 1.0 mmol), and Et_3N (0.22 mL, 1.6 mmol) in CH_2Cl_2 (5 mL) was stirred at -78 °C under N_2-atm for 4 h and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (3 × 50 mL) and the solution was washed with water (2 × 50 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2–hexane (9:1); yield 234 mg (80 %), mp 84–86 °C, yellow crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 s, 3H, OCH_3), 4.73 (d, J = 5.6 Hz, 2H, CH_2), 6.89 (d, J = 8.7 Hz, 2H, Ar), 7.25 (d, J = 8.7 Hz, 2H, Ar), 7.72 (br s, 1H, NH), 8.42 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.3 (CH_2), 55.3 (OCH_3), 114.3 (CH in Ar), 126.9 (C-5), 128.4 (C-1 in Ar), 129.2 (CH in Ar), 155.1 (C-4), 155.5 (C-6), 158 (C-2), 159.5 (C-4 in Ar); MS EI m/z (rel. %): 296/294 (4/11, M^+), 277 (89), 246 (100), 158 (30), 121 (76); HRMS: found 294.0513, calcd for $C_{12}H_{11}ClN_4O_3$ 294.052; Anal. Calcd for $C_{12}H_{11}ClN_4O_3$: C, 48.91; H, 3.76; N, 19.01. Found: C, 48.96; H, 3.89; N, 18.91.

4.12. 6-Chloro-*N*-(4-methoxybenzyl)-*N*-methyl-5-nitropyrimidine-4-amine (2h)

A mixture of 4,6-dichloro-5-nitropyrimidine **1f** (194 mg, 1.00 mmol), *N*-methyl-4-methoxybenzylamine (151 mg, 1.00 mmol), and Et_3N (0.15 mL, 1.1 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C under N_2-atm for 3 h and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (3 × 50 mL) and the solution was washed with water (2 × 50 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2–hexane (9:1); yield 222 mg (72%), mp 92–94 °C, yellow crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.86 (s, 3H, NCH_3), 3.78 s, 3H, OCH_3), 4.85 (s, 2H, CH_2), 6.89 (d, J = 8.7 Hz, 2H, Ar), 7.16 (d, J = 8.7 Hz, 2H, in Ar), 8.37 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.0 (NCH_3), 54.6 (CH_2), 55.7 (OCH_3), 114.7 (CH in Ar), 127.8 (C-1 in Ar), 129.5 (CH in Ar), 129.6 (C-5), 153.3 (C-4), 154.8 (C-6), 156.6 (C-2), 159.9 (C-4 in Ar); MS EI m/z (rel. %): 308 (0.15, M^+), 172 (34), 155 (50), 121 (100); HRMS: found 308.0664, calcd for $C_{13}H_{13}ClN_4O_3$ 308.0676; Anal. Calcd for $C_{13}H_{13}ClN_4O_3$: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.68; H, 4.36; N, 18.05.

4.13. *N*-{4-Chloro-6-[(4-methoxybenzyl)(methyl)amino] pyrimidin-5-yl}formamide (2i)

The title compound was synthesized from 4,6-dichloropyrimidin-5-ylformamide **1g** (150 mg, 0.78 mmol) and *N*-methyl-4-methoxybenzylamine (120 mg, 0.78 mmol), as described for **2a** above. EtOAc–hexane (3:2) was used as eluent for flash chromatography; yield 183 mg (77%), off-white wax. In DMSO-d_6 a mixture of amide *s-cis* and *s-trans* rotamers (14:86) of **2n** were observed. When the NMR signals for the rotamers are not overlapping, ' denotes the *s-cis* rotamer and * denotes the *s-trans* rotamer. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 3.00* (s, 3H, NCH_3), 3.07′ (s, 3H, NCH_3), 3.72 (s, 3H, OCH_3), 4.77* (s, 2H, NCH_2), 4.79′ (s, 2H, NCH_2), 6.87 (m, 2H, Ar), 7.16 (d, J = 8.6 Hz, 2H, Ar), 7.94′ (br s, 1H, CHO), 8.19* (s, 1H, CHO), 8.26* (s, 1H, H-2), 8.30′ (s, 1H, H-2), 9.49 (br s, 1H, NH). 9.85 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 37.1* (NCH_3), 38.3′ (NCH_3), 53.2 (NCH_2), 55.0 (OCH_3), 111.3 (C-5), 113.9 (CH in Ar), 128.6 (CH in Ar); 129.0 (C-1 in Ar), 154.9* (C-2), 155.1′ (C-2), 158.5 (C-4 in Ar), 159.0 (C-4), 160.7 (CHO or C-6), 160.8 (CHO or C-6), 164.9′ (CHO); MS EI m/z (rel. %): 308/306 (8/24, M^+), 291 (8), 263 (4). 150 (16), 121 (100); HRMS Found 306.0886, calcd for $C_{14}H_{15}ClN_4O_2$ 306.0884.

4.14. *N*-[4-Chloro-6-(4-methoxybenzyloxy)pyrimidin-5-yl]formamide (2j)

The title compound was synthesized from 4,6-dichloropyrimidin-5-ylformamide **1g** (380 mg, 2.00 mmol) and 4-methoxybenzyl alcohol (276 mg, 2.00 mmol) as described for **2c** above. EtOAc–hexane (1:2) followed by EtOAc–hexane (1:1) were used as eluents for flash chromatography; yield 393 mg (68%), mp 86–89 °C, off-white powdery crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 6.88 (d, J = 8.6 Hz, 2H, Ar), 7.34 (d, J = 8.6 Hz, 2H, Ar), 8.43 (br s, 2H), 8.69 (s, 1H); MS EI m/z (rel. %): 295/293 (2/6, M^+), 265 (1), 165 (1), 163 (2), 122 17), 121 (100); HRMS: found 293.0564, calcd for $C_{13}H_{12}ClN_3O_3$ 293.0567.

4.15. General procedure for the synthesis of compounds 3 from compounds 2

A mixture of chloropyrimidine **2** (0.50 mmol), (2-tributylstannyl)furan (0.60 mmol) and $(Ph_3P)_2PdCl_2$ (18 mg, 0.025 mmol) in DMF (5 mL) was stirred at 90 °C under N_2-atm for 16 h, and evaporated. KF (satd sol. in MeOH, 10 mL) was added and the resulting mixture was stirred at ambient temperature for 16 h. The mixture was evaporated and the product was purified by flash chromatography on silica gel.

4.15.1. 6-(2-Furyl)-*N*-(4-methoxybenzyl)pyrimidine-4-amine (3a)

EtOAc–hexane (1:1) followed by EtOAc–hexane (2:1) were used as eluents for flash chromatography and the reaction was performed on a 0.61 mmol scale; yield 139 mg (81%), mp 131–133 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, OCH_3), 4.50 (d, J = 5.4 Hz, 2H, CH_2), 5.28 (br s, 1H, NH), 6.51 (m, 1H, H-4 in furyl), 6.67 (s, 1H, H-5), 6.87 (d, J = 8.4 Hz, 2H, Ar), 7.12 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 7.26 (d, J = 8.4 Hz, 2H, Ar), 7.50 (br s, 1H, H-5 in furyl), 8.54 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 44.9 (CH_2), 55.2 (OCH_3), 96.4 (C-5), 110.8 (CH in furyl), 112.0 (CH in furyl), 114.1 (CH in Ar), 128.6 (CH in Ar), 129.6 (C-1 in Ar), 143.9 (CH in furyl), 152.1 (C-2 in furyl or C-6), 153.9 (C-2 in furyl or C-6), 158.4 (C-2), 158.9 (C-4 in Ar), 162.6

(C-4); MS EI *m/z* (rel. %): 281 (100, M^+), 280 (18), 266 (17), 250 (4), 146 (6), 136 (53), 121 (59); HRMS: found 281.1164, calcd for $C_{16}H_{15}N_3O_2$ 281.1164.

4.15.2. 6-(2-Furyl)-*N*-(4-methoxybenzyl)-*N*-methylpyrimidine-4-amine (3b)

EtOAc–hexane (1:3) followed by EtOAc–hexane (1:2) were used as eluents for flash chromatography; yield 99 mg (67%), colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.10 (br s, 3H, NCH_3), 3.60 (s, 3H, OCH_3), 4.82 (br s, 2H, CH_2), 6.55 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.83–6.90 (m, 3H, Ar and H-5), 7.16–7.20 (m, 3H, Ar and H-3 in furyl), 7.53 (br s, 1H, H-5 in furyl), 8.63 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.2 (NCH_3), 51.8 (CH_2), 55.3 (OCH_3), 95.5 (C-5), 110.9 (CH in furyl), 112.2 (CH in furyl), 114.1 (CH in Ar), 128.4 (CH in Ar), 129.0 (C-1 in Ar), 143.9 (CH in furyl), 152.3 (C-2 in furyl or C-6), 153.7 (C-2 in furyl or C-6), 158.0 (C-2), 158.9 (C-4 in Ar), 162. 3 (C-4); MS EI *m/z* (rel. %): 295 (97, M^+), 280 (100), 174 (23), 150 (18), 148 (9), 121 (70), 118 (13); HRMS: found 295.1317, calcd for $C_{17}H_{17}N_3O_2$ 295.1321; Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.27; H, 5.94; N, 13.80.

4.15.3. 4-(2-Furyl)-6-(4-methoxybenzyloxy)pyrimidine (3c)

EtOAc–hexane (1:4) was used for flash chromatography and the reaction was performed in 0.54 mmol scale; yield 140 mg (92%), mp 108–109 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.80 (s, 3H, CH_3), 5.38 (s, 2H, CH_2), 6.53 (m, 1H, H-4 in furyl), 6.90 (d, J = 8.6 Hz, 2H, Ar), 7.02 (s, 1H, H-5), 7.17 (br d, J = 3.4 Hz, H-3 in furyl), 7.38 (d, J = 8.6 Hz, 2H, Ar), 7.54 (br s, 1H, H-5 in furyl), 8.73 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.3 (OCH_3), 68.0 (CH_2), 101.4 (C-5), 111.6 (CH in furyl), 112.2 (CH in furyl), 113.9 (CH in Ar), 128.1 (C-1 in Ar), 129.9 (CH in Ar), 144.6 (CH in furyl), 151.6 (C-2 in furyl), 155.9 (C-4), 158.2 (C-2), 159.5 (C-4 in Ar), 169.7 (C-6); MS EI *m/z* (rel. %): 282 (67, M^+), 253 (7), 147 (13), 146 (37), 137 (7), 122 (12), 121 (100); HRMS: found 282.1006, calcd for $C_{16}H_{14}N_2O_3$ 282.1004.

4.15.4. 6-(2-Furyl)-N^4-(4-methoxybenzyl)pyrimidine-4,5-diamine (3g)

EtOAc–hexane (1:5) followed by EtOAc–hexane (1:2) and EtOAc–hexane (1:1) were used as eluents for flash chromatography and the reaction was performed on 0.63 mmol scale; yield 84 mg (45%), mp 157–159 °C, off-white powdery crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, OCH_3), 4.04 (br s, 2H, NH_2), 4.61 (d, J = 5.0 Hz, 2H, CH_2), 5.04 (br s, 1H, NH), 6.56 (m, 1H, H-4 in furyl), 6.87 (d, J = 8.2 Hz, 2H, Ar), 7.13 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 7.29 (d, J = 8.2 Hz, 2H, Ar), 7.56 (br s, 1H, H-5 in furyl), 8.31 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 45.0 (CH_2), 55.2 (OCH_3), 110.7 (CH in furyl), 111.8 (CH in furyl), 113.9 (CH in Ar), 121.1 (C-5), 129.2 (CH in Ar), 130.4 (C-1 in Ar), 135.5 (C-6), 142.6 (C-5 in furyl or C-2), 149.6 (C-5 in furyl or C-2), 153.5 (C-2 in furyl or C-4), 155.4 (C-2 in furyl or C-4), 158.9 (C-4 in Ar); MS EI *m/z* (rel. %): 296 (36, M^+), 278 (1), 264 (1), 187 (1), 148 (29), 136 (4), 122 (9), 121 (100); HRMS: found 296.1264, calcd for $C_{16}H_{16}N_4O_2$ 296.1273.

4.15.5. 6-(2-Furyl)-N^4-(4-methoxybenzyl)-N^4-methylpyrimidine-4,5-diamine (3h)

EtOAc–hexane (1:1) was used as eluent for flash chromatography and the reaction was performed on 1.00 mmol scale; yield 288 mg (93%), yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.83 (br s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.39 (s, 2H, CH_2), 4.53 (br s, 2H, NH_2), 6.57 (dd J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.86 (d, J = 8.8 Hz, 2H, Ar), 7.16 (br d, J = 1.8 Hz, 1H, H-3 in furyl), 7.22 (d, J = 8.8 Hz, 2H, Ar), 7.57 (br s, 1H, H-5 in furyl), 8.34 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.4 (NCH_3), 54.8 (CH_2), 55.2 (OCH_3), 111.1 (CH in furyl), 111.9 (CH in furyl), 113.9 (CH in Ar), 127.2 (C-5), 128.8 (CH in Ar), 129.6 (C-1 in Ar), 136.8 (C-6), 142.9 (C-5 in furyl C-2), 147.6 (C-5 in furyl or C-2), 153.1 (C-2 in furyl), 158.2 (C-4 in Ar or C-4), 158.7 (C-4 in Ar or C-4); MS EI *m/z* (rel. %): 310 (41, M^+), 295 (10), 281 (10), 189 (9). 150 (8), 121 (100), 106 5), 78 (8), 77 (6); HRMS: found 310.1422, calcd for $C_{17}H_{18}N_4O_2$ 310.1430; Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 66.13; H, 5.97; N, 17.68.

4.15.6. 4-(2-Furyl)-6-(4-methoxybenzyloxy)pyrimidine-5-amine (3i)

EtOAc–hexane (1:3) was used as eluent for flash chromatography and the reaction was performed in 1.37 mmol scale; yield 247 mg (61%), mp 114–116 °C, yellow crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.80 (s, 3H, OCH_3), 4.73 (br s, 2H, NH_2), 5.40 (s, 2H, CH_2), 6.57 (m, 1H, H-4 in furyl), 6.91 (d, J = 8.4 Hz, 2H, Ar), 7.15 (m 1H, H-3 in furyl), 7.39 (d, J = 8.4 Hz, 2H, Ar), 7.57 (br s, 1H, H-5 in furyl), 8.22 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.2 (CH_3), 68.3 (CH_2), 110.3 (CH in furyl), 111.8 (CH in furyl), 113.9 (CH in Ar), 124.4 (C-5), 128.2 (C-1 in Ar), 130.0 (CH in Ar), 135.1 (C-2 in furyl or C-4), 142.8 (C-5 in furyl or C-2), 146.0 (C-5 in furyl or C-2), 153.4 (C-2 in furyl or C-4), 158.6 (C-4 in Ar or C-6), 159.7 (C-4 in Ar or C-6); MS EI *m/z* (rel. %): 297 (46, M^+), 177 (3), 149 (2), 148 (2), 122 (17), 121 (100), 78 (7), 77 (6); HRMS: found 297.1115, calcd for $C_{16}H_{15}N_3O_3$ 297.1113.

4.15.7. 6-(2-Furyl)-*N*-(4-methoxybenzyl)-5-nitropyrimidine-4-amine (3m)

EtOAc–hexane (3:7) was used as eluent for flash chromatography; yield 104 mg (63%), mp 118.5–119.0 °C, yellow crystals. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.70 (s, 3H, CH_3), 4.56 (d, J = 5.8 Hz, 2H, CH_2), 6.73 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.87 (d, J = 8.7 Hz, 2H, Ar), 7.24 (d, J = 8.7 Hz, 2H, Ar), 7.32 (dd, J = 3.5 and 0.8 Hz, 1H, H-3 in furyl), 7.95 (dd, J = 1.7 and 0.8 Hz, 1H, H-5 in furyl), 8.49 (t, J = 5.8 Hz, 1H, NH), 8.52 (s, 1H, H-2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 43.2 (CH_2), 55.0 (CH_3), 112.7 (C-4 in furyl), 113.7 (CH in Ar), 115.7 (C-3 in furyl), 126.4 (C-5), 128.6 (CH in Ar), 130.6 (C-1 in Ar), 143.9 (C-6), 147.3 (C-5 in furyl), 148.1 (C-2 in furyl), 153.3 (C-4), 158.2 (C-2), 158.3 (C-4 in Ar); MS EI *m/z* (rel. %): 326 (11, M^+), 309 (100), 278 (96), 250 (22), 190 (42), 121 (78); HRMS: found 326.1014, calcd for $C_{16}H_{14}N_4O_4$ 326.1015; Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.96; H, 4.35; N, 17.05. An alternative procedure for the synthesis of **3m** starting from **4f** is given below.

4.15.8. 6-(2-Furyl)-*N*-(4-methoxybenzyl)-*N*-methyl-5-nitropyrimidine-4-amine (3n)

Hexane followed by EtOAc–hexane (1:1) were used as eluents for flash chromatography and the reaction was run in 0.43 mmol scale; yield 104 mg (63%), mp 79–81 °C, yellow crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.86 (s, 2H, CH_2), 6.53 (dd, J = 3.6 and 1.7 Hz, 1H, H-4 in furyl), 6.86 (d, J = 8.7 Hz, 2H, Ar), 7.18 (d, J = 8.7 Hz, 2H, Ar), 7.26 (dd, J = 3.6 and 0.7 Hz, 1H, H-3 in furyl), 7.56 (dd, J = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 8.55 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.0 (NCH_3), 54.3 (CH_2), 55.3 (OCH_3), 112.3 (C-4 in furyl), 114.2 (CH in Ar), 116.0 (C-3 in furyl), 127.4 (C-5), 128.2 (C-1 in Ar), 128.9 (CH in Ar), 146.0 (C-5 in furyl), 146.6 (C-6), 148.0 (C-2 in furyl), 153.9 (C-4), 156.5 (C-2), 159.2 (C-4 in Ar); MS EI *m/z* (rel. %): 340 (0.1, M^+), 204 (29), 187 (100), 121 (94); HRMS: found 340.1178, calcd for $C_{17}H_{16}N_4O_4$ 340.1172; Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.43. Found: C, 59.92; H, 4.79; N, 16.43.

4.16. 2-Chloro-6-(2-furyl)-*N*-(4-methoxybenzyl)pyrimidine-4-amine (3d)

A mixture of 2,4-dichloro-6-(2-furyl)pyrimidine **4a** (320 mg, 1.50 mmol), 4-methoxybenzylamine (200 mg, 1.50 mmol) and

Et_3N (0.28 mL, 2.00 mmol) in abs. EtOH (15 mL) was stirred at ambient temperature under N_2-atm for 24 h and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (3 × 30 mL) and the solution was washed with water (2 × 50 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2–hexane (3:7); yield 234 mg (50%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H, CH_3), 4.49 (d, J = 5.8 Hz, 2H, CH_2), 5.75 (br s, 1H, NH), 6.43 (dd, J = 3.4 and 1.7 Hz, 1H, H-4 in furyl), 6.75 (d, J = 8.6 Hz, 2H, Ar), 6.83 (s, 1H, H-5), 7.06 (br s, 1H, H-3 in furyl), 7.17 (d, J = 8.6 Hz, 2H, Ar), 7.45 (br d, J = 1.7 Hz, 1H, H-5 in furyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.0 (CH_2), 55.2 (CH_3), 104.0 (C-5), 112.3 (C-4 in furyl), 112.5 (C-3 in furyl), 113.9 (CH in Ar), 128.9 (CH in Ar), 130.7 (C-1 in Ar), 144.9 (C-5 in furyl), 151.4 (C-2 in furyl), 157.3 (C-6), 158.8 (C-4 in Ar), 161.6 (C-2), 161.9 (C-4); MS EI m/z (rel. %): 317/315 (35/100, M^+), 300 (13), 179 (6), 136 (48), 121 (91), 78 (9); HRMS: found 315.0779, calcd for $C_{16}H_{14}ClN_3O_2$ 315.0775; Anal. Calcd for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.91; H, 4.45; N, 13.69.

4.17. 2-Chloro-6-(2-furyl)-*N*-(4-methoxybenzyl)-*N*-methylpyrimidine-4-amine (3e)

The title compound was prepared from 2,4-dichloro-6-(2-furyl)pyrimidine **4a** (259 mg, 1.20 mmol) and *N*-methyl-4-methoxybenzylamine (180 mg, 1.20 mmol) as described for the synthesis of **3d** above. CH_2Cl_2–hexane (3:7) was used as eluent for flash chromatography; yield 270 mg (68%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.07 (br s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 4.74 (br s, 2H, CH_2), 6.55 (dd, J = 3.4 and 1.7 Hz, 1H, H-4 in furyl), 6.71 (s, 1H, H-5), 6.87 (d, J = 8.6 Hz, 2H, Ar), 7.17 (m, 3H, Ar and H-3 in furyl), 7.54 (br s, 1H, H-5 in furyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.8 (NCH_3), 52.3 (CH_2), 55.6 (OCH_3), 94.4 (C-5), 112.2 (C-3 in furyl), 112.6 (C-4 in furyl), 114.4 (CH in Ar), 128.9 (CH in Ar), 144.9 (C-5 in furyl), 152.1 (C-6), 156.2 (C-1 in Ar or C-2), 159.5 (C-4 in Ar), 160.8 (C-1 in Ar or C-2), 164.2 (C-4); MS EI m/z (rel. %): 331/329 (16/46, M^+), 314 (41), 208 (18), 150 (17), 121, (100), 91 (7), 78 (11); HRMS: found 329.0934, calcd for $C_{17}H_{16}ClN_3O_2$ 329.0931; Anal. Calcd for $C_{17}H_{16}ClN_3O_2$: C, 61.91; H, 4.89; N, 12.74. Found: C, 61.78; H, 4.77; N, 12.63.

4.18. 2-Chloro-4-(2-furyl)-6-(4-methoxybenzyloxy)pyrimidine (3f)

A solution of 4-methoxybenzyl alcohol ((288 mg, 2.00 mmol) in dry THF (5 mL) was added over 5 min to a stirring suspension of NaH (95 mg, ca. 65% in oil, ca 2.20 mmol) in dry THF (5 mL) under N_2-atm. The resulting mixture was stirred at ambient temperature for 1 h and cooled to 0 °C before 2,4-dichloro-6-(2-furyl)pyrimidine **4a** (430 mg, 2.00 mmol) in THF (5 mL) was added over 15 min. The resulting mixture was stirred at ambient for 16 h. Satd aq NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2–hexane (3:2); yield 332 mg (50%), mp 110–111 °C, colorless powdery crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 6.43 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.85–6.78 (m, 3H, Ar and H-5), 7.14 (dd, J = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.29 (d, J = 8.7 Hz, 2H, Ar), 7.44 (dd, J = 1.7 and 0.7 Hz, 1H, H-5 in furyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2 (CH_3), 69.0 (CH_2), 99.6 (C-5), 112.4 (C-4 in furyl), 113.1 (C-3 in furyl), 113.9 (CH in Ar), 127.4 (C-1 in Ar), 130.3 (CH in Ar), 145.2 (C-5 in furyl), 150.6 (C-2 in furyl), 157.7 (C-2 or C-6), 159.8 (C-4 in Ar), 160.0 (C-2 or C-6), 170.8 (C-4); MS EI m/z (rel. %): 318/316 (7/22, M^+), 122 (9), 121 (100), 91 (4), 78 (8); Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 59.83; H, 4.14; N, 8.76.

4.19. 6-(2-Furyl)-N^4-(4-methoxybenzyl)-N^5-methylpyrimidine-4,5-diamine (3j)

Et_3N (0.12 mL, 0.80 mmol) was added to a stirring suspension of 4-methoxybenzylamine (104 mg, 0.76 mmol) in *n*-BuOH (10 mL) under N_2-atm. After stirring for 10 min, 4-chloro-6-(2-furyl)-*N*-methylpyrimidine-5-amine **4c** (80 mg, 0.38 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C, cooled to ambient temperature, evaporated in vacuo and purified by flash chromatography on silica gel eluting with CH_2Cl_2–hexane–EtOAc (7:2:1); yield 90 mg (76%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H, NCH_3), 3.72 (br s, 4H, OCH_3 and NH), 4.57 (d, J = 5.7 Hz, 2H, CH_2), 6.02 (br s, 1H, NH), 6.49 (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.81 (d, J = 8.7 Hz, 2H, Ar), 7.12 (dd, J = 3.5 and 0.4 Hz, 1H, H-3 in furyl), 7.21 (d, J = 8.7 Hz, 2H, Ar), 7.48 (br s, 1H, H-5 furyl), 8.32 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.6 (NCH_3), 44.4 (CH_2), 55.2 (OCH_3), 111.9 (C-3 or C-4 in furyl), 112.0 (C-3 or C-4 in furyl), 114.0 (CH in Ar), 123.8 (C-5), 128.9 (CH in Ar), 130.8 (C-1 in Ar), 143.0 (C-6), 143.4 (C-5 in furyl), 153.0 (C-2 in furyl), 153.6 (C-2), 158.9 (C-4 in Ar), 159.6 (C-4); MS EI m/z (rel. %): 310 (34, M^+), 189 (16), 161 (5), 146 (2), 121 (100), 78 (7), 77 (7); HRMS: found 310.1428, calcd for $C_{17}H_{18}N_4O_2$ 310.1430; Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 66.02; H, 5.89; N, 18.07.

4.20. N^5-Ethyl-6-(2-furyl)-N^4-(4-methoxybenzyl)pyrimidine-4,5-diamine (3k)

The title compound was synthesized from 4-chloro-*N*-ethyl-6-(2-furyl)-pyrimidine-5-amine **4d** (60 mg, 0.27 mmol) as described for compound **3j** above. CH_2Cl_2–hexane–EtOAc (14:5:1) was used as eluent for flash chromatography; yield 60 mg (69%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, J = 7.2 Hz, 3H, CH_3), 2.82 (q, J = 7.2 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.86 (br s, 1H, NH), 4.56 (d, J = 5.7 Hz, 2H, CH_2), 5.99 (br s, 1H, NH), 6.49 (dd, J = 3.5, and 1.7 Hz, 1H, H-4 in furyl), 6.81 (d, J = 8.7 Hz, 2H, Ar), 7.10 (dd, J = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.20 (d, J = 8.7 Hz, 2H, Ar), 7.48 (dd, J = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 8.32 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7 (CH_3), 42.5 (CH_2CH_3), 44.4 (CH_2Ar), 55.3 (OCH_3), 111.9 (C-3 and C-4 in furyl), 114.0 (CH in Ar), 122.6 (C-5), 128.8 (CH in Ar), 130.9 (C-1 in Ar), 143.2 (C-5 in furyl), 143.4 (C-6), 153.3 (C-2 in furyl), 153.6 (C-2), 158.9 (C-4 in Ar), 159.8 (C-4); MS EI m/z (rel. %): 324 (58, M^+), 295 (16), 203 (36), 175 (11), 121 (100), 78 (6); HRMS: found 324.1584, calcd for $C_{20}H_{22}N_2O_2$ 324.1586.

4.21. N^5,N^5-Dimethyl-6-(2-furyl)-N^4-(4-methoxybenzyl)pyrimidine-4,5-diamine (3l)

The title compound was synthesized from *N*,*N*-dimethyl-4-chloro-6-(2-furyl)pyrimidine-5-amine **4e** (60 mg, 0.27 mmol) as described for compound **3j** above. EtOAc–hexane (2:3) was used as eluent for flash chromatography; yield 29 mg (21%), mp 91–92 °C, colorless powdery crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 [s, 6H, $N(CH_3)_2$], 3.79 (s, 3H, OCH_3), 4.62 (d, J = 5.8 Hz, 2H, CH_2), 6.47 (br s, 1H, NH), 6.56 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.87 (d, J = 8.7 Hz, 2H, Ar), 7.16 (br d, J = 3.5 Hz, 1H, H-3 in furyl), 7.25 (d, J = 8.7 Hz, 2H, Ar), 7.60 (dd, J = 1.7, 0.8 Hz, 1H, H-5 in furyl), 8.43 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.1 [$N(CH_3)_2$], 44.9 (CH_2), 55.7 (OCH_3), 112.6 (C-4 in furyl), 113.7 (C-3 in furyl), 114.6 (CH in Ar), 126.7 (C-5), 129.3 (CH in Ar), 131.1 (C-1 in Ar), 144.4 (C-5 in furyl), 147.3 (C-6), 150.6 (C-2 in furyl), 154.4 (C-2), 159.5 (C-4), 162.1 (C-4 in Ar); MS EI m/z (rel. %): 324

(100, M^+), 280 (8), 203 (80), 175 (35), 121 (90), 91 (5); HRMS: found 324.1590, calcd for $C_{18}H_{20}N_4O_2$ 324.1586.

4.22. 6-(2-Furyl)-*N*-(4-methoxybenzyl)-5-nitropyrimidine-4-amine (3m)

4-Chloro-6-(2-furyl)-5-nitropyrimidine **4f** (225 mg, 1.00 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution was stirred under N_2-atm. Et_3N (0.07 mL, 0.50 mmol) was added and the mixture was cooled to –78 °C. 4-Methoxybenzylamine (137 mg, 1.00 mmol) was added and the resulting mixture was stirred at –78 °C for 1 h. The reaction mixture was washed with water (2 × 20 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (3:7); yield 140 mg (87%), data and synthesis from compound **2h**, see above.

4.23. 4-(2-Furyl)-6-(4-methoxybenzyloxy)-5-nitropyrimidine (3o)

The title compound was synthesized from 4-chloro-6-(2-furyl)-5-nitropyrimidine **4f** (110 mg, 0.50 mmol) as described for compound **3f** above. The reaction time was 3.5 h and EtOAc–hexane (1:9) was used as eluent for flash chromatography; yield 168 mg (91%), mp 119–120 °C, colorless powdery crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 6.48 (dd, J = 3.6 and 1.7 Hz, 1H, H-4 in furyl), 6.80 (d, J = 8.7 Hz, 2H, CH in Ar), 7.31–7.21 (m, 3H, CH in Ar and H-3 in furyl), 7.53–7.48 (m, 1H, H-5 in furyl), 8.61 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2 (CH_3), 69.7 (CH_2), 112.6 (C-4 in furyl), 114.0 (CH in Ar), 116.6 (C-3 in furyl), 126.7 (C-1 in Ar), 128.8 (C-5), 130.0 (CH in Ar), 145.4 (C-4), 146.9 (C-5 in furyl), 147.7 (C-2 in furyl), 157.4 (C-2), 159.9 (C-6), 160.8 (C-4 in Ar); MS EI *m/z* (rel. %): 327 (1, M^+), 191 (15), 121 (100), 91 (5); HRMS: found 327.0859, calcd for $C_{16}H_{13}N_3O_5$ 327.0855; Anal. Calcd for $C_{16}H_{13}N_3O_5$: C, 58.72; H, 4.0; N, 12.84. Found: C, 58.80; H, 4.07; N, 12.78.

4.24. 2,4-Dichloro-6-(2-furyl)pyrimidine (4a)

A mixture of $Pd_2(dba)_3$ (55 mg, 0.060 mmol) and tri(2-furyl)phosphine (100 mg, 0.440 mmol) in DMF (10 mL) was stirred for 30 min at ambient temperature under N_2-atm before 2,4,6-trichloropyrimidine **1b** (360 mg, 2.00 mmol) in DMF (5 mL) followed by 2-(tributylstannnyl)furan (650 μL, 2.05 mmol) were added. The mixture was stirred for 16 h at 30 °C and evaporated in vacuo. KF (satd sol. in THF, 30 mL) was added and the reaction mixture was stirred for 16 h, evaporated in vacuo, and the product was purified by flash chromatography on silica gel eluting with PhMe-CH_2Cl_2–hexane (3:2:1); yield 230 mg (55%), colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.56 (dd, J = 3.6 and 1.7 Hz, 1H, H-4 in furyl), 7.32 (dd, J = 3.6 and 0.7 Hz, 1H, H-3 in furyl), 7.46 (s, 1H, H-5), 7.59 (dd, J = 1.7 and 0.7 Hz, 1H, H-5 in furyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 112.7 (C-5), 113.1 (C-4 in furyl), 115.5 (C-3 in furyl), 146.6 (C-5 in furyl), 149.4 (C-2 in furyl), 158.4 (C-2), 160.6 (C-4 or C-6), 162.6 (C-4 or C-6); MS EI *m/z* (rel. %): 216/214 (64/100, M^+), 188 (6), 118 (16), 90 (7); HRMS: found 213.9700, calcd for $C_8H_4Cl_2N_2O$ 213.9701.

4.25. 4-Chloro-6-(2-furyl)pyrimidine-5-amine (4b)

The title compound was synthesized from 4,6-dichloropyrimidine-5-amine **1c** (880 mg, 4.90 mmol) as described for compound **4a** above. The reaction temperature was 70 °C and CH_2Cl_2–EtOAc–hexane (16:1:4) was used as eluent for flash chromatography; yield 200 mg (27%), mp 100–101 °C, powdery crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.07 (br s, 2H, NH_2), 6.51 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.19 (dd, J = 3.6 and 0.8 Hz, 1H, H-3 furyl), 7.53 (dd, J = 1.8 and 0.8 Hz, 1H, H-5 furyl), 8.22 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 112.2 (C-4 in furyl), 112.8 (C-3 in furyl), 133.1 (C-4), 138.5 (C-6), 143.8 (C-5 in furyl), 146.4 (C-2 in furyl), 146.7 (C-5), 152.3 (C-2 in furyl); MS EI *m/z* (rel. %): 197/195 (33/100, M^+), 166 (32), 160 (3), 130 (25), 106 (15), 77 (8); HRMS: found 195.0203, calcd for $C_8H_6ClN_3O$ 195.0199; Anal. Calcd for $C_8H_6ClN_3O$: C, 49.12; H, 3.09; N, 21.48. Found: C, 49.00; H, 3.14; N, 21.32.

4.26. 4-Chloro-6-(2-furyl)-*N*-methylpyrimidine-5-amine (4c)

The title compound was synthesized from 4,6-dichloro-*N*-methylpyrimidine-5-amine **1d** (180 mg, 1.00 mmol) as described for compound **4b** above. EtOAc–hexane (3:7) was used as eluent for flash chromatography; yield 70 mg (30%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84 (s, 3H, CH_3), 4.53 (br s, 1H, NH), 6.54 (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 7.22 (dd, J = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.57 (dd, J = 1.8 and 0.7 Hz, 1H, H-5 in furyl), 8.41 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.1 (CH_3), 112.2 (C-4 in furyl), 114.7 (C-3 in furyl), 137.2 (C-5), 144.3 (C-5 in furyl), 145 (C-6), 149.3 (C-2), 150.6 (C-2 in furyl), 152 (C-4); MS EI *m/z* (rel. %): 211/209 (32/100, M^+), 182 (39), 180 (91), 166 (15), 153 (10), 144 (20), 118 (17), 117 (17); HRMS: found 209.0358, calcd for $C_9H_8ClN_3O$ 209.0356.

4.27. 4-Chloro-*N*-ethyl-6-(2-furyl)-pyrimidine-5-amine (4d)

The title compound was synthesized from 4,6-dichloro-*N*-ethylpyrimidine-5-amine **1e** (191 mg, 1.00 mmol) as described for compound **4a** above. The reaction temperature was 80 °C and acetone–hexane (1:9) was used as eluent for flash chromatography; yield 85 mg (27%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, J = 7.2 Hz, 3H, CH_3), 3.16 (q, J = 7.2 Hz, 2H, CH_2), 4.06 (br s, 1H, NH), 6.57 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 7.29 (dd, J = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.60 (dd, J = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 8.46 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0 (CH_3), 42.1 (CH_2), 112.3 (C-4 in furyl), 114.9 (C-3 in furyl), 136.0 (C-5), 144.4 (C-5 in furyl), 145.9 (C-6), 149.7 (C-2), 150.7 (C-2, furyl), 153.0 (C-4); MS EI *m/z* (rel. %): 225/223 (30/90, M^+), 208 (33), 194 (40), 180 (100), 144 (14); HRMS: found 223.0515, calcd for $C_{10}H_{10}ClN_3O$ 223.0512.

4.28. *N,N*-Dimethyl-4-chloro-6-(2-furyl)pyrimidine-5-amine (4e)

A solution of 4-chloro-6-(2-furyl)pyrimidine-5-amine **4b** (150 mg, 0.80 mmol) in THF (10 mL) under N_2-atm was treated with NaH (100 mg, ca. 65% in oil, ca. 2.50 mmol) in THF (15 mL) at 0 °C before the mixture was allowed to warm to ambient temperature and stirred for 20 min. MeI (0.22 mL, 2.40 mmol) and *n*-Bu_4NBr (800 mg, 2.50 mmol) where added and the resulting mixture was stirred for 2 h, evaporated in vacuo and the product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4); yield gave 80 mg (45%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.77 [s, 6H, ($N(CH_3)_2$], 6.54 (dd, J = 3.5 and 1.8 Hz, 1H, H-3 in furyl), 7.41 (dd, J = 3.5 and 0.7 Hz, 1H, H-2 in furyl), 7.61 (dd, J = 1.8 and 0.7 Hz, 1H, H-4 in furyl), 8.67 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.2 (CH_3), 112.8 (C-4 in furyl), 117.9 (C-3 in furyl), 138.6 (C-5), 145.5 (C-5 in furyl), 149.1 (C-2 in furyl), 154.4 (C-2), 155.2 (C-4 or C-6), 161.6 (C-4 or C-6); MS EI *m/z* (rel. %): 225/223 (25/72, M^+), 208 (12), 194 (100), 180 (22), 167 (11), 132 (14); HRMS: found 223.0511, calcd for $C_{10}H_{10}ClN_3O$ 223.0512.

4.29. 4-Chloro-6-(2-furyl)-5-nitropyrimidine (4f)

The title compound was synthesized from 4,6-dichloro-5-nitropyrimidine **1f** (380 mg, 2.00 mmol) as described for conversion of

compounds **2** to compounds **3** above. The reaction was performed at ambient temperature, THF (5 mL) was used as solvent and EtOAc–hexane (3:17) was used as eluent for flash chromatography; yield 165 mg (73%), mp 110–111 °C, yellow powdery crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.64 (dd, J = 3.7 and 1.7 Hz, 1H, H-4 in furyl), 7.51 (dd, J = 3.7 and 0.7 Hz, 1H, H-3 in furyl), 7.66 (dd, J = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 8.92 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.3 (C-4 in furyl), 118.7 (C-3 in furyl), 138.3 (C-5), 146.6 (C-2 in furyl or C-6), 147.0 (C-2 in furyl or C-6), 148.2 (C-5 in furyl), 152.8 (C-4), 157.7 (C-2); MS EI m/z (rel. %): 227/225 (7/21, M^+), 190 (20), 180 (28), 83 (100), 68 (4); HRMS: found 224.9935, calcd for $C_8H_4ClN_3O_3$ 224.9941.

4.30. *N*-{4-(2-Furyl)-6-[(4-methoxybenzyl)(methyl)amino] pyrimidin-5-yl}formamide (6i)

Method A: The title compound was prepared from *N*-{4-Chloro-6-[(4-methoxybenzyl)(methyl)amino]pyrimidin-5-yl}formamide **2i** (0.49 mmol) and (2-tributylstannyl)furan following the general procedure for synthesis of compounds **3** from compounds **2** described above. EtOAc–hexane (1:1) followed by EtOAc–hexane (2:1) were used as eluents for flash chromatography; 128 mg (77%), pale yellow oil, 12 mg (8%) unreacted **2i** was also isolated. In DMSO-d_6 a mixture of amide s-*cis* and s-*trans* rotamers of **6i** were observed. When the NMR signals for the rotamers are not overlapping, 'denotes the s-*cis* rotamer and * denotes the s-*trans* rotamer. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.98′ (s, 3H, NCH_3), 3.03* (s, 3H, NCH_3), 3.71 (s, 3H, OCH_3), 4.75′ (br s, 2H, CH_2), 4.77* (br s, 2H, CH_2), 6.65′ (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.69* (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.87 (d, J = 8.7 Hz, 2H, Ar), 7.15* (dd, J = 3.5 and 0.8 Hz, H-3 in furyl), 7.18 (d, J = 8.7 Hz, 2H, Ar), 7.23′ (dd, J = 3.5 and 0.8 Hz, H-3 in furyl), 7.81* (br, 1H, CHO), 7.88′ (dd, J = 1.8 and 0.8 Hz, 1H, H-5 in furyl), 7.91* (dd, J = 1.8 and 0.8 Hz, 1H, H-5 in furyl), 8.18′ (d, J = 1.3 Hz, 1H, CHO), 8.41′ (s, 1H, H-2), 8.46* (s, 1H, H-2), 9.48* (br 1H, NH), 9.78′ (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 38.1 (NCH_3), 54.1 (CH_2), 55.4 (OCH_3), 110.2′ (C-5), 111.1* (C-5), 112.4′ (C-4 in furyl), 112.6* (C-4 in furyl), 114.2 (CH in Ar), 114.8′ (C-3 in furyl), 115.8* (C-3 in furyl), 128.9′ (CH in Ar), 129.1* (CH in Ar), 129.8* (C-1 in Ar), 129.9′ (C-1 in Ar), 145.5′ (C-5 in furyl), 145.9* (C-5 in furyl), 150.8* (C-2 in furyl), 151.0′ (C-2 in furyl), 152.4′ (C-4), 153.4* (C-4), 155.7′ (C-2), 156.1* (C-2), 158.7′ (C-4 in Ar), 158.8* (C-4 in Ar), 161.3′ (CHO), 161.9′ (C-6), 162.5* (C-6), 165.0* (CHO); MS EI m/z (rel. %): 338 (58, M^+), 323 (18), 295 (16), 150 (30), 122 (14), 121 (100); HRMS: found 338.1378, calcd for $C_{18}H_{18}N_4O_3$ 338.1379.

Method B: 6-(2-Furyl)-N^4-(4-methoxybenzyl)-N^4-methylpyrimidine-4,5-diamine **3h** (210 mg, 0.68 mmol) was dissolved in concd formic acid (2 mL) and cooled to 0 °C. Acetic acid anhydride (0.64 mL, 6.8 mmol) was added drop wise over 5 min. The resulting mixture was stirred at ambient temperature for 2 h and evaporated in vacuo. The residue was dissolved in benzene (5 mL) and evaporated (×4). The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (3:5) followed by EtOAc–hexane (1:1) and EtOAc–hexane (2:1); yield 122 mg (53%). Unreacted **3h** (18%) was also isolated. Data for **6i**, see above.

4.31. *N*-[4-(2-Furyl)-6-(4-methoxybenzyloxy)pyrimidin-5-yl]formamide (6j)

The title compound was prepared from *N*-[4-chloro-6-(4-methoxybenzyloxy)pyrimidin-5-yl]formamide **2j** and (2-tributylstannyl)furan following the general procedure for synthesis of compounds **3** from compounds **2** described above. EtOAc–hexane (1:1) was used as eluent for flash chromatography; yield 66 mg (40%), m.p. 154–156 °C, off-white powdery crystals. In DMSO-d_6 a mixture of amide s-*cis* and s-*trans* rotamers were observed. When the NMR signals for the rotamers are not overlapping, ' denotes the s-*cis* rotamer and * denotes the s-*trans* rotamer. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.74 (s, 3H, CH_3), 5.37′ (s, 2H, CH_2), 5.39* (s, 2H, CH_2), 6.69′ (dd, J = 3.6 and 1.7 Hz, 1H H-4 in furyl), 6.72* (m, 1H, H-4 in furyl), 6.93′ (d, J = 8.6 Hz, 2H, Ar), 6.93* (m, 2H, Ar), 7.26* (m, 1H, H-3 in furyl), 7.30′ (br d, J = 3.6 Hz, 1H, H-3 in furyl), 7.38′ (d, J = 8.6 Hz, 2H, Ar), 7.40* (m, 2H, Ar), 7.93′ (br d, J = 1.7 Hz, 1H, H-5 in furyl), 7.98* (br s, 1H, H-5 in furyl), 8.12* (d, J = 11.1 Hz, 1H, CHO), 8.29′ (d, J = 1.1 Hz, 1H, CHO), 8.67 (s, 1H, H-2), 9.43* (br d, J = 11.1 Hz, NH), 9.80′ (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 55.1 (CH_3), 68.1′ (CH_2), 68.4* (CH_2), 112.3′ (C-4 in furyl), 112.4* (C-4 in furyl), 113.8 (CH in Ar), 115.2′ (C-3 in furyl), 115.6 * (C-3 in furyl), 127.8* (C-1 in Ar), 128.0′ (C-1 in Ar), 129.7 (CH in Ar), 145.9′ (C-5 in furyl), 146.1* (C-5 in furyl), 149.7 (C-2 in furyl or C-4), 150.9 (C-2 in furyl or C-4), 155.1* (C-2), 155.6′ (C-2), 159.1′ (C-4 in Ar), 159.3* (C-4 in Ar), 160.5′ (CHO), 164.7* (CHO), 165.4 (C-6), C-5 was hidden; MS EI m/z (rel. %): 325 (3, M^+), 298 (5), 297 (28), 177 (2), 122 (11), 121 (100); HRMS: found 325.1052, calcd for $C_{17}H_{16}N_3O_4$ 325.1063.

4.32. *N*-[4-(2-Furyl)-6-oxo-1,6-dihydropyrimidin-5-yl]-*N*-(4-methoxybenzyl)formamide (7)

The title compound was prepared by reacting 4-(2-furyl)-6-(4-methoxybenzyloxy)pyrimidine-5-amine **3i** (102 mg, 0.34 mmol) with acetic acid anhydride (0.32 mL, 3.4 mmol) and formic acid (1 mL) as described for the synthesis of compound **6i** from **3h** above. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (1:1) followed by EtOAc; yield 42 mg (38%), mp 164–167 °C, off-white crystals. In DMSO-d_6 a mixture of amide s-*cis* and s-*trans* rotamers were observed. When the NMR signals for the rotamers are not overlapping, ' denotes the major rotamer and * denotes the minor rotamer. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.64 (s, 3H, CH_3), 4.57′ (d, J = 14.2 Hz, 1H, H_a in CH_2), 4.63* (d, J = 14.4 Hz, 1H, H_a in CH_2), 4.68 (m, 1H, H_b in CH_2), 6.54* (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.61′ (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.67′ (d, J = 8.7 Hz, 2H, Ar), 6.70* (d, J = 8.7 Hz, 2H, Ar), 6.99* (dd, J = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.00′ (dd, J = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.04′ (d, J = 8.7 Hz, 2H, Ar), 7.11* (d, J = 8.7 Hz, 2H, Ar), 7.74* (dd, J = 1.8 and 0.7 Hz, 1H, H-5 in furyl), 7.82′ (dd, J = 1.8 and 0.7 Hz, 1H, H-5 in furyl), 8.07′ (s, 1H, H-2 or CHO), 8.12* (s, 1H, H-2 or CHO), 8.14′ (s, 1H, H-2 or CHO), 8.46* (s, 1H, H-2 or CHO), 12.8 (br s, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 54.9 (CH_3), 46.5′ (CH_2), 50.7* (CH_2), 112.0* (C-4 in furyl), 112.3′ (C-4 in furyl), 113.2 (CH in Ar), 115.6* (C-3 in furyl), 116.1′ (C-3 in furyl), 118.5* (C-5), 120.1′ (C-5), 127.1* (C-1 in Ar), 127.9′ (C-1 in Ar), 130.4′ (CH in Ar), 130.5* (CH in Ar), 146.1* (C-5 in furyl), 146.5′ (C-5 in furyl), 148.3–148.5 (C-2 and C-4 both rotamers), 149.1* (C-2 in furyl), 149.6′ (C-2 in furyl), 158.4′ (C-4 in Ar), 158.6* (C-4 in Ar), 158.9* (C-6), 160.3′ (C-6), 163.0* (CHO), 163.5′ (CHO); MS EI m/z (rel. %): 325 (37, M^+), 297 (3), 296 (4), 268 (4), 122 (9), 121 (100); HRMS: found 325.1057, calcd for $C_{17}H_{16}N_3O_4$ 325.1063.

4.33. 1-(4-Methoxybenzyl)-4-tributylstannyl-1*H*-imidazole (9)

A solution of MeMgI in Et_2O (1.1 mL, 3.4 mmol, 3.0 M) was added to a solution of 4-iodo-1-(4-methoxybenzyl)-1*H*-imidazole **8** (880 mg, 2.80 mmol) in CH_2Cl_2 (3 mL) under Ar-atm at ambient temperature, and the resulting mixture was stirred for 1 h. Tributyltin chloride (0.90 mL, 3.4 mmol) was added, and the reaction was stirred for 18 h, quenched by the addition of satd aq NH_4Cl (5 mL), and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash chro-

matography on a silica gel eluting with EtOAc; yield 860 mg, (65%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80–1.52 (m, 27H, 3 × Bu), 3.67 (s, 3H, OCH_3), 4.96 (s, 2H, NCH_2), 6.73 (br s, 1H, H-5), 6.75 (d, J = 8.7 Hz, 2H, Ar), 7.04 (d, J = 8.7 Hz, 2H, Ar), 7.69 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8 (3 × CH_2), 14.0 (3 × CH_3), 27.3 (3 × CH_2), 29.6 (3 × CH_2), 50.3 (NCH_2), 55.6 (OCH_3), 114.6 (CH in Ar), 127.7 (C-4), 128.9 (C-1 in Ar), 129.5 (CH in Ar), 140.0 (C-5), 140.9 (C-2), 159.8 (C-4 in Ar); MS ESI *m/z* (rel. %): 479/477/475 (100/55/10, *M*+1).

4.34. 4-Chloro-5-[1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]pyrimidine (10)

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (33 mg, 0.032 mmol) and tri(2-furyl)phosphine (25 mg, 0.11 mmol) in toluene (2 mL) was stirred for 30 min at ambient temperature under N_2-atm and transferred to a stirring solution of 4-chloro-5-iodopyrimidine (250 mg, 1.04 mmol) in toluene (2 mL) at ambient temperature under N_2-atm in a Pyrex sealed tube. Subsequently, 1-(4-methoxybenzyl)-4-tributylstannyl-1*H*-imidazole **9** (500 mg, 1.04 mmol) in toluene (4 mL) was added and the resulting mixture was stirred at 130 °C for 18 h. The reaction mixture was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with water (10 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in satd KF in THF (20 mL), stirred at ambient temperature for 16 h, and evaporated in vacuo together with a small amount of SiO_2. The residue was placed on top of a flash chromatography column and the product eluted with EtOAc–hexane (4:1); yield 180 mg (60%), mp 130–132 °C, colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.67 (s, 3H, OCH_3), 5.07 (s, 2H, NCH_2), 6.85 (d, J = 8.6 Hz, 2H, Ar), 7.13 (d, J = 8.6 Hz, 2H, Ar), 7.58 (s, 1H, H-5 in imidazole), 7.66 (s, 1H, H-2 in imidazole), 8.77 (s, 1H, H-6), 9.42 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.7 (NCH_2), 55.2 (OCH_3), 114.4 (CH in Ar), 121.1 (C-2 in imidazole), 127.1 (C-1 in Ar), 127.4 (C-5), 128.8 (CH in Ar), 133.6 (C-4 in imidazole), 137.6 (C-5 in imidazole), 155.4 (C-6), 155.7 (C-4), 157.0 (C-2), 159.7 (C-4 in Ar); MS EI *m/z* (rel. %): 300 (13, M^+), 122 (15), 121 (100); HRMS: found 300.0785, calcd for $C_{15}H_{13}ClN_4O$ 300.0778; Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 60.15; H, 4.33; N, 18.41.

4.35. 4-(2-Furyl)-5-[1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]pyrimidine (11)

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (17 mg, 0.016 mmol) and tri(2-furyl)phosphine (13 mg, 0.56 mmol) in toluene (4 mL) was stirred for 30 min at ambient temperature under N_2-atm and transferred to a stirring solution of 4-chloro-5-[1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]pyrimidine **10** (160 mg, 0.532 mmol) in DMF (4 mL) at ambient temperature under N_2-atm. Subsequently, (2-furyl)tributyltin (0.20 mL, 0.63 mmol) was added and the mixture was stirred at 110 °C for 18 h. The reaction was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water (5 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in satd KF in THF (20 mL), stirred at ambient temperature for 16 h, and evaporated in vacuo together with a small amount of SiO_2. The residue was placed on top of a flash chromatography column and the product was eluted with EtOAc–MeOH (19:1); yield 90 mg (51%), yellow oil. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 3.69 (s, 3H, OCH_3), 5.09 (s, 2H, NCH_2), 6.47 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.92 (m, 3H, Ar and H-3 in furyl), 6.97 (br d, J = 1.3 Hz, 1H, H-5 in furyl), 7.20 (d, J = 8.7 Hz, 2H, Ar), 7.46 (s, 1H, H-5 in imidazole), 7.63 (s, 1H, H-2 in imidazole), 8.87 (s, 1H, H-6), 9.04 (s, 1H, H-2); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 50.9 (NCH_2), 55.6 (OCH_3), 112.2 (CH in furyl), 114.6 (CH in Ar), 114.9 (CH in furyl), 119.4 (CH in furyl), 124.7 (C-5), 128.5 (C-1 in Ar), 129.3 (CH in Ar), 136.5 (C-4 in imidazole), 137.7 (C-2 in imidazole), 144.6 (C-5 in imidazole), 151.7 (C-2 in furyl), 152.4 (C-4), 157.2 (C-2), 159.0 (C-6), 160.1 (C-4 in Ar); MS EI *m/z* (rel. %): 332 (26, M^+), 122 (15), 121 (100); HRMS: found 332.1268, calcd for $C_{19}H_{16}N_4O_2$ 332.1273; Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.71; H, 4.71; N, 16.57.

4.36. 1-[(4-Methoxyphenyl)(tributystannyl)methyl)]-1*H*-imidazole (13)

A stirring solution of TMEDA (1.25 mL, 8.29 mmol) in hexane (4 mL) under N_2-atm was cooled to −20 °C [NaCl, H_2O(s)]. *n*-BuLi (5.18 mL, 8.29 mmol; 1.6 M sol. in hexane) was added drop wise over 15 min. The resulting mixture was stirred at −20 °C for 20 min, before a solution of 1-(4-methoxybenzyl)-1*H*-imidazole **12** (646 mg, 3.44 mmol) in THF (3 mL) was added drop wise over 20 min. The cooling bath was removed and the reaction mixture was stirred for 1 h. The mixture was again cooled to −20 °C and tributyltin chloride (2.32 mL, 6.60 mmol) was added before the reaction mixture was stirred at ambient temperature for 20 h. EtOAc (10 mL) and water (10 mL) were added, the layers were separated and the water phase was extracted with EtOAc (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in hexane and extracted with MeCN (5 × 6 mL). The combined MeCN extracts were evaporated and the product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (1:2); yield 224 mg (14%), yellow oil. Further elution with EtOAc afforded recovered starting material **12** (49%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.79–1.46 (m, 27H, Bu), 3.74 (s, 3H, OCH_3), 5.10 [1H (s, NCHSn) and (d, J = 47 Hz, $NCH^{119}Sn$)], 6.74–6.84 (m, 4H, Ar), 6.86 (s, 1H, H-5), 7.05 (s, 1H, H-4), 7.47 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.6 (3 × CH_2), 13.5 (3 × CH_3), 27.2 (3 × CH_2), 28.4 (3 × CH_2), 51.0 (NCH), 55.3 (OCH_3), 114.1 (CH in Ar), 121.1 (C-5), 125.4 (CH in Ar), 129.2 (C-1 in Ar), 134.9 (C-4), 138.4 (C-2), 157.6 (C-4 in Ar); MS EI *m/z* (rel. %): 478/477/476/475/474 (88/39/66/29/37, M^+), 385 (60), 384 (23), 383 (45), 382 (18), 235 (39), 234 (13), 233 (30), 232 (11), 231 (18), 187 (100), 179 (60); HRMS: found 478.1995, calcd for $C_{23}H_{38}N_2OSn$ 478.2006.

4.37. 1-(4-Methoxybenzyl)-5-tributylstannyl-1*H*-imidazole (15)

MeMgI in Et_2O (0.40 mL, 1.2 mmol, 3.0 M in Et_2O) was added to a solution of 5-iodo-1-(4-methoxybenzyl)-1*H*-imidazole **14** (320 mg, 1.02 mmol) in CH_2Cl_2 (3 mL) under Ar-atm at ambient temperature, and the resulting mixture was stirred for 1 h. Tributyltin chloride (0.42 mL, 1.5 mmol) was added and the reaction was stirred for 18 h, quenched by the addition of satd aq NH_4Cl (5 mL), and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on a silica gel column eluting with MeOH–EtOAc (1:19); yield 300 mg (63%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89–1.40 (m, 27H, 3 × Bu), 3.67 (s, 3H, OCH_3), 5.05 (s, 2H, NCH_2), 6.81 (d, J = 8.7 Hz, 2H, Ar), 6.88 (d, J = 8.7 Hz, 2H, Ar), 7.04 (br s, 1H, H-4), 7.68 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.0 (3 × CH_2), 14.0 (3 × CH_3), 27.3 (3 × CH_2), 29.5 (3 × CH_2), 51.6 (NCH_2), 55.7 (OCH_3), 114.7 (CH in Ar), 129.4 (CH in Ar), 129.6 (C-5), 139.7 (C-4), 141.5 (C-2), 159.8 (C-4 in Ar), C-1 in Ar was hidden; MS ESI *m/z* (rel. %): 479/477/475 (100/65/20, *M*+1).

4.38. 4-Bromo-6-[1-(4-methoxybenzyl)-1*H*-imidazol-5-yl]pyrimidine (16)

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (17 mg, 0.017 mmol) and tri(2-furyl)phosphine (12 mg, 0.052 mmol) in toluene (2 mL) was stirred

for 30 min at ambient temperature under N_2-atm and transferred to a stirring solution of 4,6-dibromopyrimidine (125 mg, 0.524 mmol) in toluene (2 mL) at ambient temperature under N_2-atm in a Pyrex sealed tube. Subsequently, 1-(4-methoxybenzyl)-5-tributylstannyl-1*H*-imidazole **15** (250 mg, 0.524 mmol) in toluene (4 mL) was added and the resulting mixture was stirred at 130 °C for 18 h. The reaction mixture was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with water (10 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in satd KF in THF (20 mL), stirred at ambient temperature for 16 h, and evaporated in vacuo together with a small amount of SiO_2. The residue was placed on top of a flash chromatography column and the product eluted with EtOAc–hexane (7:3); yield 100 mg (56%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H, OCH_3), 5.67 (s, 2H, NCH_2), 6.78 (d, J = 8.6 Hz, 2H, Ar), 7.03 (d, J = 8.6 Hz, 2H, Ar), 7.64 (br s, 1H, H-4 in imidazole), 7.65 (s, 1H, H-5), 7.70 (br s, 1H, H-2 in imidazole), 8.84 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.8 (NCH_2), 55.6 (OCH_3), 114.6 (CH in Ar), 121.1 (C-5), 128.0 (C-5 in imidazole), 128.7 (C-1 in Ar), 129.1 (CH in Ar), 135.5 (C-2 in imidazole), 143.2 (C-4 in imidazole), 152.8 (C-6), 155.7 (C-4), 158.6 (C-2), 159.7 (C-4 in Ar); MS EI *m/z* (rel. %): 346/344 (7/7, M^+), 122 (11), 121 (100); HRMS: found 344.0275, calcd for $C_{15}H_{13}BrN_4O$ 344.0273; Anal. Calcd for $C_{15}H_{13}BrN_4O$: C, 52.19; H, 3.80; N, 16.23. Found: C, 52.39; H, 3.94; N, 16.02.

4.39. 4-(-Furyl)-6-[1-(4-methoxybenzyl)-1*H*-imidazol-5-yl]pyrimidine (17)

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 0.005 mmol) and tri(2-furyl)phosphine (3 mg, 0.01 mmol) in toluene (2 mL) was stirred for 30 min at ambient temperature under N_2-atm and transferred to a stirring solution of 4-bromo-6-[1-(4-methoxybenzyl)-1*H*-imidazol-5-yl]pyrimidine **16** (50 mg, 0.15 mmol) in toluene (3 mL) at ambient temperature under N_2-atm. Subsequently, (2-furyl)tributyltin (0.05 mL, 0.2 mmol) was added and the mixture was stirred at 110 °C under N_2-atm for 18 h. The reaction was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water (5 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in satd KF in THF (20 mL), stirred at ambient temperature for 16 h, and evaporated in vacuo together with a small amount of SiO_2. The residue was placed on top of a flash chromatography column and the product was eluted with EtOAc–MeOH (9:1); yield 25 mg (52%), yellow oil. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 3.74 (s, 3H, OCH_3), 5.75 (s, 2H, NCH_2), 6.60 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.79 (d, J = 8.6 Hz, 2H, Ar), 7.10 (d, J = 8.6 Hz, 2H, Ar), 7.27 (dd, J = 3.5 and 0.5 Hz, 1H, H-3 in furyl), 7.64 (br s, 1H, H-5 in furyl), 7.67 (s, 1H, H-4 in imidazole), 7.76 (br s, 1H, H-2 in imidazole), 7.79 (s, 1H, H-5), 9.02 (s, 1H, H-2); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 50.4 (NCH_2), 55.4 (OCH_3), 110.6 (C-5), 112.5 (CH in furyl), 112.8 (CH in furyl), 114.4 (CH in Ar), 129.0 (CH in Ar), 129.2 (C-5 in imidazole), 129.6 (C-1 in Ar), 134.3 (C-2 in imidazole), 142.8 (C-4 in imidazole), 145.6 (CH in furyl), 152.2 (C-2 in furyl), 155.5 (C-4), 157.6 (C-6), 159.6 (C-2), 161.3 (C-4 in Ar); MS EI *m/z* (rel. %): 332 (63, M^+), 317 (15), 121 (100); HRMS: found 332.1269, calcd for $C_{19}H_{16}N_4O_2$ 332.1273; Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.30; H, 5.24; N, 16.90.

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References and notes

1. (a) Bakkestuen, A. K.; Gundersen, L.-L.; Langli, G.; Liu, F.; Nolsøe, J. M. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1207; (b) Gundersen, L.-L.; Nissen-Meyer, J.; Spilsberg, B. *J. Med. Chem.* **2002**, *45*, 1383; (c) Andresen, G.; Gundersen, L.-L.; Nissen-Meyer, J.; Rise, F.; Spilsberg, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 567; (d) Bakkestuen, A. K.; Gundersen, L.-L.; Utenova, B. T. *J. Med. Chem.* **2005**, *48*, 2710; (e) Brændvang, M.; Gundersen, L.-L. *Bioorg. Med. Chem.* **2005**, *13*, 6360; (f) Brændvang, M.; Gundersen, L.-L. *Bioorg. Med. Chem.* **2007**, *15*, 7144; (g) Brændvang, M.; Bakken, V.; Gundersen, L.-L. *Bioorg. Med. Chem.* **2009**, *17*, 6512.
2. See for instance: Bhowruth, V.; Dover, L. G.; Besra, G. S. *Prog. Med. Chem.* **2007**, *45*, 169.
3. (a) Brændvang, M.; Gundersen, L.-L. *Tetrahedron Lett.* **2007**, *48*, 3057; (b) Brændvang, M.; Charnock, C.; Gundersen, L.-L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3297; (c) Miranda, P. O.; Gundersen, L.-L. *Arch. Pharm. Chem. Life Sci.* **2010**, *343*, 40.
4. Strekowski, L.; Harden, M. J.; Grubb, W. B., III; Patterson, S. E.; Czarny, A.; Mokrosz, M. J.; Cegla, M. T.; Wydra, R. L. *J. Heterocycl. Chem.* **1990**, *27*, 1393.
5. (a) Raoul, S.; Bardet, M.; Cadet, J. *Chem. Res. Toxicol.* **1995**, *8*, 924; (b) Fenn, M. D.; Lister, J. H. *J. Chem. Soc., Perkin Trans. 2* **1976**, 29.
6. (a) Seley, K. L.; Zhang, L.; Hagos, A. *Org. Lett.* **2001**, *3*, 3209; (b) Seley, K. L.; Zhang, L.; Hagos, A.; Quirk, S. *J. Org. Chem.* **2002**, *67*, 3365; (c) Seley, K. L.; Quirk, S.; Salim, S.; Zhang, L.; Hagos, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1985; (d) Seley, K. L.; Salim, S.; Zhang, L.; O'Daniel, P. L. *J. Org. Chem.* **2005**, *70*, 1612; (e) Seley, K. L.; Salim, S.; Zhang, L. *Org. Lett.* **2005**, *7*, 63; (f) Quirk, S.; Seley, K. L. *Biochemistry* **2005**, *44*, 10854; (g) Polak, M.; Seley, K. L.; Plavec, J. *J. Am. Chem. Soc.* **2004**, *126*, 8159; (h) Bardon, A. B.; Wetmore, S. D. *J. Phys. Chem. A* **2005**, *109*, 262.
7. Ressner, E. C.; Fraher, P.; Edelman, M. S.; Mertes, M. P. *J. Med. Chem.* **1976**, *19*, 194.
8. (a) Gaare, K.; Repstad, T.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1993**, *47*, 57; (b) Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; McDermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Lu, Y. *Org. Process Res. Dev.* **2003**, *7*, 676.
9. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
10. Reno, M. J.; Stevens, K. L.; Waterson, A. G.; Zhang, Y. PCT Int. Appl. 2005, p 132.
11. Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125.
12. Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. *J. Med. Chem.* **1990**, *33*, 187.
13. Baggaley, K. H.; Heald, M.; Hindley, R. M.; Morgan, B.; Tee, J. L.; Green, J. *J. Med. Chem.* **1975**, *18*, 833.
14. Temple, C., Jr.; McKee, R. L.; Montgomery, J. A. *J. Org. Chem.* **1963**, *28*, 923.
15. Liu, J.; Dang, Q.; Wei, Z.; Shi, F.; Bai, X. *J. Comb. Chem.* **2006**, *8*, 410.
16. Borzilleri, R. M.; Cornelius, L. A. M.; Schmidt, R. J.; Schroeder, G. M.; Kim, Kyoung S. U.S. Pat. Appl. Publ. 2005, p 128.
17. Yanaka, M.; Nishijima, F.; Enari, H.; Ise, M. Eur. Pat. Appl. 1995, p 24.