Towards the Syntheses of *N*-H and *N*-Alkylated Derivatives of Meridianins

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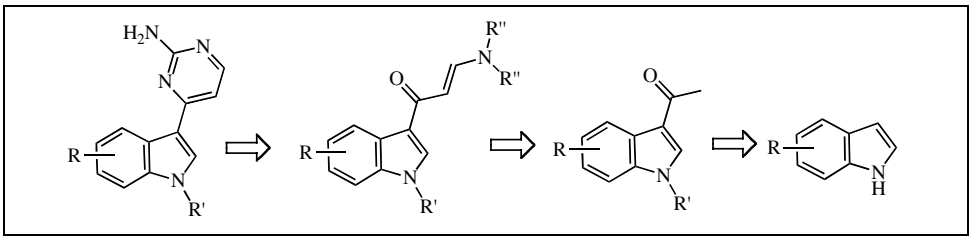

Novel *N*-H and *N*-alkylated derivatives of meridianins have been synthesized as potential antitumor agents by a two-step conversion of *N*-tosyl-3-acetylindoles or *N*-alkyl-3-acetylindoles to the corresponding enaminones using DMF-DMA, with or without added pyrrolidine. Further cyclization with guanidine gave the corresponding 2-aminopyrimidines. The structures of the compounds, thus obtained, were proved by ^{1}H and ^{13}C NMR spectroscopy, NOE experiments and X-ray analysis.

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INTRODUCTION

Marine organisms are very promising sources of bioactive molecules [1]. Among a huge diversity of structures indole alkaloids have been isolated from sponges and tunicates [2] have been considered as lead compounds for the discovery of new drugs in medicinal chemistry. Among these, 3-substituted indoles are potent inhibitors of various protein kinases which show cytotoxicity towards diverse human tumor cell lines. The substituent, at the 3-position of the indole ring, is another heterocyclic ring such as imidazole [3], dihydroimidazole [3a], maleimide [4], oxazole [5], oxadiazine [6], piperazine [7], pyrimidine, pyranone and pyrazolol [8] and 2-aminopyrimidine [9].

Meridianins A-E (Figure 1) which are representatives of this family of 3-(2-aminopyrimidine)-indoles were initially isolated [9a] from the sub Antarctic tunicate *Aplidium meridianum*.

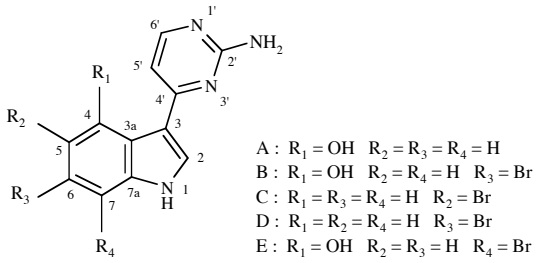
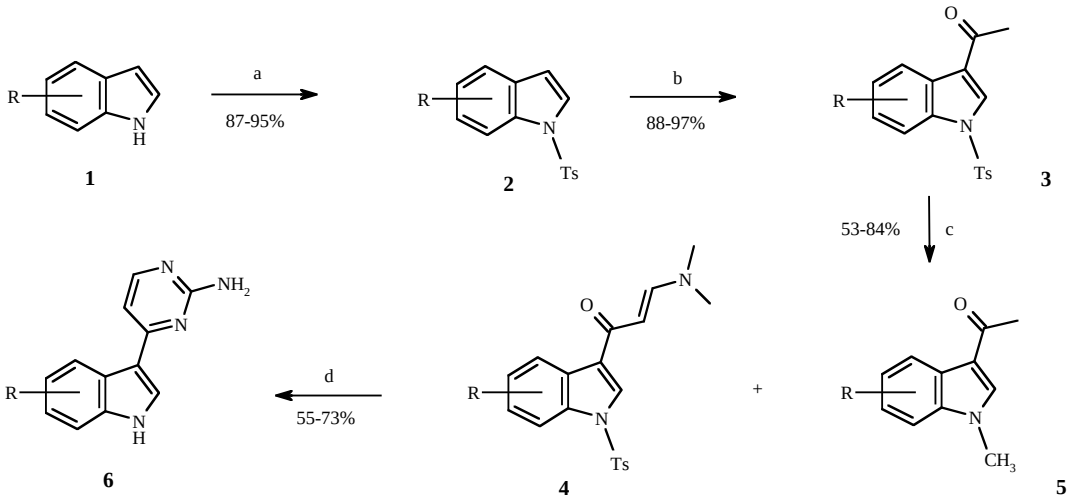


Figure 1 - Meridianins A-E.

Meridianins show cytotoxicity toward LMM3 (murine mammarian adenocarcinoma cell line) with IC_{50} values in the 10 μM scale and inhibit various protein kinases, prevent cell proliferation and induce apoptosis as shown by Gompel M. *et al.* [10] These results suggest that meridianins constitute a promising route to more potent and selective protein kinase inhibitors could be designed.

In order to conduct a detailed structure-activity relationship (SAR) study we had to develop an efficient route to analogues and derivatives of these new marine alkaloids. Three syntheses of natural meridianines have been described so far: Jiang B. *et al.* [11] used the palladium cross-coupling procedure, between the suitable 3-indolylboronic acid and 2-amino-4-chloropyrimidine, to get the meridianin D and its 6-debromoanalogue; Fresneda P. M. *et al.* [12] synthesized the meridianins A, C-E from the appropriate *N*-tosyl-3-acetylindoles in two steps: treatment with dimethylformamide dimethylacetal (DMF-DMA) [13] and further cyclization of the resulting enaminones with guanidine [14]. Müller T. J. J. developed a carbonylative alkynylation of N_1-protected-3-iodoindoles using carbon monoxide, TMS-acetylene and a Pd catalyst [15]. The TMS-ynones, thus obtained, were proved to be versatile synthetic equivalents of β-ketoaldehyde and to undergo cyclocondensation with guanidine to give the title compounds in moderate to good yields.



R = H (**a**), 4-Cl (**b**), 5-Cl (**c**), 6-Cl (**d**), 4-Br (**e**), 5-Br (**f**), 4-F (**i**), 5-F (**j**), 6-F (**k**)

Scheme 1 - Synthesis of meridianin *N*-H analogues **6a-k**. *Reagents and conditions*: a) TsCl, $Bu_4N^+HSO_4^-$, NaOH 50%, CH_2Cl_2, RT; b) Ac_2O, $AlCl_3$, CH_2Cl_2, RT; c) DMF-DMA, DMF, 110°C; d) guanidine.HCl, EtONa, EtOH, reflux.

RESULTS AND DISCUSSION

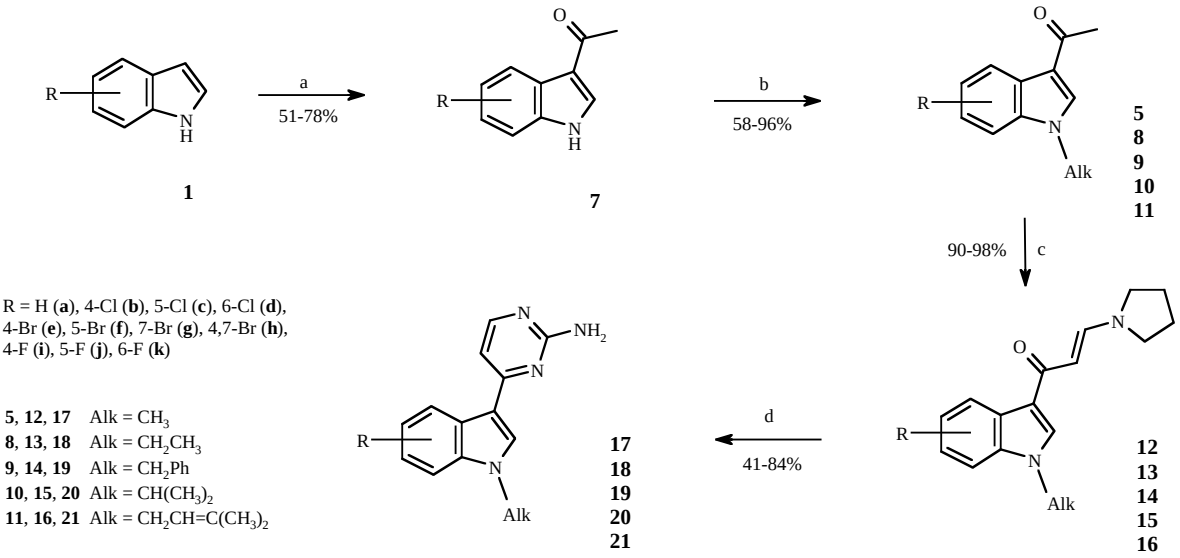
Our initial attempt to use the Jiang B. *et al.* [11] cross-coupling procedure ended in very poor yields of the expected meridianin analogues. This was probably the result of the delicate preparation of the corresponding 3-indolylboronic acid and of capricious palladium cross-coupling reaction. We then decided to investigate an alternative route, the linear synthesis previously reported by Fresneda P. M. *et al.* [12] Herein, we wish to report the preparation of *N*-H and *N*-alkylated analogues of meridianins.

Synthesis of *N*-H meridianin analogues. Following the protocol (see Scheme 1), indole precursors **1** [16,17] were tosylated using a previously reported phase transfer reaction [18] to give *N*-tosylindoles **2** in very good yields (87-95%). We found this protocol more convenient than sodium hydride anion formation and tosylation (see Fresneda 2001) [12]. Then, *N*-tosylindoles **2** were selectively acylated using aluminium chloride-acetic anhydride in dichloromethane [19] giving *N*-tosyl-3-acetylindoles **3** (88-97% yield). The third step was more delicate than expected. When compounds **3** were treated with an excess of dimethylformamide dimethylacetal in DMF at 110°C, a mixture of two compounds was obtained: enaminones **4** (53-84%) and *N*-methyl-3-acetylindoles **5** (16-47%). These *N*-methyl-3-acetyl-indoles, which were never mentioned in Fresneda's work, came from the methylation of the *N*-deprotected acetyl-indole. The reaction conditions (DMF, 110°C) probably lead to disproportionation of DMF-DMA, [14a] nucleophilic displacement of the tosyl group by methylate or dimethylamide formed *in situ*, and *N*-methylation of the indole ring by DMF-DMA. Alkylating properties of formamide acetals are well-known [20] and the DMF-DMA *N*-methylation of 3-nitroazaindole was reported [21]. In order to prevent any additional loss of material, enaminones (fully characterized by ^1H and ^{13}C NMR) were not purified at this stage and used as is in the next step. Formation of the 2-aminopyrimidine ring and *N*-tosyl deprotection were achieved (55-73%), by reacting crude enaminones **4** with guanidine in ethanol, [22] to give the *N*-H meridianin analogues **6** (overall yields 28-45%).

Synthesis of *N*-alkylated meridianin derivatives. The substitution of a heterocyclic nitrogen atom by an alkyl group may result in significant modification of the bioactivity. Indeed, in the purine series, among other compounds, olomoucine, roscovitine and purvalanol have been identified as cyclin-dependent kinase inhibitors and potential anti-tumor agents [23]. Indolic alkaloids such as keramamide K [24], flustramines A and B [25] or BG2001 [26] are substituted *N*-alkylated compounds. Since we wanted to study the influence of substituents on the *N*-indole ring we searched for a practical method to make the title compounds.

N-Alkylated indole derivatives of meridianins were prepared following the four-step sequence, as described in Scheme 2.

As mentioned in the first part and according to monographs [27], the way to get *N*-alkyl-3-acetylindoles required, at first, the acetylation and then alkylation. The best reaction conditions relied upon *N*-arylsulfonyl protection before electrophilic acylation [19] as used above, or the direct acylation of a tin complex [28].



Scheme 2 - Synthesis of meridianin *N*-alkylated derivatives **17**-**21**. *Reagents and conditions*: a) Ac_2O, $SnCl_4$, CH_2Cl_2, CH_3NO_2, RT; b) Alk = CH_3: $(CH_3)_2SO_4$, Aliquat 336, CH_2Cl_2, NaOH 50%, RT; Alk = Et: 1) KOH, EtOH 2) $BrCH_2CH_3$, acetone, RT; Alk = CH_2Ph: $BrCH_2Ph$, KOH, DMF, RT; Alk = isopropyl: 1) KOH, EtOH 2) isopropyl iodide, acetone, RT; Alk = 3-methyl-2-butenyl: 1) KOH, EtOH 2) $BrCH_2CH=CH(CH_3)_2$, acetone, RT; c) DMF-DMA, pyrrolidine, DMF, 110°C; d) guanidine.HCl, EtONa, EtOH, reflux.

We found the Ottoni *et al*. one-pot protocol [28] more practical: tin chloride ($SnCl_4$) was first added to a methylene chloride solution of the indoles, to give a yellow suspension. Then, acetic anhydride and nitromethane (co-solvent) were added to give, after work-up, 3-acetylindoles **7** (51-78%). In step b, depending upon alkylating reagents, two experimental conditions were used for the *N*-alkylation [29]: a phase transfer process and dimethylsulfate led to *N*-methylated compounds **5c**, **5e**, **5g** and **5h** (72-91%); addition of alkylhalides into mixtures of potassium hydroxide and indoles in polar solvents (ethanol, acetone or DMF) to give *N*-alkylated compounds **8** to **11** (58-96%). Compounds **5d**, **5f** and **5k** were by-products of the enaminones syntheses **4** (see part 1). In step c, treating *N*-alkyl-3-acetylindoles **5** and **7**-**11** with DMF-DMA in the usual manner led to the enaminones **12**-**16** in very poor yields. More vigorous conditions, a large excess of DMF-DMA and longer reaction times ended in 40-50% yields of the expected enaminones. Therefore, changing the *N*-protecting group from *N*-arylsulfonyl, an electrowithdrawing group, to *N*-alkyl, lowered the reactivity of the acetyl group towards DMF-DMA, a reagent that decomposed on extended heating. According to J. Berger *et al*. [30] the more stable Bredereck's reagent [*tert*-butoxy-bis(dimethylamino) methane] [31] was used successfully: three equivalents of the Bredereck's reagent, in DMF, at 110°C, resulted in the complete conversion of **5a** into (2*E*)-3-(dimethylamino)-1-(1-methyl-1*H*-indol-3-yl)-2-propen-1-one, in 4 hours. However, the price of this reagent is dissuasive enough to search for other experimental conditions. We found out a modified Leimgruber-Batcho's procedure [16] more convenient to make enaminones **12**-**16**: equimolecular amounts of DMF-DMA and pyrrolidine were heated at 80°C for one hour before adding a DMF solution of 3-acetylindoles **5** and **7**-**11**. Heating and stirring this mixture until no starting material was left (2-3 h) and gave, after workup, enaminones **12**-**16**, in very good yields (90-98%), which were used as they were in the next step, the heterocyclization [20]. Upon treatment with guanidine hydrochloride and sodium ethoxide in refluxing ethanol, crude enaminones **12**-**16** led to the *N*-alkylated meridianin derivatives **17**-**21** in 41-84% yields (overall yields 21-76%).

Structure of 4-(1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine 17a. As mentioned earlier, it has been shown that meridianins inhibit various protein kinases, prevent cell proliferation and induce apoptosis [10] but their mode of action remains unknown.

Recently potent and selective inhibitors of CDKs [32] and GSK-3 [33] have been studied. These inhibitors act through competition with ATP binding [34]. The molecular modelling approach [35] was used to understand and design new pharmacological inhibitors of CDKs and GSK-3.

In order to gain insight into the interactions between meridianin analogues and kinases and to make molecular mechanics docking-scoring calculation, the structure of compound **17a** was determined by X-ray single crystal analysis* (see Figure 2). The NMR NOESY spectrum (see Figure 3) of an acetone-d_6 solution of compounds **17a** was also recorded.

The ORTEP drawing shows that indole and pyrimidine rings are twisted with respect to each other with a dihedral

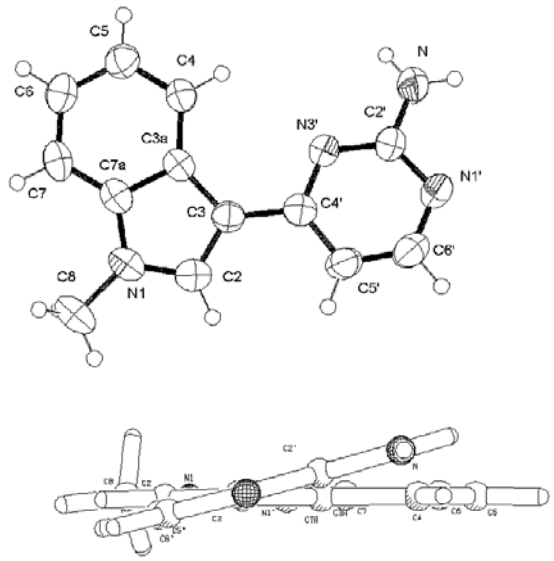


Figure 2. ORTEP drawing of the X-ray structure 4-(1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine **17a –** Crystal structure data: monoclinic $P2_{1/c}$ with $a = 10{,}214(2)$ Å; $b = 8{,}882(2)$ Å; $c = 12{,}205(2)$ Å; $\beta = 91{,}726(15)°$; $V = 1106.7(4)$ Å^3; $Z = 4$; n° of observations: 2859.

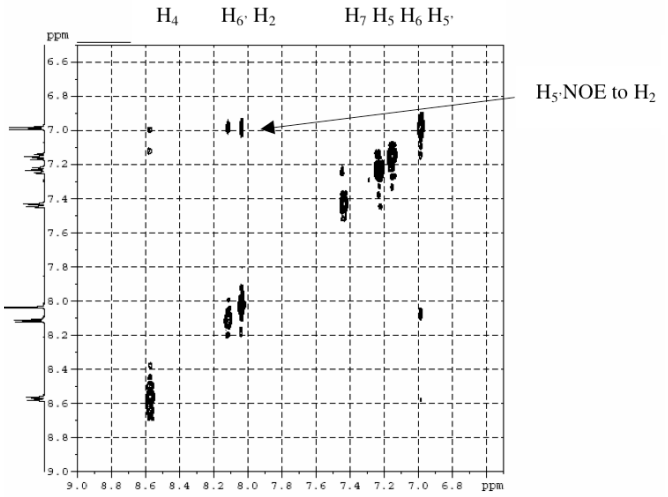


Figure 3 – NOESY spectrum of 4-(1methyl-1*H*-indole-3-yl)-2-pyrimidinamine **17a**.

angle of 14.23°. It is worth noting that N_1 of the indole ring, $N_{3'}$ and NH_2 of the pyrimidine ring are in a *trans* position with respect to each other. The structure resembles the 2-amino-4-(2-pyridyl) pyrimidine X-ray structure reported by Balavoine *et al.* [20a] and to a lesser extent to 2-amino-3-(H-tosyl-3'-indolyl)-5-bromopyrazine [36].

The NMR NOESY spectrum analysis of the acetone-d_6 solution of compound **17a** leads to the same favoured conformation at room temperature. H_2 and $H_{5'}$ are close together, as shown by the NOE correlation observed between them (see Figure 3).

These results should help with a molecular modelling approach of the interaction of meridianin analogues within the ATP pocket of kinases.

In summary, we have synthesized a series of novel meridianin *N*-H and *N*-alkylated derivatives through adaptation to previously reported approach [12]. A by-product which results from *N*-deprotection of N-tosyl-3-acetylindole and *N*-methylation of 3-acetylindole by DMF-DMA is described. *N*-alkylated derivatives were obtained using a modified Batcho et al. procedure, reacting first DMF-DMA and pyrrolidine before enaminone formation. Treatment of enaminones with guanidine leads to 2-aminopyrimidine moiety. These procedures are quite general and will allow the synthesis of more complexe analogues to conduct SAR study and design new kinase inhibitors for anticancer drug research. Studies of the structure-activity relationship are currently underway and will be reported elsewhere.

EXPERIMENTAL

All reagent grade chemicals were used as purchased (Aldrich, Lancaster). Solvents were purified, when necessary, using standard procedures. All manipulations were conducted with magnetic stirring under anhydrous argon or nitrogen.

Chromatography was carried out on silica gel: TLC on silica gel plates (Merck, art. 5554); column chromatography on silica gel 60, 70-230 mesh (Merck, art. 10832).

Elemental analyses were performed at the CNRS microanalysis service, ICNS, Gif-sur-Yvette (France).

NMR spectra were obtained on a Brucker DRX 400 spectrometer at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C) using $CDCl_3$, DMSO-d_6 or acetone-d_6 as solvent. Chemical shifts (δ) are reported in ppm units downfield from TMS (δ = 0.00), traces of $CHCl_3$, DMSO-d_5H, acetone-d_5H being used as internal standard. Coupling constants (J) are in Hz. IR spectra were recorded on a Perkin Elmer FT IR Spectrometer Spectrum One. Melting points were measured on a Köffler apparatus and are uncorrected. Crystal data were collected on an Oxford Diffraction X-calibur four circle diffractometer (KM4) using Mo radiation (λ = 0.71073 Å) and a sapphire CCD detector.

General procedure for *N*-tosylated indoles (2). To a solution of indole (8.5 mmol) and tetrabutylammonium hydrogen sulfate (162 mg, 0.85 mmol) of in CH_2Cl_2 (25 mL) was added NaOH 50% (5 mL). After stirring a few minutes, *p*-toluenesulfonylchloride (1.8 g, 12.75 mmol) was added to the reaction mixture, which was then stirred vigorously at room temperature for 3 h. The solution was poured into water and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The remaining solid was recrystallized from toluene to give **2**.

General procedure for *N*-tosylated 3-acetylindoles (3). To a suspension of aluminium chloride (13.6 g, 72.0 mmol) in dichloromethane (160 mL) was added acetic anhydride (4.7 mL, 51.0 mmol). The reaction mixture was stirred until $AlCl_3$ was completely dissolved. Then, 2 (17.0 mmol) in dichloromethane (15 mL) was added to the solution and a vigorous stirring was kept at room temperature for 3 h. The resulting mixture was

washed with brine, saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to dryness. The brown solid thus obtained was recrystallized from ether to give a white powder.

General procedure for enaminones (4). To a solution of **3** (4.0 mmol) in dry DMF (5 mL) was added a solution of dimethylformamide dimethylacetal (0.75 mL, 6.0 mmol) in the same solvent (2 mL). The resultant solution was heated at 110°C for 4 h. After cooling, the solution was poured into water and then extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness under reduce pressure. The residue can be recrystallized from ether to give yellow prisms.

General procedure for 3-acetylindoles (7). To a stirring solution of indole (10.0 mmol) in CH_2Cl_2 (20 mL) at 0°C, $SnCl_4$ (1.44 mL, 12.0 mmol) was added in a single portion. After the ice bath was removed, the mixture was stirred at room temperature for 30 min, and then acetic anhydride (2.1 mL, 10.0 mmol) was added in small portions to the suspension, followed by nitromethane (15 mL). The mixture was stirred for 3 h at room temperature. After being quenched with ice and water (30 mL), the mixture was filtered to remove inorganic precipitates, and the organic material was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated at reduce pressure to give the product as a solid which was recrystallized from chloroform to give colourless prisms.

General procedure for *N*-methylated 3-acetylindoles (5). A mixture of 7 (13.2 mmol), Aliquat 336 (85 mg, 0.2 mmol), dimethyl sulfate (1.50 mL, 15.8 mmol), CH_2Cl_2 (20 mL) and 50% NaOH aqueous solution (10 mL) was stirred vigorously for 1 hour until TLC did not detect **7**. The organic solution was separated, washed with water, dried with $MgSO_4$ and concentrated to give a solid that was recrystallized from toluene to give colourless prisms.

General procedure for *N*-ethylated 3-acetylindoles (8). To a solution of **7** (11.7 mmol) in ethanol (30 mL) at room temperature, KOH pellets were added (0.83 g, 17.6 mmol), and the mixture was stirred until total solubilization. The ethanol was completely removed *in vacuo* and replaced by acetone (30 mL). Ethyl bromide (0.87 mL, 11.7 mmol) was added and a precipitate formed instantly. The solid was filtered and the solution concentrated *in vacuo*. The residue was chromatographed on silica gel column using EtOAc/hexane 1/1 as eluent to give colourless prisms.

General procedure for *N*-benzylated 3-acetylindoles (9). A mixture of KOH pellets (0.30 g, 5.4 mmol) and 7 (3.6 mmol) in dry DMF (10 mL) was stirred at room temperature until solubilization of the KOH pellets. Benzyl bromide (0.50 mL, 3.9 mmol) was then added and the reaction mixture was stirred until TLC did not detect 3-acetylindole. The mixture was poured into water and the product extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated under reduce pressure. The residue is recrystallized from ether to give colourless prisms.

General procedure for *N*-isopropylated 3-acetylindoles (10). KOH pellets were added (0.23 g, 3.9 mmol) to a solution of 7 (3.1 mmol) in ethanol (10 mL) and the mixture was stirred, at room temperature, until total solubilization. The ethanol was completely removed *in vacuo* and replaced by acetone (10 mL). Isopropyl iodide (0.58 g, 3.4 mmol) was added and a precipitate formed instantly. The solid was filtered and the solution concentrated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc/hexane: 1/3) gave 10 as colourless prisms.

General procedure for *N*-(3-methyl-2-butenyl) 3-acetylindoles (11). KOH pellets were added (0.36 g, 6.3 mmol) to a solution of **7** (5.0 mmol) in ethanol (20 mL) and the mixture was stirred, at room temperature, until total solubilization. The ethanol was completely removed *in vacuo* and replaced by acetone (20 mL). 3-Methyl-2-butenyl bromide (0.75 g, 5.0 mmol) was added and a precipitate formed instantly. The solid was filtered and the solution concentrated *in vacuo*. Column chromatography of the residue on a silica gel (EtOAc/hexane: 1/3) gave colourless oil.

General procedure for enaminones (12-16). DMF-DMA (0.31 mL, 2.6 mmol) and pyrrolidine (0.21 mL, 2.6 mmol) were heated under stirring for 1 h at 80°C. Then, **5** (1.7 mmol) in DMF (2 mL) was added and the reaction mixture was heated at 110°C and the stirring was continued until TLC did not detect any starting material. After cooling, the solution was poured into EtOAc and washed with water. The organic layer was dried ($MgSO_4$) and concentrated at reduce pressure to give a red oil. This crude product was used with no more purification in the next step.

General procedure for analogues (6) and derivatives (17-21). To a solution of **4** (2.9 mmol) and guanidine hydrochloride (0.35 g, 3.6 mmol) in refluxing ethanol (5 mL) was added a solution of sodium (0.13 g, 5.8 mmol) in ethanol (10 mL). The resulting mixture was heated at reflux for 24 h. After cooling, the solution was poured into water and then extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The remaining residue was recrystallized from chloroform to give the title compounds.

4-(1*H*-Indol-3-yl)-2-pyrimidinamine (6a). Yellow powder (62%); mp 183-185°C; ^{1}H NMR (acetone-d_6): δ 5.91 (brs, NH_2), 7.04 (d, 1H, J=5.3, H5'), 7.10-7.22 (m, 2H, H5, H6), 7.46 (d, 1H, J=7.3, H7), 8.12 (m, 2H, H6', H2), 8.58 (d, 1H, J=7.7, H4), 10.86 (brs, NH); ^{13}C NMR (acetone-d_6): δ 111.5 (C5'), 117.2 (C7), 120.2 (C3), 126.0/127.7/128.0 (C4/C5/C6), 131.4 (C3a), 133.0 (C2), 143.0 (C7a), 162.7 (C6'), 168.7/169.5 (C2'/C4'); IR (KBr): 3408, 3329, 3173, 1660, 1568, 1520, 1452, 1413, 1246, 751, 735 cm^{-1}. *Anal.* Calcd. for $C_{12}H_{10}N_4$ (210.24): C 68.56, H 4.79. Found: C 68.45, H 4.78.

4-(4-Chloro-1*H*-indol-3-yl)-2-pyrimidinamine (6b). Yellow prisms (55%); mp 202-204°C; ^{1}H NMR (acetone-d_6): δ 5.79 (brs NH_2), 6.92 (d, 1H, J=4.9, H5'), 7.12-7.18 (m, 2H, H5, H6), 7.49 (dd, 1H, J=7.1, 2.0, H7), 7.76 (s, 1H, H2), 8.19 (d, 1H, J=4.9, H6'), 10.88 (brs, NH); ^{13}C NMR (acetone-d_6): δ 111.8 (C5'), 112.9 (C7), 117.5 (C3), 122.4/123.5 (C5/C6), 126.3/129.4 (C4/C3a), 129.5 (C2), 139.5 (C7a), 157.4 (C6'), 163.2/164.4 (C2'/C4'); IR (KBr): 3395, 3319, 3173, 2926, 1647, 1576, 1524, 1489, 1464, 1310, 1254, 1170, 825, 777, 739 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9ClN_4$ (244.68): C 58.90, H 3.71. Found: C 58.76, H 3.62.

4-(5-Chloro-1*H*-indol-3-yl)-2-pyrimidinamine (6c). Yellow prisms (67%); mp 239-241°C; ^{1}H NMR (acetone-d_6): δ 5.96 (brs, NH_2), 7.02 (d, 1H, J=5.3, H5'), 7.17 (dd, 1H, J=8.6, 2.1, H6), 7.48 (d, 1H, J=8.6, H7), 8.13 (d, 1H, J=5.3, H6'), 8.19 (s, 1H, H2), 8.67 (d, 1H, J=2.1, H4), 10.91 (brs, NH); ^{13}C NMR (DMSO-d_6): δ 105.2 (C3), 113.4/113.6 (C5'/C7), 121.7/122.1 (C4/C6), 125.2 (C2), 126.6/130.0 (C3a/C5), 135.7 (C7a), 157.3 (C6'), 162.5/163.8 (C4'/C2'); IR (KBr): 3506, 3477, 3373, 3119, 2872, 1574, 1548, 1528, 1455, 1423, 1220, 802, 672 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9ClN_4$ (244.68): C 58.90, H 3.71. Found: C 58.80, H 3.58.

4-(6-Chloro-1*H*-indol-3-yl)-2-pyrimidinamine (6d). Yellow prisms (73%); mp 192-194°C; ^{1}H NMR (acetone-d_6): δ 5.93 (brs NH_2), 7.03 (d, 1H, J=5.3, H5'), 7.12 (dd, 1H, J=8.5, 1.7, H5), 7.51 (d, 1H, J=1.7, H7), 8.14 (d, 1H, J=5.3, H6'), 8.17 (s, 1H, H2), 8.61 (d, 1H, J=8.5, H4), 10.91 (brs NH); ^{13}C NMR (acetone-d_6): δ 106.7 (C5'), 112.3 (C7), 115.6 (C3), 121.6/ 124.7 (C4/C5), 125.4/128.4/129.1 (C2/C6/C3a), 138.6 (C7a), 158.2 (C6'), 163.6/164.7 (C4'/C2'); IR (KBr): 3445, 3168, 1661, 1573, 1518, 1448, 816 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9ClN_4$ (244.68): C 58.90, H 3.71. Found: C 58.78, H 3.64.

4-(4-Bromo-1*H*-indol-3-yl)-2-pyrimidinamine (6e). Yellow prisms (67%); mp 217-219°C; ^{1}H NMR (acetone-d_6): δ 5.77 (brs NH_2), 6.86 (d, 1H, J=5.1, H5'), 7.08 (t, 1H, J=7.9, H6), 7.32 (d, 1H, J=7.6, H7), 7.53 (d, 1H, J=8.2, H5),7.70 (s, 1H, H2), 8.19 (d, 1H, J=5.1, H6'), 10.91 (brs NH). ^{13}C NMR (acetone-d_6): δ 112.3 (C7), 113.5 (C5'), 114.3 (C3), 123.7/125.1 (C5/C6), 129.1/129.2 (C4/ C3a), 138.9 (C7a), 157.3 (C6'), 163.2/164.4 (C4'/C2'); IR (KBr): 3408, 3304, 3158, 1648, 1578, 1527, 1464, 1310, 738 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9BrN_4$ (289.13): C 49.85, H 3.14. Found: C 49.70, H 3.12.

4-(5-Bromo-1*H*-indol-3-yl)-2-pyrimidinamine (6f). Yellow prisms (57%); mp 106-108°C, litt.[9a] 103-106°C; ^{1}H NMR (acetone-d_6): δ 5.61 (brs NH_2), 7.02 (d, 1H, J=5.3, H5'), 7.29 (dd, 1H, J=8.6, 2.0, H6), 7.43 (d, 1H, J=8.6, H7), 8.14 (d, 1H, J=5.3, H6'), 8.18 (m, 1H, H2), 8.83 (d, 1H, J=2.0, H4), 10.83 (brs NH); ^{13}C NMR (acetone-d_6): δ 106.4 (C5'), 114.1 (C7), 114.3 (C3), 115.0 (C5), 127.7 (C4, C6), 128.2 (C3a), 129.4 (C2), 136.8 (C7a), 158.1 (C6'), 163.4/164.7 (C4'/C2'); IR (KBr): 3476, 3371, 3120, 1576, 1527, 1453, 1419, 1332, 1291, 1212, 800, 658 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9BrN_4$ (289.13): C 49.85, H 3.14. Found: C 49.72, H 3.10.

4-(4-Fluoro-1*H*-indol-3-yl)-2-pyrimidinamine (6i). Colourless prisms (61%); mp 188-190°C; ^{1}H NMR (acetone-d_6): δ 5.73 (brs NH_2), 6.88 (dd, 1H, J=7.8, 12.4, H5), 7.15 (m, 2H, H6, H5'), 7.35 (d, 1H, J=8.1, H7), 8.10 (s, 1H, H2), 8.22 (d, 1H, J=5.3, H6'), 11.02 (brs, NH); ^{13}C NMR (acetone-d_6): δ 105.8 (C5, d, J=22), 107.6 (C3, d, J=14), 108.9 (C5), 112.8 (C3a, d, J=19), 113.8 (C7), 122.6 (C6, d, J=8), 128.8 (C2), 140.0 (C7a, d, J=11), 155.5 (C4, d, J=245), 157.9 (C6'), 160.8/163.4 (C2'/C4'); IR (KBr): 3397, 3320, 3182, 1655, 1567, 1506, 1475, 1457, 1417, 1356, 1417, 1356, 1318, 1229, 1122, 1036, 1028, 821, 781, 774, 743, 730, 707 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9FN_4$ (228.23): C 63.15, H 3.97. Found: C 63.02, H 3.86.

4-(5-Fluoro-1*H*-indol-3-yl)-2-pyrimidinamine (6j). Colourless prisms (69%); mp 160-162°C; ^{1}H NMR (acetone-d_6): δ 5.91 (brs NH_2), 6.98 (td, 1H, J=9.2, 2.6, H6), 7.01 (d, 1H, J=5.4, H5'), 7.46 (dd, 1H, J=8.8, 4.6, H7), 8.14 (d, 1H, J=5.4, H6'), 8.20 (d, 1H, J=1.8, H2), 8.36 (dd, 1H, J=2.6, 9.4, H4), 10.87 (brs, NH); ^{13}C NMR (acetone-d_6): δ 106.4 (C5'), 108.4 (C4, d, J=9), 111.2 (C6, d, J=27), 113.4 (C7, d, J=10), 130.3 (C2), 157.7 (C2'), 157.9 (C6'), 161.5 (C5, d, J=235), 164.7 (C4'); IR (KBr): 3415, 3329, 3180, 1658, 1569, 1520, 1486, 1453, 1235, 1181, 806, 793 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9FN_4$ (228.23): C 63.15, H 3.97. Found: C 62.99, H 3.88.

4-(6-Fluoro-1*H*-indol-3-yl)-2-pyrimidinamine (6k). Yellow prisms (63%); mp 230-232°C; ^{1}H NMR (acetone-d_6): δ 5.61 (brs NH_2), 6.93 (td, 1H, J=2.1, 8.9, H5), 7.02 (d, 1H, J=5.3, H5'), 7.20 (dd, 1H, J=9.8, 2.1, H7), 8.13 (m, 2H, H6', H2), 8.63 (dd, 1H, J=8.9, 5.7, H4), 10.83 (brs, NH); ^{13}C NMR (acetone-d_6): δ 98.5 (C7, d, J=26), 106.6 (C5'), 109.6 (C5, d, J=24), 115.6 (C3), 123.4 (C3a), 124.7 (C4, d, J=10), 128.2 (C2), 138.2 (C7a, d, J=8), 158.1 (C6'), 160.8 (C6, d, J=235), 163.7/164.8 (C2'/C4'); IR (KBr): 3497, 3324, 3172, 2919, 1634, 1576, 1540, 1454, 1143, 808 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9FN_4$ (228.23): C 63.15, H 3.97. Found: C 63.04, H 3.92.

4-(1-Methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17a). Yellow prisms (81%); mp 216-218°C; ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 3H, CH_3), 5.07 (brs, NH_2), 6.99 (d, 1H, J=5.4, H5'), 7.25-7.39 (m, 3H, H5, H6, H7), 7.79 (s, 1H, H2), 8.22 (d, 1H, J=5.4, H6'), 8.35 (m, 1H, H4); ^{13}C NMR (DMSO-d_6): δ 33.4 (CH_3), 107.2 (C5'), 109.9 (C7), 113.5 (C3), 121.5/121.7/ 122.8 (C4/C5/C6), 125.9 (C3a), 131.7 (C2), 137.9 (C7a), 156.3 (C6'), 162.3 (C4'), 163.1 (C2'); IR (KBr): 3454, 3288, 3153, 2934, 1625, 1575, 1534, 1480, 1456, 1418, 1371, 1235, 1218, 1105, 743 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{12}N_4$ (224.26): C 69.62, H 5.39. Found: C 69.54, H 5.31.

4-(5-Chloro-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17c). Yellow prisms (55%); mp 224-226°C; ^{1}H NMR (acetone-d_6): δ 3.92 (s, 3H, CH_3), 5.96 (brs, NH_2), 6.96 (d, 1H, J=5.2, H5'), 7.22 (d, 1H, J=8.2, H6), 7.42 (d, 1H, J=8.2, H7), 8.13 (m, 2H, H2, H6'), 8.67 (s, 1H, H4); ^{13}C NMR (DMSO-d_6): δ 35.3 (CH_3), 105.2 (C3), 111.9/112.3 (C7/C5'), 121.7/122.1 (C4/C6), 125.6/126.7 (C3a/C5), 133.7/136.1 (C7a/C2), 157.0 (C6'), 162.0/ 163.4 (C4'/C2'); IR (KBr): 3467, 3289, 3146, 1627, 1571, 1533, 1462, 1420, 1368, 1217, 1106, 799, 681 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{11}ClN_4$ (258.71): C 60.35, H 4.29. Found: C 60.25, H 4.18.

4-(6-Chloro-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17d). Yellow prisms (46%); mp 239-241°C; ^{1}H NMR (acetone-d_6): δ 3.89 (s, 3H, CH_3), 5.74 (brs, NH_2), 6.89 (d, 1H, J=5.1, H5'), 7.23 (m, 2H, H4, H7), 7.46 (dd, 1H, J=8.1, 1.0, H5), 7.68 (s, 1H, H2), 8.18 (d, 1H, J=5.1, H6'); ^{13}C NMR (acetone-d_6): δ 33.1 (CH_3), 104.2 (C3), 110.0 (C5'), 112.9 (C7), 122.5 (C4/C5), 123.0 (C6/C3a), 123.3 (C4/C5), 126.3 (C6/C3a), 133.7 (C2), 140.5 (C7a), 157.4 (C6'), 163.0/164.4 (C4'/C2'); IR (KBr): 3312, 3160, 1658, 1568, 1523, 1463, 1418, 1315, 1198, 1119, 812 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{11}ClN_4$ (258.71): C 60.35, H 4.29. Found: C 60.26, H 4.20.

4-(4-Bromo-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17e). Yellow prisms (65%); mp 250-252°C; ^{1}H NMR (DMSO-d_6): δ 3.84 (s, 3H, CH_3), 6.43 (brs, NH_2), 6.73 (d, 1H, J=5.3, H5'), 7.13 (t, 1H, J=7.8, H6), 7.33 (d, 1H, J=7.5, H5/H7), 7.57 (d, 1H, J=8.0, H5/H7), 7.95 (s, 1H, H2), 8.16 (d, 1H, J=5.1, H6'); ^{13}C NMR (DMSO-d_6): δ 33.0 (CH_3), 110.1/111.8/113.1/114.8 (C5/C7/C5'/C3), 122.9/123.9/125.0 (C4/C6/C3a), 133.2 (C7a), 138.2 (C2), 155.5 (C6'), 161.9/162.2 (C4'/C2'); IR (KBr): 3320, 3165, 1656, 1563, 1536, 1518, 1459, 1414, 1245, 1194, 1112, 774, 739 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{11}BrN_4$ (303.16): C 51.50, H 3.66. Found: C 51.37, H 3.56.

4-(5-Bromo-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17f). Yellow powder (65%); mp 214-216°C; ^{1}H NMR (acetone-d_6): δ 3.84 (s, 3H, CH_3), 5.13 (brs, NH_2), 6.89 (d, 1H, J=5.3, H5'), 7.21 (d, 1H, J=8.8, H7), 7.39 (d, 1H, J=8.8, H6), 7.73 (s, 1H, H2), 8.21 (d, 1H, J=5.3, H6'), 8.57 (s, 1H, H4); ^{13}C NMR ($CDCl_3$): δ 33.5 (CH_3), 107.1 (C4), 111.2 (C5'), 113.3 (C3), 114.9 (C6), 124.6/125.6 (C2/C7), 127.5 (C7a), 131.9 (C5), 136.5 (C3a), 157.4 (C6'), 162.4/162.9 (C2'/C4'); IR (KBr): 3457, 3285, 3144, 1629, 1572, 1534, 1462, 1420, 1372, 1219, 799, 680 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{11}BrN_4$ (303.16): C 51.50, H 3.66. Found: C 51.43, H 3.55.

4-(7-Bromo-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17g). Yellow powder (78%); mp 175-177°C; ^{1}H NMR (acetone-d_6): δ 4.17 (s, 3H, CH_3), 6.48 (brs, NH_2), 6.92 (d, 1H, J=5.4, H5'), 7.03 (t, 1H, J=7.7, H5), 7.38 (d, 1H, J=8.0, H6), 8.12 (d, 1H, J=5.4, H6'), 8.24 (s, 1H, H2), 8.70 (d, 1H, J=7.6, H4); ^{13}C NMR (acetone-d_6): δ

38.8 (CH_3), 105.4/108.8/110.7 (C7/C3/ C5'), 116.8/122.4 (C4/C5), 132.8 (C3a), 137.9/139.8 (C2/C7a), 157.8 (C6'), 161.0/162.9 (C4'/C2'); IR (KBr): 3316, 3162, 1653, 1562, 1524, 1461, 1408, 1303, 1075, 811, 738 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{11}BrN_4$ (303.16): C 51.50, H 3.66. Found: C 51.36, H 3.62.

4-(4,7-Dibromo-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17h). Yellow powder (71%); mp 218-220°C; ^1H NMR (acetone-d_6): δ 4.17 (s, 3H, CH_3), 6.50 (brs, NH_2), 6.66 (d, 1H, J=5.4, H5'), 7.21 (d, 1H, J=8.0, H5/H6), 7.32 (d, 1H, J=8.0, H5/H6), 7.73 (s, 1H, H2), 8.18 (d, 1H, J=5.4, H6'); ^{13}C NMR (acetone-d_6): δ 37.1 (CH_3), 103.2 (C3), 112.9/115.4 (C4/C7), 125.8/ 126.7/127.5 (C5/C6/C3a), 133.5/135.4 (C7a/ C2), 156.6 (C6'), 161.2/163.0 (C4'/C2'); IR (KBr): 3411, 3308, 3154, 1639, 1576, 1556, 1458, 1430, 1389, 1309, 1193, 1112, 1099, 1067, 1010, 867, 818, 797, 680 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{10}Br_2N_4$ (382.05): C 40.87, H 2.64. Found: C 40.70, H 2.58.

4-(6-Fluoro-1-methyl-1*H*-indol-3-yl)-2-pyrimidinamine (17k). Yellow prisms (44%); mp 210-213°C; ^1H NMR (acetone-d_6): δ 3.86 (s, 3H, CH_3), 5.82 (brs, NH_2), 6.95 (m, 2H, J=2.3, 8.9, H5, H5'), 7.22 (dd, 1H, J=2.3, 9.9, H7), 8.05 (s, 1H, H2), 8.13 (d, 1H, J=5.4, H6'), 8.62 (dd, 1H, J=8.9, 5.7, H4); ^{13}C NMR (acetone-d_6): δ 33.5 (CH_3), 96.9 (C7, d, J=25), 106.8 (C5'), 109.5 (C5, d, J=25), 115.0 (C3), 124.3 (C3a), 124.9 (C4, d, J=9), 132.9 (C2), 139.2 (C7a, d, J=10), 158.1 (C6'), 160.8 (C6, d, J=235), 163.5/164.9 (C2'/C4'); IR (KBr): 3454, 3266, 3133, 1628, 1580, 1533, 1454, 1418, 1364, 1332, 1242, 1221, 1173, 1093, 928, 836, 819, 798, 678 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{11}FN_4$ (242.25): C 64.45, H 4.58. Found: C 64.32, H 4.47.

4-(1-Ethyl-1*H*-indol-3-yl)-2-pyrimidinamine (18a). Yellow prisms (65%); mp 142-144°C; ^1H NMR (DMSO-d_6): δ 1.40 (t, 3H, J=7.3, CH_3), 4.24 (d, 2H, J=7.3, CH_2), 6.42 (brs, NH_2), 6.95 (d, 1H, J=5.3, H5'), 7.14 (t, 1H, H5/H6), 7.21 (t, 1H, H5/H6), 7.52 (d, 1H, J=8.0, H7), 8.10 (d, 1H, J=5.3, H6'), 8.23 (s, 1H, H2), 8.58 (d, 1H, J=8.0, H4); ^{13}C NMR (DMSO-d_6): δ 15.3 (CH_3), 40.8 (CH_2), 105.2 (C3), 110.2 (C5'), 112.9 (C7), 120.5/122.0 (C4/C5/C6), 122.7 (C3a), 125.9 (C4/C5/C6), 130.6 (C7a), 136.5 (C2), 157.0 (C6'), 162.3/163.5 (C4'/C2'); IR (KBr): 3304, 3168, 2976, 1663, 1571, 1562, 1521, 1462, 1394, 1216, 811, 749 cm^{-1}. *Anal.* Calcd. for $C_{14}H_{14}N_4$ (238.29): C 70.57, H 5.92. Found: C 70.58, H 5.90.

4-(5-Chloro-1-ethyl-1*H*-indol-3-yl)-2-pyrimidinamine (18c). Yellow prisms (84%); mp 155-157°C; ^1H NMR (DMSO-d_6): δ 1.40 (t, 3H, J=7.3, CH_3), 4.24 (q, 2H, J=7.3, CH_2), 6.50 (brs, NH_2), 6.94 (d, 1H, J=5.3, H5'), 7.21 (dd, 1H, J=8.7, 2.1, H6), 7.57 (d, 1H, J=7.9, H7), 8.10 (d, 1H, J=5.3, H6'), 8.33 (s, 1H, H2), 8.63 (d, 1H, J=2.1, H4); ^{13}C NMR (DMSO-d_6): δ 15.3 (CH_3), 40.9 (CH_2), 109.7/111.5/114.7 (C3/C7/C5'), 121.5/ 122.4/122.6/124.8 (C5/C6/C4/C3a), 131.5/137.5 (C2/C7a), 156.4 (C6'), 161.6/ 163.1 (C4'/C2'); IR (KBr): 3452, 3296, 3155, 2973, 1626, 1575, 1533, 1458, 1430, 1396, 1335, 1210, 1145, 792, 680 cm^{-1}. *Anal.* Calcd. for $C_{14}H_{13}ClN_4$ (272.73): C 61.65, H 4.80. Found: C 61.63, H 4.79.

4-(7-Bromo-1-ethyl-1*H*-indol-3-yl)-2-pyrimidinamine (18g). Yellow prisms (67%); mp 165-167°C; ^1H NMR (DMSO-d_6): δ 1.42 (t, 3H, J=7.1, CH_3), 4.62 (q, 2H, J=7.1, CH_2), 6.49 (brs, NH_2), 6.95 (d, 1H, J=5.4, H5'), 7.05 (t, 1H, J=7.8, H5), 7.42 (d, 1H, J=7.7, H6), 8.13 (d, 1H, J=5.4, H6'), 8.31 (s, 1H, H2), 8.73 (d, 1H, J=7.9, H4); ^{13}C NMR (DMSO-d_6): δ 15.4 (CH_3), 40.9 (CH_2), 102.9 (C5'), 105.5 (C3), 113.0 (C7), 122.4/122.8/127.3 (C4, C5, C6), 129.4/132.5 (C2, C3a), 134.1 (C7a), 157.4 (C6'), 161.5/163.5 (C2', C4'); IR (KBr): 3328, 3193, 3126, 2974, 2922, 1651, 1573, 1554, 1534, 1481, 1469, 1450, 1413, 1385, 1327, 1220, 1204, 1110, 824, 816, 804, 786, 681,581 cm^{-1}. *Anal.* Calcd. for $C_{14}H_{13}BrN_4$ (317.18): C 53.01, H 4.13. Found: C 52.89, H 4.09.

4-(4,7-Dibromo-1-ethyl-1*H*-indol-3-yl)-2-pyrimidinamine (18h). Yellow prisms (76%); mp 173-175°C; ^1H NMR (DMSO-d_6): δ 1.39 (t, 3H, J=7.0, CH_3), 4.63 (q, 2H, J=7.0, CH_2), 6.51 (brs, NH_2), 6.67 (d, 1H, J=5.3, H5'), 7.21 (d, 1H, J=8.2, H5/H6), 7.33 (d, 1H, J=8.2, H5/H6), 7.80 (s, 1H, H2), 8.18 (d, 1H, J=5.3, H6');^{13}C NMR (DMSO-d_6): δ 15.3 (CH_3), 40.8 (CH_2), 102.7 (C5'), 105.6/106.7/108.2 (C3, C4, C7), 113.0/116.0 (C5, C6), 127.0/127.9 (C2, C3a), 132.3 (C7a), 156.7 (C6'), 161.2/163.0 (C2', C4'); IR (KBr): 3306, 3169, 2980, 1650, 1570, 1524, 1471, 1390, 1323, 1231, 1216, 1186, 1115, 1076, 1016, 869, 817, 791, 668 cm^{-1}. *Anal.* Calcd. for $C_{14}H_{12}Br_2N_4$ (396.08): C 42.45, H 3.05. Found: C 42.34, H 3.01.

4-(1-Ethyl-5-fluoro-1*H*-indol-3-yl)-2-pyrimidinamine (18j). Yellow prisms (51%); mp 165-167°C; ^1H NMR (DMSO-d_6): δ 1.40 (t, 3H, J=7.3, CH_3), 4.24 (d, 2H, J=7.3, CH_2), 6.42 (brs, NH_2), 6.94 (d, 1H, J=5.3, H5'), 7.05 (td, 1H, J=9.1, 2.5, H6), 7.55 (dd, 1H, J=8.9, 4.6, H7), 8.09 (d, 1H, J=5.3, H6'), 8.32 (s, 1H, H2), 8.38 (dd, 1H, J=10.6, 2.5, H4); ^{13}C NMR (DMSO-d_6): δ 15.2 (CH_3), 41.0 (CH_2), 104.8 (C5'), 107.6 (C4/C6, d, J=25), 110.0 (C4/C6, d, J=26), 111.3 (C3a, d, J=10), 112.7 (C3), 126.2 (C7, d, J=11), 132.1 (C7a), 133.2 (C2), 157.0 (C6'), 158.2 (C5', d, J=233), 162.0/163.4 (C2'/C4'); IR (KBr): 3470, 3285, 3143, 2972, 2935, 1628, 1573, 1534, 1481, 1456, 1397, 1337, 1213, 1198, 1110, 804, 695 cm^{-1}. *Anal.* Calcd. for $C_{14}H_{13}FN_4$ (256.28): C 65.61, H 5.11. Found: C 65.56, H 5.09.

4-(1-Benzyl-1*H*-indol-3-yl)-2-pyrimidinamine (19a). Colourless prisms (56%); mp 162-164°C; ^1H NMR (acetone-d_6): δ 5.52 (s, 2H, CH_2), 5.85 (brs, NH_2), 7.02 (d, 1H, J=5.3, H5'), 7.16 (m, 2H, H5, H6), 7.24-7.34 (m, 5H, Ph), 7.45 (d, 1H, J=7.2, H7), 8.13 (d, 1H, J=5.3, H6'), 8.22 (s, 1H, H2), 8.59 (dd, 1H, J=1.8, 7.0, H4); ^{13}C NMR (DMSO-d_6): δ 50.0 (CH_2), 105.4 (C3), 111.0 (C5'), 113.6 (C7), 120.9/122.3/122.8 (C4/C5/C6), 126.2 (C3a), 127.4 (2C, Ph), 127.9 (C, Ph), 129.0 (2C, Ph), 131.8 (C2), 136.9/137.8 (C, Ph/C7a), 157.1 (C6'), 161.9/163.7 (C4'/C2'); IR (KBr): 3454, 1624, 1573, 1532, 1455, 1388, 1182, 743 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{16}N_4$ (300.36): C 75.98, H 5.37. Found: C 75.87, H 5.35.

4-(1-Benzyl-6-chloro-1*H*-indol-3-yl)-2-pyrimidinamine (19d). Yellow prisms (63%); mp 166-168°C; ^1H NMR (acetone-d_6): δ 5.49 (s, 2H, CH_2), 6.49 (brs, NH_2), 6.96 (d, 1H, J=5.3, H5'), 7.13 (dd, 1H, J=1.9, 8.6 Hz, H5), 7.22-7.35 (m, 5H, Ph), 7.67 (d, 1H, J=1.9, H7), 8.12 (d, 1H, J=5.3, H6'), 8.42 (s, 1H, H2), 8.60 (d, 1H, J=8.6, H4); ^{13}C NMR (acetone-d_6): δ 49.5 (CH_2), 105.3 (C3), 110.6 (C5'), 113.6 (C7), 120.9 (C4/C5), 124.1 (C6), 124.7 (C4/C5), 127.2 (2C, Ph), 127.3 (C3a), 127.7 (C, Ph), 128.7 (2C, Ph), 132.4 (C7a), 137.2/137.3 (C2/C, Ph), 157.4 (C6'), 161.7/163.5 (C2'/C4'); IR (KBr): 3454, 3283, 3141, 2926, 1625, 1551, 1573, 1529, 1455, 1376, 1176, 816, 699 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{15}ClN_4$ (334.80): C 68.16, H 4.52. Found: C 68.22, H 4.51.

4-(1-Benzyl-5-bromo-1*H*-indol-3-yl)-2-pyrimidinamine (19f). Yellow prisms (71%); mp 208-210°C; ^1H NMR (acetone-d_6): δ 5.55 (s, 2H, CH_2), 6.02 (brs, NH_2), 7.00 (d, 1H, J=5.3, H5'), 7.27-7.34 (m, 6H, H6, Ph), 7.42 (d, 1H, J=8.7, H7), 8.14 (d, 1H, J=5.3, H6'), 8.38 (s, 1H, H2), 8.85 (d, 1H, J=2.0, H4); ^{13}C NMR (DMSO-d_6): δ 53.1 (CH_2), 108.7 (C3), 116.3/116.4/117.3 (C4/C7/C5'), 128.2/128.3 (C5/C6), 130.6 (2C, Ph), 131.0/131.1 (C, Ph/C3a), 132.2 (2C, Ph), 136.3/139.0/140.7 (C2/C7a/C, Ph), 160.8 (C6'), 165.2/167.0 (C4'/C2'); IR (KBr): 3480, 3290, 3151, 3000, 2929, 1627, 1578, 1536, 1463, 1433, 1392, 1190, 1181,

790, 742, 703 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{15}BrN_4$ (379.25): C 60.17, H 3.99. Found: C 60.06, H 3.88.

4-(1-Benzyl-6-fluoro-1*H*-indol-3-yl)-2-pyrimidinamine (19k). Yellow prisms (75%); mp 167-169°C; ^1H NMR (DMSO-d_6): δ 5.45 (s, 2H, CH_2), 6.49 (brs, NH_2), 6.95 (td, 1H, J=2.2, 8.8, 10.2, H5), 6.99 (d, 1H, J=5.3, H5'), 7.23 (dd, 1H, J=2.2, 10.2, H7), 7.29-7.35 (m, 5H, Ph), 8.13 (d, 1H, J=5.3, H6'), 8.23 (s, 1H, H2), 8.64 (dd, 1H, J=8.8, 5.8, H4); ^{13}C NMR (DMSO-d_6): δ 49.5 (CH_2), 97.1 (C7, d, J=26), 105.2 (C3), 109.0 (C5, d, J=24), 113.6 (C5'), 122.7 (C3a), 124.0 (C4, d, J=10), 127.3 (2C, Ph), 127.7 (C, Ph), 128.7 (2C, Ph), 132.1 (C, Ph), 137.0 (C7a, d, J=12), 137.3 (C2), 157.2 (C6'), 159.1 (C6, d, J=235), 161.9/163.5 (C4'/C2'); IR (KBr): 3461, 3280, 3141, 2924, 1619, 1575, 1554, 1533, 1456, 1438, 1379, 1179, 930, 818, 712 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{15}FN_4$ (318.35): C 71.68, H 4.75. Found: C 71.57, H 4.75.

4-(1-Isopropyl-1*H*-indol-3-yl)-2-pyrimidinamine (20a). Yellow prisms (41%); mp 189-191°C; ^1H NMR (DMSO-d_6): δ 1.49 (d, 6H, J=6.5, CH_3), 4.80 (m, 1H, J=6.5, CH), 6.42 (brs, NH_2), 7.03 (d, 1H, J=5.2, H5'), 7.14 (m, 1H, H5/H6), 7.20 (m, 1H, H5/H6), 7.56 (d, 1H, J=8.0, H7), 8.09 (d, 1H, J=5.2, H6'), 8.32 (s, 1H, H2), 8.58 (d, 1H, J=8.0, H4); ^{13}C NMR (DMSO-d_6): δ 22.4 (2 CH_3), 47.0 (CH), 105.5 (C3), 110.4 (C5'), 113.1 (C7), 120.7/122.1/122.7 (C4/C5/C6), 125.8/128.0 (C2/C3a), 136.5 (C7a), 156.1 (C6'), 162.8/163.0 (C4'/C2'); IR (KBr): 3313, 3168, 2980, 1645, 1562, 1519, 1460, 1407, 1365, 1306, 1213, 1177, 809, 743 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{16}N_4$ (252.32): C 71.40, H 6.39. Found: C 71.33, H 6.31.

4-(5-Chloro-1-isopropyl-1*H*-indol-3-yl)-2-pyrimidinamine (20c). Yellow prisms (42%); mp 181-183°C; ^1H NMR (DMSO-d_6): δ 1.49 (d, 6H, J=6.6, CH_3), 4.81 (m, 1H, J=6.6, CH), 6.51 (brs, NH_2), 7.04 (d, 1H, J=5.4, H5'), 7.21 (dd, 1H, J=8.8, 2.0, H6), 7.61 (d, 1H, J=8.8, H7), 8.10 (d, 1H, J=5.4, H6'), 8.43 (s, 1H, H2), 8.65 (d, 1H, J=2.0, H4); ^{13}C NMR (DMSO-d_6): δ 22.3 (2 CH_3), 48.7 (CH), 105.1 (C5'), 112.7 (C3), 115.9 (C7), 122.1/123.3 (C4/C6), 126.7 (C5), 127.3 (C2), 134.9/135.5 (C7a/C3a), 143.0 (C2'), 155.9 (C6'), 168.3 (C4'); IR (KBr): 3320, 3167, 2974, 2931, 1656, 1563, 1517, 1463, 1209, 798, 789 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{15}ClN_4$ (286.76): C 62.83, H 5.27. Found: C 62.71, H 5.18.

4-(5-bromo-1-isopropyl-1*H*-indol-3-yl)-2-pyrimidinamine (20f). Yellow prisms (41%); mp 193-195°C; ^1H NMR (DMSO-d_6): δ 1.48 (d, 6H, J=6.7, CH_3), 4.79 (m, 1H, J=6.7, CH), 6.50 (brs, NH_2), 7.03 (d, 1H, J=5.3, H5'), 7.31 (d, 1H, J=8.7, H6), 7.56 (d, 1H, J=8.7, H7), 8.10 (d, 1H, J=5.3, H6'), 8.41 (s, 1H, H2), 8.78 (s, 1H, H4); ^{13}C NMR (DMSO-d_6): δ 22.5 (2 CH_3), 47.5 (CH), 105.3 (C3), 112.5/112.6/113.8 (C5'/C7/C5), 124.8/127.4 (C6/C4/C3a), 129.6 (C7a), 135.3 (C2), 155.7 (C2'), 162.7 (C4'/C6'); IR (KBr): 3308, 3163, 2974, 2929, 1655, 1570, 1516, 1462, 1410, 1367, 1287, 1208, 1178, 798, 789 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{15}BrN_4$ (331.21): C 54.39, H 4.56. Found: C 54.41, H 4.52.

4-(5-Fluoro-1-isopropyl-1*H*-indol-3-yl)-2-pyrimidinamine (20j). Yellow prisms (45%); mp 154-156°C; ^1H NMR (acetone-d_6): δ 1.58 (d, 6H, J=6.7, CH_3), 4.84 (m, 1H, J=6.7, CH), 5.94 (brs, NH_2), 7.01 (m, 2H, H5', H7), 7.54 (dd, 1H, J=9.0, 4.4, H6), 8.10 (d, 1H, J=5.3, H6'), 8.31 (s, 1H, H2), 8.38 (dd, 1H, J=10.7, 2.6, H4); ^{13}C NMR (DMSO-d_6): δ 22.4 (2 CH_3), 47.5 (CH), 105.0 (C5'), 107.8 (C4/C6, d, J=25), 110.2 (C4/C6, d, J=26), 111.5 (C7, d, J=10), 112.8 (C3), 126.1 (C3a, d, J=9), 130.0 (C2), 133.2 (C7a), 155.0 (C6'), 158.1 (C5, d, J=233), 162.3/162.9 (C2'/C4'); IR (KBr): 3323, 3172, 2972, 1662, 1621, 1563, 1518, 1484, 1463, 1210, 1194, 799 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{15}FN_4$ (270.30): C 66.65, H 5.59. Found: C 66.54, H 5.57.

4-[1-(3-Methyl-2-butenyl)-1*H*-indol-3-yl]-2-pyrimidinamine (21a). Yellow prisms (50%); mp 168-170°C; ^1H NMR (DMSO-d_6): δ 1.76 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 4.85 (d, 2H, J=6.9, CH_2), 5.42 (t, 1H, J=6.9, CH), 5.85 (brs, NH_2), 6.99 (d, 1H, J=5.3, H5'), 7.17 (m, 1H, H5/H6), 7.19 (m, 1H, H5/H6), 7.44 (d, 1H, J=8.0, H7), 8.06 (s, 1H, H2), 8.11 (d, 1H, J=5.3, H6'), 8.57 (d, 1H, J=7.9, H4); ^{13}C NMR (DMSO-d_6): δ 18.0 (CH_3), 25.4 (CH_3), 44.1 (CH_2), 105.3 (C3), 110.5/112.9 (C5'/C7), 119.8/120.6/122.1/122.6 (C4/C5/C6/CH), 126.0 (C2), 130.9 (C3a), 136.3/136.8 (C7a/C), 157.1/162.3/163.5 (C2'/ C4'/C6'); IR (KBr): 3464, 3276, 3135, 3052, 2959, 2936, 2911, 1625, 1613, 1572, 1533, 1473, 1457, 1440, 1392, 1379, 1326, 1211, 1170, 815, 747, 736 cm^{-1}. *Anal.* Calcd. for $C_{17}H_{18}N_4$ (278.35): C 73.35, H 6.52. Found: C 73.21, H 6.41.

4-[5-Bromo-1-(3-methyl-2-butenyl)-1*H*-indol-3-yl]-2-pyrimidinamine (21j). Yellow prisms (51%); mp 166-168°C; ^1H NMR (acetone-d_6): δ 1.76 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 4.86 (d, 2H, J=6.9, CH_2), 5.43 (t, 1H, J=6.9, CH), 5.87 (brs, NH_2), 6.97 (d, 1H, J=5.4, H5'), 7.29 (dd, 1H, J=8.7, 1.9, H6), 7.36 (d, 1H, J=8.7, H7), 8.10 (s, 1H, H2), 8.11 (d, 1H, J=5.4, H6'), 8.81 (d, 1H, J=1.9, H4); ^{13}C NMR (DMSO-d_6): δ 18.1 (CH_3), 25.5 (CH_3), 44.3 (CH_2), 105.1 (C3), 112.6/114.35 (C5'/C7), 120.8/122.5/ 122.9/124.8 (C4/C5/C6/CH), 126.5 (C2), 133.1 (C3a), 135.9/ 136.4 (C7a/C), 155.7 (C6'), 162.5/162.7 (C2'/C4'); IR (KBr): 3484, 3294, 3146, 2943, 2851, 1634, 1577, 1537, 1487, 1466, 1423, 1401, 1385, 1359, 1334, 1212, 893, 809, 786 cm^{-1}. *Anal.* Calcd. for $C_{17}H_{17}BrN_4$ (357.25): C 57.15, H 4.80. Found: C 57.03, H 4.79.

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Supporting information available: experimental details and analytical data for intermediates **2**-**5** and **7**-**16** are available, free of charge, via e-mail at bernard.corbel@univ-brest.fr.

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