

# On the preparation of 1-aryl-2-heteroaryl- and 2-aryl-1-heteroaryl-pyrroles as useful building blocks for biologically interesting heterocycle

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**Dedicated to Professor Rudolph A. Abramovitch on the occasion of his 70<sup>th</sup> birthday**  
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## Abstract

A series of 1-aryl-2-pyridinyl/pyrimidinyl-pyrroles and 2-aryl-1-pyridinyl/pyrimidinyl-pyrroles were prepared by using 4+1 ring synthesis. The yields were strongly dependant on the reactivity of the starting amines. Synthetic procedures involving a 3+2 ring formation were discussed. Few 1-heteroaryl derivatives showed weak activity when tested as COX-1 and COX-2 inhibitors.

**Keywords:** 4+1 Pyrrole ring synthesis, 1-aryl-2-pyridinyl/pyrimidinyl-pyrroles, 2-aryl-1-pyridinyl /pyrimidinyl-pyrroles, anti-inflammatory activity

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## Introduction

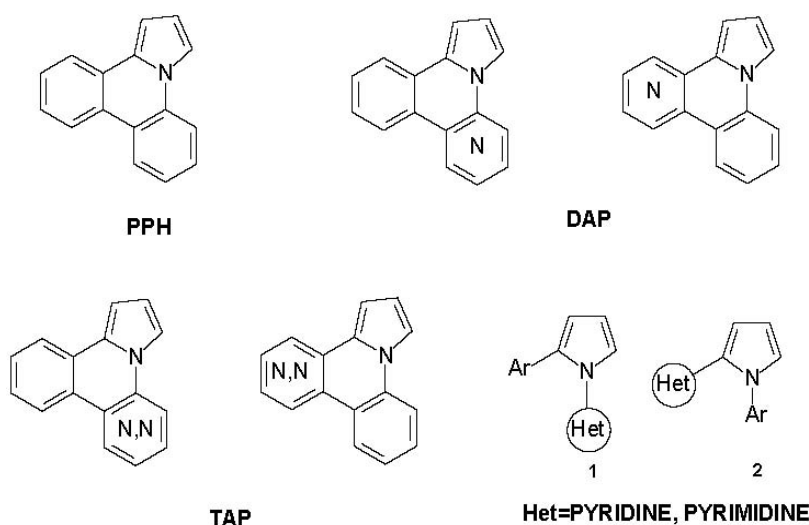
As our aim was devoted to study polycyclic nitrogen heterocycles we have been exploring synthetic pathways leading to the pyrrolo[1,2-*f*]phenanthridine ring system (**PPH**) to prepare derivatives with antineoplastic/antiviral activity.<sup>1-4</sup> In preliminary biological screening tests, several PPHs have shown antiproliferative activity against cell lines derived from human tumors, sensible (FLC) and multidrug resistant (DRTL) with IC<sub>50</sub> in the range 5-50 μM.<sup>5</sup> More recently they were demonstrated to possess a weak anti-HIV activity, joined to a capability of stimulating the multiplication of MT-4 cells at low concentrations.<sup>6</sup>

To further explore the biological features of related classes of planar molecules we decided to modify their carbon skeleton introducing the isosteric nitrogen. In particular the introduction of one or two nitrogens in the phenanthridine moiety could lead to several new heterocyclic systems annelated with the pyrrole ring, such as **DiAzaPhenanthrenes (DAP)** or **TriAza-Phenanthrenes (TAP)**. To extend previously successful synthetic approaches for the preparation of PPHs we

needed the access to large quantities of pyrrole derivatives of type **1** and **2**, suitably substituted in the aryl/heteroaryl moiety.

These compounds should be useful starting materials for the synthesis of DAP and TAP which incorporate the pyrrole moiety, to be screened for their biological features. Moreover derivatives of type **1** and **2** themselves may be of interest in medicinal chemistry as they are related to 1,2-diaryl substituted pyrroles and pyrazoles that recently have been shown to possess interesting antiviral<sup>7</sup> and anti-inflammatory<sup>8,9</sup> activities.

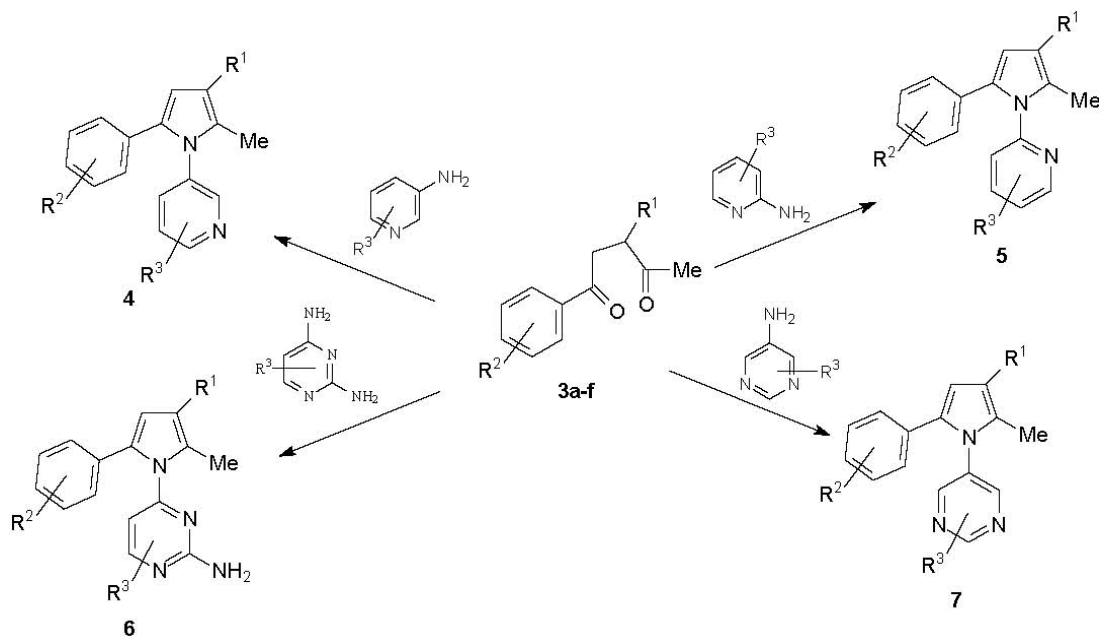
However despite the apparent simplicity of the preparation of pyrroles of this type, some problems arise for their synthesis on a preparative scale as testified by the large number of papers dealing with pyrrole preparation.<sup>10,11</sup> Moreover a literature survey indicated that whereas few 2-pyridinyl-pyrroles have been reported, 2-pyrimidinyl-pyrroles of type **2** were unknown.



## Results and Discussion

In this paper we report our findings on the preparation of the title compounds exploring and comparing the synthetic routes leading to these compounds on a preparative scale on the basis of considerations about (a) low cost and ready availability of starting materials, (b) easy introduction of appropriate substituent in suitable positions of the rings, (c) reasonable yields. The experimental problems related to the synthesis of 1-heteroaryl or 2-heteroaryl-pyrroles are different and will be treated separately.

The preparation of 2-aryl-1-heteroarylpyrroles can be accomplished by a Paal-Knorr synthesis from 1,4-diketones of type **3** and commercially available aminopyridines / aminopyrimidines (Scheme 1).



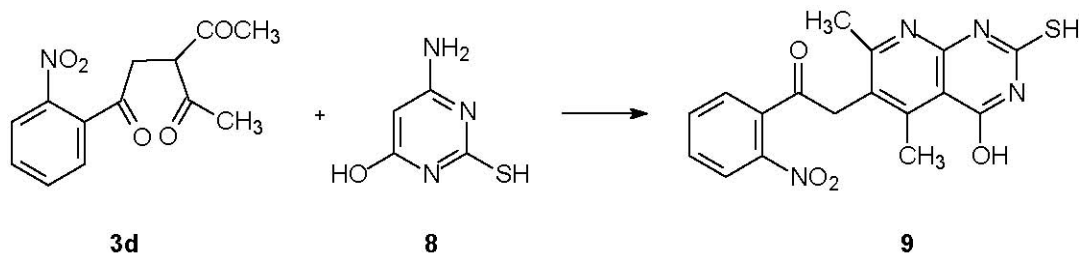
**Scheme 1:** 3a, R<sup>1</sup>=COOEt, R<sup>2</sup>=3-NO<sub>2</sub>; 3b, R<sup>1</sup>=COOEt, R<sup>2</sup>=H; 3c, R<sup>1</sup>=Ac, R<sup>2</sup>=H; 3d, R<sup>1</sup>=Ac, R<sup>2</sup>=2-NO<sub>2</sub>; 3e, R<sup>1</sup>=Ac, R<sup>2</sup>=3-OMe; 3f, R<sup>1</sup>=H, R<sup>2</sup>=3-OMe.

In the case of derivatives of type **4** and **5**, the yields were strongly dependent on the nucleophilicity of the starting amine. In fact, for example, pyrroles **4g** and **4h** were prepared in good yields whereas **5j** and **5l** were obtained only in 40-20% yields [together with the corresponding N-acetylated derivatives **5k** and **5m** (yields 20% - traces) when the reaction was carried out in acetic acid]. By using diketone **3a** and 2-aminopyridine a furan derivative, arising from intramolecular cyclization of the starting diketone, was always isolated and no traces of 1-(pyridin-2-yl)pyrrole of type **5i** could be detected.

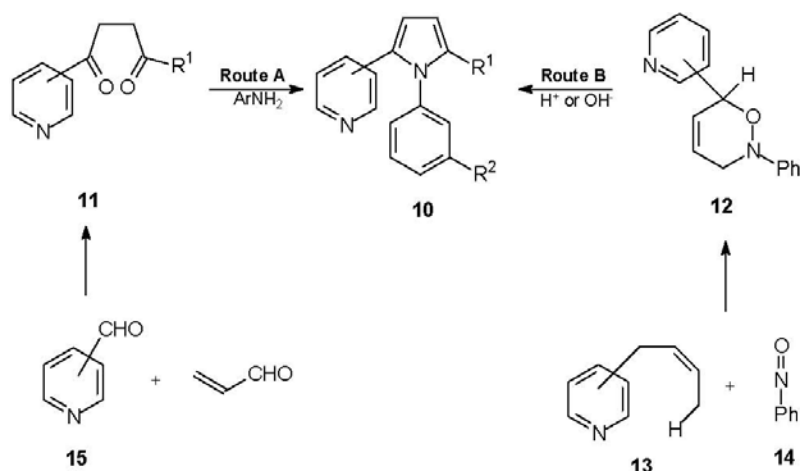
In the case of aminopyrimidines it was possible to obtain pyrrole derivatives when the reacting amino group was in the 5 position of the starting pyrimidine (compounds of type **7**) in yields ranging from 54 to 95%. When the cyclization reactions were carried out on the less reactive 4-amino derivatives only compound **6n** was isolated in 20% yield, whereas compound **6o** could not be obtained from the corresponding reactants. From the reaction of 1,4-diketone **3d** and 4-amino-6-hydroxy-2-mercaptopyrimidine **8** unexpectedly a pyrido[2,3-d]pyrimidine derivative **9** was formed (Scheme 2). In this case the diketone **3d**, being also a 1,3-dicarbonyl compound, preferentially reacted on the unsubstituted 5 position of the pyrimidine ring giving rise to a more stable bicyclic system.

**Table 1.** 1-Heteroarylpyrrole derivatives and yields (%)

Compounds	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yields
<b>4g</b>	COOEt	3-NO <sub>2</sub>	H	90
<b>4h</b>	COOEt	3-NO <sub>2</sub>	2,6-diOMe	60
<b>5i</b>	COOEt	3-NO <sub>2</sub>	H	0
<b>5j</b>	COOEt	H	6-NH <sub>2</sub>	40
<b>5k</b>	COOEt	H	6-NHAc	20
<b>5l</b>	Ac	H	6-NH <sub>2</sub>	20
<b>5m</b>	Ac	H	6-NHAc	traces
<b>6n</b>	Ac	H	H	20
<b>6o</b>	Ac	2-NO <sub>2</sub>	6-OH	0
<b>7p</b>	COOEt	3-NO <sub>2</sub>	2,4-diOH	90
<b>7q</b>	Ac	2-NO <sub>2</sub>	2,4-diOH	54
<b>7r</b>	Ac	3-OMe	4-NH <sub>2</sub> -6-OH	95
<b>7s</b>	H	3-OMe	4-NH <sub>2</sub> -6-OH	70

**Scheme 2**

In the case of the synthesis of 1-aryl-2-heteroarylpyrroles the main problem is related to the accessibility of suitable 1,4-diketones or their synthetic equivalents. In fact for example the preparation of 2-pyridinyl-1-phenylpyrroles of type **10** was achieved so far according to the procedure outlined in the Scheme 3. Route A<sup>12</sup> involved the condensation of pyridinyl derivatives of type **11** and aniline whereas in the case of route B<sup>13</sup> the key intermediate was the oxazine **12**, accessible in turn from 1,3-butadienes **13** and nitrosobenzene **14**, which afforded the pyrrole **10** upon treatment with bases or acids. The yields obtained are listed in Table 2.



Scheme 3

Table 2. 2-Heteroarylpyrrole derivatives **10** and yields (%)

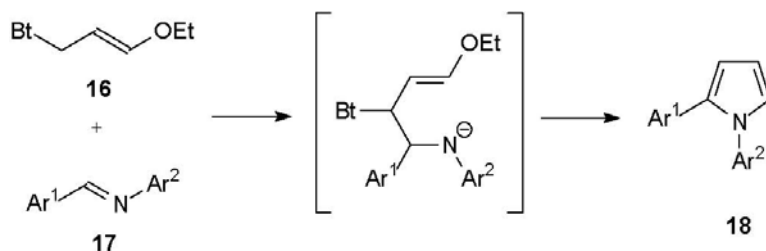
Compounds		R <sup>1</sup>	R <sup>2</sup>	Route	Yields
<b>a</b>	pyridin-2-yl	Me	H	A	nr <sup>a</sup>
				B	86 <sup>b</sup>
<b>b</b>	pyridin-2-yl	Ph	H	A	nr <sup>a</sup>
<b>c</b>	pyridin-3-yl	Me	H	A	nr <sup>a</sup>
<b>d</b>	pyridin-3-yl	Ph	H	A	nr <sup>a</sup>
<b>e</b>	pyridin-4-yl	Me	H	A	nr <sup>a</sup>
<b>f</b>	pyridin-2-yl	H	H	B	93 <sup>b</sup>
<b>g</b>	pyridin-3-yl	H	H	B	96 <sup>b</sup>
<b>h</b>	pyridin-4-yl	H	H	B	98 <sup>b</sup>
<b>i</b>	pyridin-2-yl	H	NO <sub>2</sub>	A	40
<b>j</b>	pyridin-3-yl	H	NO <sub>2</sub>	A	40

nr = not reported; <sup>a</sup>yields according to ref. 12; <sup>b</sup>yields according to ref 13.

Since our aim is devoted to the preparation of suitably substituted derivatives of type **10** we synthesized 2-pyridinylpyrroles **10i** and **10j**, from 1,4-diketones **11** and 3-nitroaniline according to route A. The pyridinylketoaldehydes **11i** and **11j** (70-60% yields) were prepared from the commercially available heterocyclic aldehydes **15** and acrolein in the presence of KCN.

However it was not possible to find commercially available pyrimidin-aldehydes and the synthetic procedure outlined by route A was not suitable for the preparation of 2-pyrimidinylpyrroles. On the other hand attempts to prepare other diketones analogues of **11**, by acylation of methylene active compounds with heterocyclic acyl bromides failed since it was impossible to obtain suitably substituted pyridin- or pyrimidin-COCH<sub>2</sub>Br from the corresponding acetyl derivatives.

Therefore a different approach was undertaken involving a 3+2 ring formation. In fact Katritzky and coworkers reported<sup>14</sup> a new method for the synthesis of 1,2-diarylpyrroles **18** according to Scheme 4. This route employed as starting compounds the easy synthesizable Schiff bases, accessible in turn from aldehydes and amines. To verify if the reaction could be successful also in the case of heteroarylpyrroles, the imines **17** were prepared, generally in good yields (Table 3), and reacted according to literature procedure with 3-(benzotriazol-1-yl)-1-ethoxyprop-1-ene **16**.



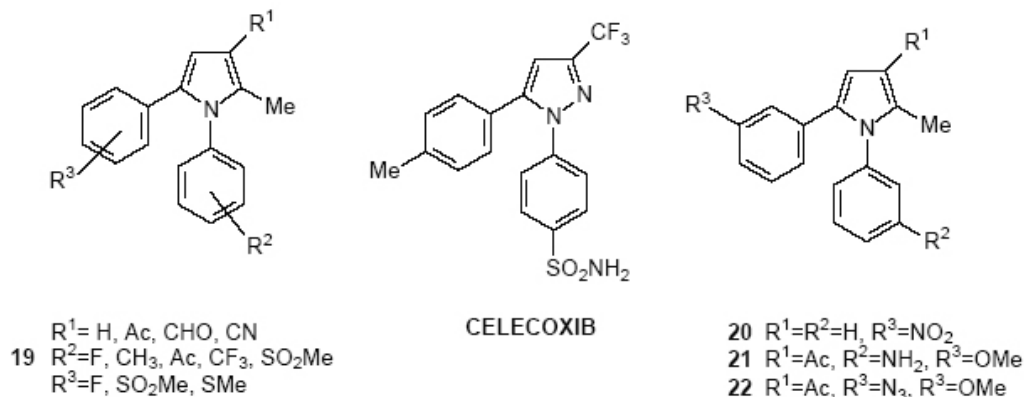
**Scheme 4.** Bt = benzotriazol-1-yl.

**Table 3.** Derivatives **17** and yields (%)

Compounds	Ar <sup>1</sup>	Ar <sup>2</sup>	Yields
<b>a</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	pyridin-3-yl	97
<b>b</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	6-OMe-pyridin-3-yl	85
<b>c</b>	pyridin-2-yl	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	40
<b>d</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	2-SH-6-OH-pyrimidin-4-yl	69
<b>e</b>	3-OMe-C <sub>6</sub> H <sub>4</sub>	6-NH <sub>2</sub> -4-OH-pyrimidin-5-yl	98

From these reactions it was possible to isolate the pyrrole derivative **18** only when imine **17a** was the starting material; in all the other cases extensive decomposition of the starting material was observed and intractable tars were mainly obtained. Therefore the method fails in the preparation of 2-pyrimidinyl-pyrroles that still remain unknown.

All the new 1-heteroarylpyrrole derivatives were proposed for a preliminary screening as anti-inflammatory agents. In fact it seems that the presence of aryl moieties, substituted with electron-withdrawing groups, in the positions 1 and/or 2 of the five membered ring is necessary for the appearance of the activity, as it was observed in the case of derivatives of type **19**.<sup>9</sup>



This is even more evident in the case of the isoster pyrazole derivatives (i.e. celecoxib). However, in pyrrole series the structure-activity relationships are less straightforward although recently analogous behaviour was evidenced in the series of 3-aryl-4-aryl compounds.<sup>8</sup> Therefore we decided to include in the screening tests also some 1,2-diarylpyrroles, selected from our available database, such as compounds **20**,<sup>3</sup> **21**,<sup>4</sup> and **22**.<sup>4</sup>

The results of the screening tests for the 1-heteroarylpyrroles and related 1,2-diaryl derivatives **20-22** are reported in Table 4.

The only compounds which showed some activity against COX-1 at concentration 1-10  $\mu\text{M}$  were **22**, **4g** and **7s**, whereas derivative **7s** weakly inhibited also COX-2. Therefore also in this case the presence of electron-withdrawing substituents or electron deficient rings seems necessary for the appearance of the activity.

**Table 4.** Inhibitory activity<sup>a</sup> (%) of selected pyrroles

Compound	Conc ( $\mu\text{M}$ )	COX-2/PGG <sub>2</sub> (ng/mL)	Inhib (%)	COX-1/TXB <sub>2</sub> (ng/mL)	Inhib (%)
<b>20</b>	0.1	23.622	0	763	4
	1	27.446	0	695	13
	10	35.850	0	711	11
<b>21</b>	0.1	32.813	0	843	0
	1	28.053	0	652	18
	10	33.410	0	732	8
<b>22</b>	0.1	31.513	0	570	28
	1	30.418	0	582	27
	10	41.798	0	720	10
<b>4g</b>	0.1	32.647	0	769	4
	1	32.647	0	765	4
	10	48.283	0	575	28

**Table 4.** Continued

<b>7s</b>	0.1	32.156	0	687	14
	1	15.997	16	623	22
	10	15.075	20	657	18

<sup>a</sup> Expression and purification of human COX-1 and COX-2 enzymes and *in vitro* COX-1 and COX-2 enzyme assays were carried out according to reference 15. The inhibition of LPS-induced PGG<sub>2</sub> production and A23187-induced TBX<sub>2</sub> production in the human whole blood was studied utilizing the literature protocols.<sup>16,17</sup>

In conclusion from the data reported in this paper the best method for the preparation of heteroarylpyrroles remains the Paal-Knorr synthesis once the suitable 1,4-dicarbonyl compounds are available. 1-Heteroarylpyrroles constitute suitable model for the development of interesting biological compounds.

## Experimental Section

**General Procedures.** Melting points (uncorrected) were taken on a Buchi-Tottoli capillary apparatus; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured at 200 and 50.3 MHz respectively in (CD<sub>3</sub>)<sub>2</sub>SO solution, unless otherwise specified, using a Bruker AC-E series 200 MHz spectrometer (TMS as internal reference); mass spectra were obtained with a HP 5890 Series II and HP 5989A-GC/MS apparatus. Column chromatography was performed with Merck silica gel 230-400 Mesh ASTM or with a Biotage FLASH40i chromatography module (prepacked cartridge system). For all new compounds analyses indicated by the symbols of the elements or functions were within ±0.4% of theoretical values.

**Ethyl 2-methyl-5-(3-nitrophenyl)-1-(2,6-R<sup>3</sup>-pyridin-3-yl)-pyrrole-3-carboxylate (4g) and (4h).** A solution of 1,4-diketone **3a**<sup>3</sup> (14 mmol) and 3-aminopyridine (28 mmol) or 3-amino-2,6-dimethoxypyridine (14 mmol) in acetic acid was heated under reflux until disappearance of the starting diketone (TLC monitoring, 8 h and 3 h respectively). After cooling, the resultant solution was poured onto crushed ice. The precipitate was collected, air dried and recrystallized from ethanol.

**4g.** Yield 90%, mp 135 °C; IR v: 1697 (CO), 1531 (NO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.40 (3H, t, *J* = 7.2 Hz, CH<sub>3</sub>), 2.45 (3H, s, CH<sub>3</sub>), 4.33 (2H, q, *J* = 7.2 Hz, CH<sub>2</sub>), 6.96 (1H, s, pyrrole H-4), 7.30-7.36 (2H, m, phenyl H-5 and H-6), 7.47 (1H, dd, *J* = 8.0, 4.5 Hz, pyridine H-5), 7.61 (1H, d, *J* = 8.0 Hz, pyridine H-4), 7.88 (1H, d, *J* = 1.9 Hz, phenyl H-2), 7.97 (1H, dd, *J* = 7.2, 1.9 Hz, phenyl H-4), 8.47 (1H, s, pyridine H-2), 8.69 (1H, d, *J* = 4.5 Hz, pyridine H-6); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 12.5 (q), 14.5 (q), 59.9 (t), 112.3 (d), 114.2 (s), 121.5 (d), 122.7 (d), 124.1 (d), 129.4



(d), 131.5 (s), 133.3 (s), 133.6 (d), 134.2 (s), 135.8 (d), 139.2 (s), 148.1 (s), 149.2 (d), 149.9 (d), 164.9 (s). Anal (C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>) C, H, N.

**4h.** Yield 60%, mp 138 °C; IR v: 1694 (CO), 1532 and 1346 (NO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.38 (3H, t, *J* = 7.3 Hz, CH<sub>3</sub>), 2.35 (3H, s, CH<sub>3</sub>), 3.91 (3H, s, CH<sub>3</sub>), 3.96 (3H, s, CH<sub>3</sub>), 4.32 (2H, q, *J* = 7.3 Hz, CH<sub>2</sub>), 6.32 (1H, d, *J* = 8.0 Hz, pyridine H-5), 6.90 (1H, s, pyrrole H-4), 7.23 (1H, d, *J* = 8.0 Hz, pyridine H-4), 7.35-7.45 (2H, m, phenyl H-6 and H-5), 7.96-8.00 (2H, m, phenyl H-2 and H-4); <sup>13</sup>C NMR δ: 11.9 (q), 14.5 (q), 53.8 (q), 53.9 (q), 59.6 (t), 101.9 (d), 111.1 (d), 112.4 (s), 113.2 (s), 121.2 (d), 122.3 (d), 129.0 (d), 131.7 (s), 133.3 (d), 134.1 (s), 140.1 (s), 140.8 (d), 148.0 (s), 158.4 (s), 163.1 (s), 165.1 (s). Anal (C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub>) C, H, N.

**2-Methyl-5-phenyl-1-(6-R<sup>3</sup>-pyridin-2-yl)-pyrroles 5j-m.** A solution of 1,4-diketones **3b**<sup>18</sup> or **3c**<sup>19</sup> (4.6 mmol) was heated under reflux with 2,6-diaminopyridine (10 mmol) in acetic acid for 24 h. Water was added and the aqueous layer was extracted with dichloromethane; the combined organic extracts were dried over sodium sulphate and the solvent was then removed under reduced pressure. The crude product was purified by column chromatography (dichloromethane/ethyl acetate 1:1).

In the case of the reaction with diketone **3b**, the first compound eluted was ethyl 1-(6-aminopyridin-2-yl)-2-methyl-5-phenylpyrrole-3-carboxylate **5j**, yield 40%, mp 210 °C; IR v: 3385 and 3370 (NH<sub>2</sub>), 1682 (CO) cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.29 (3H, t, *J* = 7.2 Hz, CH<sub>3</sub>), 2.37 (3H, s, CH<sub>3</sub>), 4.22 (2H, q, *J* = 7.2 Hz, CH<sub>2</sub>), 6.31 (1H, d, *J* = 7.3 Hz, pyridine H-5), 6.38 (2H, s, NH<sub>2</sub>), 6.51 (1H, d, *J* = 7.3 Hz, pyridine H-3), 6.67 (1H, s, pyrrole H-4), 7.07-7.28 (5H, m, C<sub>6</sub>H<sub>5</sub>), 7.51 (1H, t, *J* = 7.3 Hz, pyridine H-4); <sup>13</sup>C NMR δ: 11.9 (q), 14.5 (q), 59.0 (t), 108.2 (d), 109.1 (d), 110.2 (d), 111.8 (s), 126.5 (s), 126.6 (d), 127.0 (d), 128.2 (d), 132.2 (s), 132.8 (s), 137.5 (s), 139.2 (d), 149.0 (s), 164.5 (s). Ms: *m/z* 321 (M<sup>+</sup>). Anal (C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>) C, H, N.

The second compound eluted was ethyl 1-(6-acetylamino-pyridin-2-yl)-2-methyl-5-phenylpyrrole-3-carboxylate **5k**, yield 20%, mp 178 °C; IR v: 3400 (NH), 1695 (broad CO) cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.30 (3H, t, *J* = 7.2 Hz, CH<sub>3</sub>), 2.09 (3H, s, CH<sub>3</sub>), 2.37 (3H, s, CH<sub>3</sub>), 4.23 (2H, q, *J* = 7.2 Hz, CH<sub>2</sub>), 6.70 (1H, s, pyrrole H-4), 7.00-7.26 (6H, m, C<sub>6</sub>H<sub>5</sub> and pyridine H-3), 7.90 (1H, t, *J* = 8.8 Hz, pyridine H-4), 8.20 (1H, d, *J* = 8.8 Hz, pyridine H-5); <sup>13</sup>C NMR δ: 11.9 (q), 14.4 (q), 23.9 (q), 59.2 (t), 109.5 (d), 112.3 (s), 113.3 (d), 118.4 (d), 126.8 (d), 127.2 (d), 128.4 (2d), 131.7 (s), 133.1 (s), 137.6 (s), 152.0 (s), 159.8 (s), 164.4 (s), 169.7 (s). Ms: *m/z* 363 (M<sup>+</sup>). Anal (C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N.

In the case of the reaction with diketone **3c**, the first compound eluted was 3-acetyl-1-(6-aminopyridin-2-yl)-2-methyl-5-phenylpyrrole **5l**, yield 20%, mp 185 °C; IR v: 3406 and 3333 (NH<sub>2</sub>), 1649 (CO) cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 2.47 (3H, s, CH<sub>3</sub>), 2.49 (3H, s, CH<sub>3</sub>), 4.76 (2H, s, NH<sub>2</sub>), 6.33 (1H, d, *J* = 7.3 Hz, pyridine H-5), 6.46 (1H, d, *J* = 7.3 Hz, pyridine H-3), 6.68 (1H, s, pyrrole H-4), 7.12-7.26 (5H, m, C<sub>6</sub>H<sub>5</sub>), 7.39 (1H, t, *J* = 7.3 Hz, pyridine H-4); <sup>13</sup>C NMR δ: 12.8 (q), 28.8 (q), 108.1 (d), 110.3 (d), 112.5 (d), 121.5 (s), 126.6 (d), 127.7 (d), 128.1 (d), 132.3 (s), 133.3 (s), 137.6 (s), 139.5 (d), 149.4 (s), 158.4 (s), 195.3 (s). Anal (C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O) C, H, N.

The second compound eluted was 3-acetyl-1-(6-acetylamino-pyridin-2-yl)-2-methyl-5-

phenylpyrrole **5m** [yield traces; Ms:  $m/z$  333 ( $M^+$ )].

**3-Acetyl-1-(2-aminopyrimidin-4-yl)-2-methyl-5-phenylpyrrole (6n).** A solution of 1,4-diketone **3c** (4.6 mmol) was heated under reflux with 2,4-diaminopyrimidine (11.5 mmol) in acetic acid for 24 h. After cooling, the reaction mixture was poured onto crushed ice and the insoluble dark residue was filtered off. The solution was then neutralized with  $\text{NaHCO}_3$  and extracted with dichloromethane; the combined organic extracts were dried over sodium sulphate and the solvent was then removed under reduced pressure to give an oil that solidified on addition of ethanol to give pyrrole **6n**, yield 20%, mp 228 °C, IR  $\nu$ : 3320 and 3208 ( $\text{NH}_2$ ), 1656 ( $\text{CO}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 1.79 (6H, s,  $2\times\text{CH}_3$ ), 6.31 (1H, d,  $J = 6.8$  Hz, pyrimidine H-5), 6.95 (2H, s,  $\text{NH}_2$ ), 7.28-7.36 (4H, m, phenyl H-3, H-4 and H-5, pyrrole H-4), 7.75 (2H, d,  $J = 7.8$  Hz, phenyl H-2 and H-6), 8.12 (1H, d,  $J = 6.8$  Hz, pyrimidine H-6). Anal ( $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$ ) C, H, N.

**Ethyl 1-(2,4-dihydroxypyrimidin-5-yl)-2-methyl-5-(3-nitrophenyl)-pyrrole-3-carboxylate (7p).** Diketone **3a** (3.4 mmol) and 5-aminouracil (3.4 mmol) in dry ethanol were heated under reflux for 21 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using dichloromethane/ethyl acetate 1:1 as eluant. Yield 90%, mp 132-133 °C; IR  $\nu$ : 3554 (broad OH), 3250 (broad OH), 1690 ( $\text{CO}$ ), 1545 ( $\text{NO}_2$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 1.29 (3H, t,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 2.36 (3H, s,  $\text{CH}_3$ ), 4.23 (2H, q,  $J = 6.8$  Hz,  $\text{CH}_2$ ), 6.81 (1H, s, pyrrole H-4), 7.61-7.75 (2H, m, phenyl H-4 and H-6), 7.97 (1H, s, pyrimidine H-6), 8.04 (1H, d,  $J = 3.9$  Hz, phenyl H-2), 8.11 (1H, dt,  $J = 7.8, 3.9$  Hz, phenyl H-5), 11.39 (1H, s, pyrimidine OH-4), 11.61 (1H, s, pyrimidine OH-2);  $^{13}\text{C}$  NMR  $\delta$ : 11.5 (q), 14.4 (q), 59.1 (t), 110.4 (d), 111.0 (s), 112.4 (s), 121.6 (d), 121.7 (d), 130.1 (d), 132.0 (s), 133.3 (s), 133.9 (d), 140.0 (s), 143.6 (d), 147.7 (s), 150.6 (s), 161.2 (s), 164.1 (s). Anal ( $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_6$ ) C, H, N.

**3-Acetyl-1-(2,4-dihydroxypyrimidin-5-yl)-2-methyl-5-(2-nitrophenyl)-pyrrole (7q).** A suspension of *o*-nitrodiketone **3d**<sup>20</sup> (3.94 mmol) and 5-aminouracil (3.94 mmol) was heated under reflux in dry ethanol for 12 h. The pyrrole derivative **7q** crystallized out from the solution on cooling. Yield 54%, mp >320 °C; IR  $\nu$ : 3211 (OH), 1770 ( $\text{CO}$ ), 1526 ( $\text{NO}_2$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 2.33 (3H, s,  $\text{CH}_3$ ), 2.36 (3H, s,  $\text{CH}_3$ ), 6.70 (1H, s, pyrrole H-4), 7.40 (1H, d,  $J = 7.5$  Hz, phenyl H-6), 7.53 (1H, s, pyrimidine H-6), 7.59-7.74 (2H, m, phenyl H-4 and H-5), 7.93 (1H, d,  $J = 7.5$  Hz, phenyl H-3);  $^{13}\text{C}$  NMR  $\delta$ : 12.0 (q), 28.6 (q), 109.6 (s), 110.9 (d), 121.2 (s), 123.9 (d), 125.8 (d), 128.6 (s), 129.7 (d), 132.7 (d), 133.3 (d), 138.2 (s), 144.5 (s), 149.1 (s), 151.4 (s), 160.8 (s), 193.8 (s). Anal ( $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_5$ ) C, H, N.

**1-(4-Amino-6-hydroxypyrimidin-5-yl)-5-(3-methoxyphenyl)-2-methyl-3-R<sup>1</sup>-pyrroles 7r and 7s.** The diketones **3e**<sup>21</sup> or **3f**<sup>22</sup> (4 mmol) dissolved in dry ethanol were added of 4,5-diamino-6-hydroxypyrimidine (4 mmol) and the suspension was heated under reflux in dry ethanol for 7 h. The pyrrole derivative **7r**, **7s** crystallized out from the solution on cooling.

**7r** (yield 95%), mp 223-225 °C; IR  $\nu$ : 3412 (OH), 3316 and 3281 ( $\text{NH}_2$ ), 1643 ( $\text{CO}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 2.25 (3H, s,  $\text{CH}_3$ ), 2.38 (3H, s,  $\text{CH}_3$ ), 3.68 (3H, s,  $\text{CH}_3$ ), 6.60 (2H, bs,  $\text{NH}_2$ ), 6.76 (1H, d,  $J = 2.1$  Hz, phenyl H-2), 6.79 (1H, s, pyrrole H-4), 6.90 (2H, dd,  $J = 8.6, 2.1$  Hz, phenyl H-4 and H-6), 7.19 (1H, t,  $J = 8.6$  Hz, phenyl H-5), 7.88 (1H, s, pyrimidine H-2), 8.96 (1H, bs, OH);  $^{13}\text{C}$  NMR  $\delta$ : 11.4 (q), 28.5 (q), 54.8 (q), 98.1 (s), 110.3 (d), 112.2 (d), 112.5 (d), 119.4 (d), 121.4 (s),

129.1 (d), 133.1 (s), 133.7 (s), 137.8 (s), 149.3 (d), 158.8 (s), 158.8 (s), 160.5 (s), 193.7 (s). Anal (C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>) C, H, N.

**7s** (yield 70%), mp 250-255 °C; IR  $\nu$ : 3398-3205 (OH and NH<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$ : 1.97 (3H, s, CH<sub>3</sub>), 3.66 (3H, s, CH<sub>3</sub>), 6.00 (1H, d, *J* = 3.2 Hz, pyrrole H-3), 6.27 (1H, d, *J* = 3.2 Hz, pyrrole H-4), 6.13 (2H, bs, NH<sub>2</sub>), 6.72 (1H, dd, *J* = 7.5, 2.1 Hz, phenyl H-6), 6.83 (1H, d, *J* = 2.1 Hz, phenyl H-2), 6.88 (1H, d, *J* = 7.5 Hz, phenyl H-4), 7.17 (1H, t, *J* = 7.5 Hz, phenyl H-5), 7.87 (1H, s, pyrimidine H-2), 11.86 (1H, s, OH); <sup>13</sup>C NMR  $\delta$ : 11.8 (q), 54.7 (q), 99.6 (s), 107.4 (d), 108.5 (d), 111.5 (d), 111.5 (d), 118.8 (d), 129.0 (d), 131.4 (s), 133.0 (s), 134.8 (s), 148.9 (d), 158.9 (s), 159.3 (s), 160.8 (s). Anal (C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**5,7-Dimethyl-4-hydroxy-2-mercapto-6-(2-nitrophenacyl)pyrido[2,3-d]pyrimidine (9)**. A suspension of 1,4-diketone **3d** and 4-amino-3-hydroxy-2-mercaptopyrimidine **8** in dry ethanol (60 mL) was heated under reflux for 32 h in the presence of *p*-toluensulfonic acid (0.26 mmol). After cooling of the reaction mixture, derivative **9** crystallized out from the solution. Yield 30%, mp >290 °C; IR  $\nu$ : 3283 (OH), 1697 (CO), 1548 (NO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$ : 2.52 (3H, s, CH<sub>3</sub>), 2.70 (3H, s, CH<sub>3</sub>), 4.60 (2H, s, CH<sub>2</sub>), 7.93-7.98 (4H, m, C<sub>6</sub>H<sub>4</sub>), 12.39 (1H, s, OH), 12.89 (1H, s, SH); <sup>13</sup>C NMR  $\delta$ : 16.4 (q), 23.4 (q), 41.9 (t), 108.3 (s), 124.6 (d), 124.8 (s), 128.4 (d), 132.1 (d), 134.3 (d), 135.3 (s), 146.1 (s), 150.8 (s), 151.2 (s), 160.6 (s), 163.0 (s), 163.2 (s), 174.7 (s). Anal (C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>S) C, H, N, S.

**4-Oxo-4-pyridinyl-butanal 11i and 11j**. A solution of the appropriate pyridin-carboxyaldehyde (0.05 mmol) in anhydrous DMF was added dropwise to a mixture of sodium cyanide (0.04 mmol) and anhydrous DMF at 0 °C under nitrogen. After 30 minutes acrolein (0.05 mmol) in DMF was added dropwise. The mixture was stirred for 3 h at 0 °C and then acetic acid (2.5 mL) was added, followed 10 minutes later, by ice water. The pH was adjusted to 9 and the mixture was extracted with ethyl acetate; the combined organic extracts were dried over sodium sulphate and the solvent was then removed under reduced pressure. The residue was purified by chromatography from silica gel using ethyl acetate (**11i**) or dichloromethane/methanol 95:5 (**11j**) as eluent.

**11i** (yield 70%), uncrystallizable oil; IR  $\nu$ : 1667 (broad CO) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 4.41-4.49 (2H, m, CH<sub>2</sub>), 4.75-4.58 (2H, m, CH<sub>2</sub>), 7.15-7.25 (1H, m, H-3), 7.41-7.48 (1H, m, H-5), 7.59-7.74 (2H, m, H-6 and H-4) 8.58-8.61 (1H, m, CHO). Ms: *m/z* 146 (M<sup>+</sup>-17), 133, 106, 78 (100%). Anal (C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>) C, H, N.

**11j** (yield 60%), uncrystallizable oil; Ms: *m/z* 135 (M<sup>+</sup>-28); this compound was immediately reacted without any further characterization.

**1-(3-Nitrophenyl)-2-(pyridinyl)pyrroles 10i and 10j**. A solution of **11i** or **11j** (10 mmol) and 3-nitroaniline (10 mmol) in dry ethanol with a catalytic amount of *p*-toluensulphonic acid, was heated under reflux for 7 h or 16 h, respectively. The solvent was then removed under reduced pressure and the crude product was purified by column chromatography (dichloromethane/ethyl acetate 7:3, in the case of **10i**, 95:5, in the case of **10j**).

**10i** (yield 40%), mp 125 °C; IR  $\nu$ : 1524 (NO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 7.10-7.28 (2H, m, pyrrole H-3 and H-4), 7.46-7.96 (5H, m, pyrrole H-5; pyridine H-3; phenyl H-5, H-6 and H-2),

8.14 (1H, d,  $J = 8.3$  Hz, phenyl H-4), 8.35-8.58 (2H, m, pyridine H-4 and H-5), 8.95 (1H, d,  $J = 4.2$  Hz, pyridine H-6);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 103.2 (s), 113.0 (d), 113.4 (d), 120.9 (d), 122.0 (d), 122.6 (d), 122.9 (d), 129.0 (d), 136.9 (d), 137.2 (d), 143.9 (s), 147.1 (d), 149.5 (d), 159.7 (s), 173.4 (s). Ms:  $m/z$  265 ( $\text{M}^+$ ), 218. Anal ( $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_2$ ) C, H, N.

**10j** (yield 40%), uncrystallizable oil; IR  $\nu$ : 1530 ( $\text{NO}_2$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 6.52 (1H, t,  $J = 3.1$  Hz, pyrrole H-4), 6.70 (1H, dd,  $J = 3.1, 1.6$  Hz, pyrrole H-5), 7.11 (1H, dd,  $J = 3.1, 1.6$  Hz, pyrrole H-3), 7.42-7.70 (5H, m,  $\text{C}_6\text{H}_4$  and pyridine H-2), 8.12 (1H, t,  $J = 3.3$  Hz, pyridine H-5), 8.24 (1H, dd,  $J = 8.4, 3.3$  Hz, pyridine H-4), 8.51 (1H, dd,  $J = 8.4, 3.3$  Hz, pyridine H-6). Ms:  $m/z$  265 ( $\text{M}^+$ ), 219. Anal ( $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_2$ ) C, H, N.

***N*-(3-Nitrobenzylidene)pyridin-3-amine (17a)**. A solution of 3-nitrobenzaldehyde (6.6 mmol), 3-aminopyridine (6.6 mmol) and a catalytic amount of *p*-toluenesulphonic acid was heated under reflux for 8 h. The solvent was then removed under reduced pressure and the mixture was purified by column chromatography (dichloromethane/ethyl acetate 1:1). Yield 97%, mp 105-110  $^\circ\text{C}$ ; IR  $\nu$ : 1630 ( $\text{CH}=\text{N}$ ), 1531 ( $\text{NO}_2$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.37 (1H, dd,  $J = 6.7, 4.5$  Hz, pyridine H-5), 7.59 (1H, dt,  $J = 8.1, 2.2$  Hz, phenyl H-6), 7.70 (1H, t,  $J = 8.1$  Hz, phenyl H-5), 8.27 (1H, dd,  $J = 6.7, 1.5$  Hz, pyridine H-6), 8.35 (1H, dt,  $J = 8.1, 2.2$  Hz, phenyl H-4), 8.49-8.57 (2H, m, pyridine H-2 and H-4), 8.58 (1H, s,  $\text{CH}=\text{N}$ ), 8.76 (1H, t,  $J = 2.2$  Hz, phenyl H-2);  $^{13}\text{C}$  NMR  $\delta$ : 123.5 (d), 123.7 (d), 125.9 (d), 127.7 (d), 129.9 (d), 134.2 (d), 137.2 (s), 142.5 (d), 146.6 (s), 147.9 (d), 148.6 (s), 158.9 (d). Anal ( $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_2$ ) C, H, N.

**6-Methoxy-*N*-(3-nitrobenzylidene)pyridin-3-amine (17b)**. 3-Nitrobenzaldehyde (18 mmol) and 5-amino-2-methoxypyridine (18 mmol) were dissolved in dry ethanol (100 mL) and heated under reflux for 7 h. After concentration under reduced pressure to a small volume, **17b** crystallized from the reaction mixture. Yield 85%, mp 90-92  $^\circ\text{C}$ ; IR  $\nu$ : 1624 ( $\text{CH}=\text{N}$ ), 1530 ( $\text{NO}_2$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.97 (3H, s,  $\text{CH}_3$ ), 6.80 (1H, d,  $J = 8.8$  Hz, pyridine H-5), 7.58-7.69 (1H, m, phenyl H-5), 7.65 (1H, d,  $J = 7.8$  Hz, phenyl H-4), 8.18 (1H, d,  $J = 8.8$  Hz, pyridine H-4), 8.20-8.31 (2H, m, phenyl H-2 and H-6), 8.57 (1H, s,  $\text{CH}=\text{N}$ ), 8.71 (1H, s, pyridine H-2);  $^{13}\text{C}$  NMR  $\delta$ : 53.6 (q), 111.1 (d), 123.2 (d), 125.4 (d), 129.7 (d), 130.9 (d), 133.9 (d), 137.7 (s), 140.3 (d), 140.4 (s), 148.6 (s), 155.7 (d), 163.2 (s). Anal ( $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$ ) C, H, N.

***N*-(3-Nitrophenyl)-*N*-(pyridin-2-ylmethylene)amine (17c)**. A solution of pyridin-2-carboxyaldehyde (6.6 mmol), 3-nitroaniline (6.6 mmol) and a catalytic amount of *p*-toluenesulphonic acid, was heated under reflux in dry ethanol (100 mL) for 8 h. The solvent was then removed *in vacuo* and the crude product was purified by column chromatography (dichloromethane/ethyl acetate 1:1). Yield 40%, uncrystallizable oil; Ms:  $m/z$  227 ( $\text{M}^+$ ); this compound was immediately reacted without any further characterization.

**6-[(3-Nitrobenzylidene)amino]-2-sulfanylpyrimidin-4-ol (17d)**. To a suspension of 3-nitrobenzaldehyde (6.6 mmol) and 4-amino-6-hydroxy-2-mercaptopyrimidine **8** (6.6 mmol) in dry ethanol (100 mL) 5 mL of HCl in ethanol were added. The resulting solution was heated under reflux for 3 h and then cooled to room T. The resulting precipitate was filtered off and washed with warm  $\text{H}_2\text{O}$ . Yield 69%, mp  $>290$   $^\circ\text{C}$ ; IR  $\nu$ : 3408 (OH), 1553 ( $\text{NO}_2$ ), 1636 ( $\text{CH}=\text{N}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (pyridine- $d_5$ )  $\delta$ : 4.01 (1H, s, SH), 6.27 (1H, s, pyrimidine H-5), 7.48 (1H, t,  $J =$

7.8 Hz, phenyl H-5), 7.58 (1H, s, phenyl H-2), 7.82 (1H, d,  $J = 7.8$  Hz, phenyl H-6), 8.11 (1H, d,  $J = 7.8$  Hz, phenyl H-4), 8.55 (1H, s, CH=N), 14.86 (1H, bs, OH);  $^{13}\text{C}$  NMR  $\delta$ : 121.1 (d), 112.6 (d), 123.8 (d), 129.5 (d), 134.2 (d), 142.1 (s), 149.0 (s), 150.2 (d), 155.6 (s), 165.1 (s), 175.4 (s). Anal ( $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_3\text{S}$ ) C, H, N, S.

**6-Amino-5-[(3-methoxybenzylidene)amino]pyrimidin-4-ol (17e).** To a solution of 3-methoxybenzaldehyde (7.93 mmol) in dry ethanol 4,5-diamino-6-hydroxypyrimidine (7.93 mmol) was added. The mixture was heated under reflux for 1 h. On cooling a precipitate separated which was filtered off and washed with  $\text{H}_2\text{O}$  at 60 °C. Yield 98%, mp 255-256 °C; IR v: 3462 (OH), 3290 and 3177 ( $\text{NH}_2$ ), 1626 (CH=N)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 3.83 (3H, s,  $\text{CH}_3$ ), 6.97 (1H, d,  $J = 7.5$  Hz, phenyl H-6), 6.99 (2H, s  $\text{NH}_2$ ), 7.32 (1H, t,  $J = 7.5$  Hz, phenyl H-5), 7.43 (1H, d,  $J = 7.5$  Hz, phenyl H-4), 7.51 (1H, s, phenyl H-2), 7.76 (1H, s, CH=N), 9.84 (1H, s, pyrimidine H-2), 11.83 (1H, s, OH);  $^{13}\text{C}$  NMR  $\delta$ : 55.2 (q), 107.7 (s), 111.4 (d), 116.1 (d), 120.8 (d), 129.5 (d), 139.9 (s), 147.3 (d), 154.0 (d), 156.8 (s), 159.6 (s), 161.1 (s). Anal ( $\text{C}_{12}\text{H}_{12}\text{N}_4\text{O}_2$ ) C, H, N.

**2-(3-Nitrophenyl)-1-(pyridin-3-yl)-pyrrole (18a).** To a solution of **16**<sup>14</sup> (5 mmol) in dry THF (40 mL) was added BuLi (2M, 5.5 mmol, 2.75 mL) at -78 °C under argon. After 30 minutes a solution of imine **17a** (5 mmol) in THF (10 mL) was added. The mixture was allowed to warm gradually to room T overnight.  $\text{ZnBr}_2$  (10 mmol) was added and the mixture was refluxed for 8 h. Water (150 mL) was added and the mixture was extracted with diethyl ether. The combined organic layer was dried over sodium sulphate and the solvent was removed. The residue was subjected to column chromatography (dichloromethane/methanol 95:5). Yield 15%, uncrystallizable oil; IR v: 1530 ( $\text{NO}_2$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 6.83 (1H, dd,  $J = 3.9, 2.9$  Hz, pyrrole H-5), 7.06 (1H, dd,  $J = 4.9, 3.9$ , pyrrole H-4), 7.36 (1H, dd,  $J = 4.9, 2.9$  Hz, pyrrole H-3), 7.61 (1H, t,  $J = 8.8$  Hz, phenyl H-5), 7.72 (1H, d,  $J = 5.9$  Hz, pyridine H-5), 7.80 (1H, d,  $J = 8.8$  Hz, phenyl H-6), 8.03 (1H, d,  $J = 5.9$  Hz, pyridine H-4), 8.21 (1H, d,  $J = 8.8$  Hz, phenyl H-4), 8.31 (1H, s, phenyl H-2), 8.40 (1H, d,  $J = 5.9$  Hz, pyridine H-6), 8.77 (1H, s, pyridine H-2);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 116.2 (s), 120.2 (d), 121.2 (d), 121.7 (d), 122.4 (d), 123.7 (d), 126.4 (d), 128.3 (d), 129.9 (d), 130.4 (d), 132.5 (d), 133.9 (d), 145.5 (s), 148.8 (s), 164.3 (s). Anal ( $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2$ ) C, H, N.

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This compound was obtained as uncrystallizable oil (yield 65%) from diketone **3e** upon heating under reflux for 30 min with NaOH (20% solution in ethanol).