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A new entry to the substituted pyrrolo[3,2-*c*]quinoline derivatives of biological interest by intramolecular heteroannulation of internal imines

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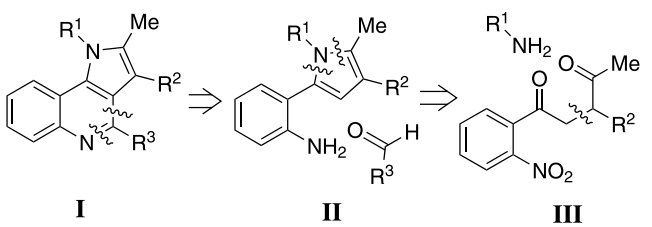
Abstract—New 1,3,4-substituted pyrrolo[3,2-*c*]quinoline derivatives were synthesised in good yields by oxidative heteroannulation of internal imines starting from easily prepared substituted 5-(2-aminophenyl)pyrroles and commercially available aryl and heteroaryl aldehydes. The reaction occurs as a one-pot process involving an intramolecular acid catalysed reaction.

1. Introduction

For many years, the pyrrolo[3,2-*c*]quinoline ring system (**I**, Scheme 1) has been known as a core structure unit of bioactive molecules of either synthetic[1] or natural source.[2] Several derivatives of such a tricyclic angular heterocycle possess a wide spectrum of biological activities,[3] including most notably antitumor properties,[4] gastric (H^+/K^+)-ATPase inhibitor,[5] hypotensive,[6] anti-inflammatory activities[7] and others. The relatively recent isolation of this framework from the organic extracts of *Martinella iquitosensis* roots, which evidenced antagonist properties against bradykinin receptors,[8] renewed interest has attracted several research groups to plan new synthetic approaches. The wide potential of such a skeleton along with our interest in targets featuring nitrogen containing aromatized polycyclic structures prompted us to develop an alternative synthetic route, so as to further investigate the interaction of such molecules with DNA.



Scheme 1. Disconnection approach of the pyrrolo[3,2-*c*]quinoline core.

A perusal of the literature highlights a large number of different synthetic pathways to such rings. However, only a few convenient cases concern entirely planar aromatic ring systems; such as those concerning the Fischer-indole synthesis,[9] metal mediated reactions,[1,10] and aryl radical cyclization onto pyrroles.[11]

As an extension of our ongoing work in the field directed to the development of new synthetic approaches to polycyclic nitrogen heterocycles,[12] as well as exploration of their biological and structural properties, we report here an alternative and convenient pathway leading, in good yields, to a series of new substituted pyrrolo[3,2-*c*]quinoline compounds.

The retrosynthetic approach proposed is illustrated in Scheme 1. It involves a double disconnection at the central pyridine ring to afford the 5-(*o*-aminophenyl) pyrroles **II**, which in turn would arise from the corresponding 1,4-diketone **III** and alkyl, aryl, heteroaryl amines simply formed by a Paal-Knorr reaction. Precursors **III** were easily synthesized according to the literature procedures[13,14] modified by us to achieve higher yields (see Section 4). Such a strategy, in combination with the possibility of using a wide range of commercially available reactants, allows functionalization of crucial positions of the pyrrole ring and can be suitable in combinatorial chemistry for the synthesis of a small library.

Reported synthetic pathways have mainly considered the

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construction of the pyrrolo[3,2-*c*]quinoline core starting from a preformed quinoline moiety,[15] fluorinated synthons,[16] substituted hydropyridine,[17] but limitations and/or low overall yields are often encountered. Often, the introduction of a specific substituent, especially in position 4 of the preformed skeleton, required laborious steps coupled with drastic experimental conditions. Moreover, it did not appear to offer much flexibility for preparing derivatives with groups other than simple alkyl ones in the 4 position.[18]

In this case, for our target molecules, we considered *o*-aminophenylpyrroles **II** as strategic precursors. Although, they have proved to be very versatile key intermediates, leading to a wide variety of pyrrolo-fused heterocycles,[19–22] to our knowledge, none of the previous synthetic pathways explored their reactivity via imine formation and intramolecular cyclization. The only reported example involving a carbonyl function concerned the use of formic acid, which in boiling benzene cyclized to the dihydro-pyrroloquinazoline ring.[14]

Here, we report our results on the development of a new and convenient one pot access to the title ring system starting from precursor **II**.

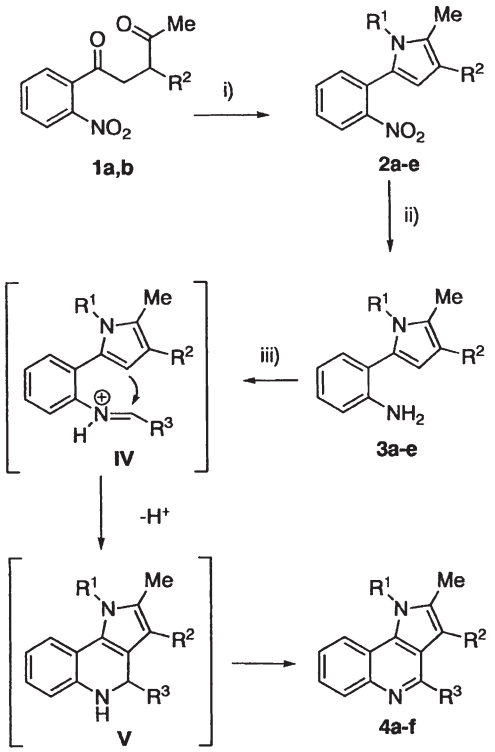
2. Results and discussion

The reaction sequence starts with the Paal-Knorr reaction between 1,4-diketones **1a**,**b**[13,14] and commercial alkyl, aryl, heteroaryl amines, which under reflux (3–8 h) in acetic acid, afforded the corresponding 5-(*o*-nitrophenyl)-1-substitued pyrroles **2a-e** in 60–87% isolated yield. Reduction with Pd/C in a Parr apparatus furnished the amino derivatives **3a-e**, in yields from good to excellent (Scheme 2).

Treatment of the latter amines with a slight excess of aldehydes in the presence of 15 mol% of *p*-toluenesulfonic acid (*p*-TsOH) in DMF at 100 °C provided compounds **4a-f** in good yields (72–94%) within 3 h.

Such a result may be reasonably accounted for on the basis of an intramolecular addition of pyrrole β-carbon on the transiently formed protonated imine (**IV**) to give the tricyclic intermediate (**V**), followed by spontaneous dehydrogenation (Scheme 2).

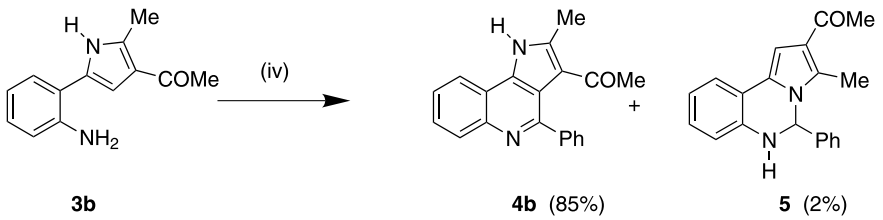
Attempted isolation of the imines **IV** or the cycloadduct **V** from the reaction as intermediates failed, even when operating under milder reaction condition.[23] Only during GC–MS monitorage of the reaction was a trace amount of a peak corresponding to the mass of the supposed imine **IV** or the dihydro cycloadduct **V** detected. Probably, this fact reflects the high reactivity of the internal nucleophile (pyrrole C-3) which immediately evolves to the fully aromatic system. It should be noted that isolation of the oxidized aromatic derivatives was also observed even in the presence of reductive condition,[11] confirming that the thermodynamic gain involved in the aromatization process is relevant.



	R^1	R^2	R^3	Yield%
1a		CO_2Et		78
1b		COMe		92
2a	Ph	CO_2Et		73
2b	H	COMe		80
2c	Me	COMe		87
2d	Et	COMe		60
2e	Ph	COMe		80
3a	Ph	CO_2Et		95
3b	H	COMe		97
3c	Me	COMe		91
3d	Et	COMe		82
3e	Ph	COMe		85
4a	Ph	CO_2Et	Ph	84
4b	H	COMe	Ph	85
4c	Me	COMe	Ph	77
4d	Et	COMe	Ph	84
4e	Ph	COMe	Ph	94
4f	Ph	COMe	5-Me-Furan-2*yl*	72

Reagents and conditions: i) R^1NH_2, AcOH, reflux, 3-8h; ii) H_2, 10% Pd/C, EtOH, rt, overnight; iii) R^3CHO, DMF, 100°C, 15 mol% *p*-TsOH within 3h.

Scheme 2. General procedure for the preparation of the novel pyrroloquinoline derivatives.



3b **4b** (85%) **5** (2%)

Reagents and conditions: (iv): PhCHO 1.1 eq, 15 mol% *p*-TsOH, DMF, 100°C, 2.5h.

Scheme 3. Formation of the competitive pyrrolo[1,2-*c*]quinazoline ring.

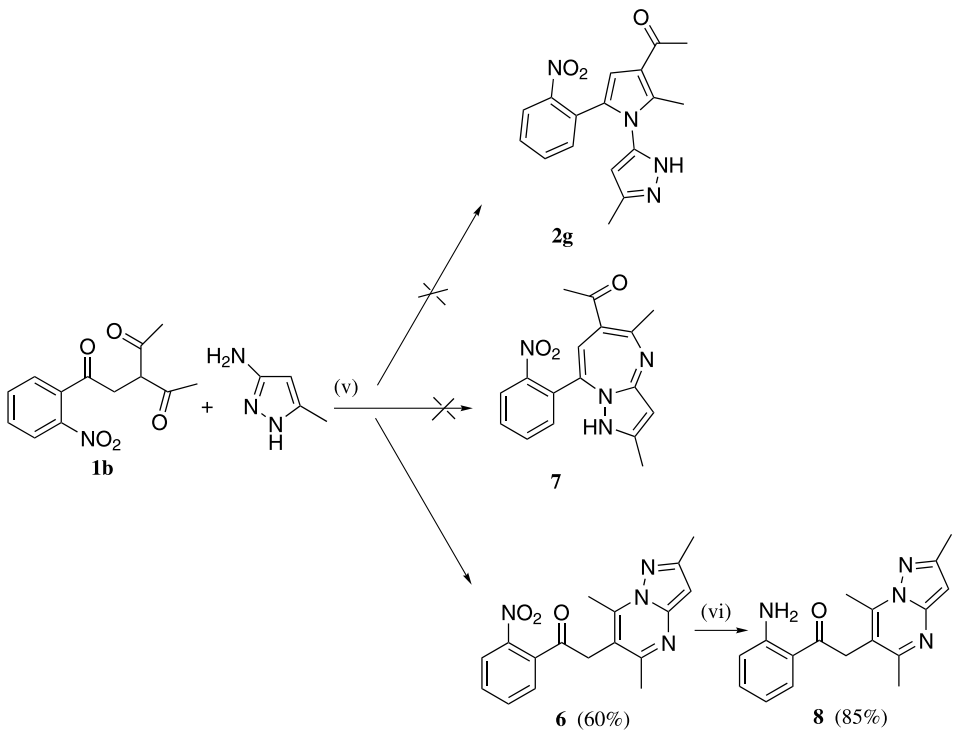
It is interesting to note the key step of this sequence is strongly related to a variant of the well-known Mannich reaction, and in particular the Pictet-Spengler condensation, which also features the first step on intramolecular addition of the position 3 of an indole derivative onto an in situ generated iminium ion.[24]

When the pyrroloaniline **3b** was treated with PhCHO under the same experimental conditions as before (Scheme 3), the expected compound **4b** was isolated as major product (85%) along with traces of the cycloadduct 5,6-dihydro-pyrrolo[1,2-*c*]quinazoline derivative **5** (2%) which appears to result from competitive NH pyrrole addition on the intermediate protonated imine.

In fact, besides the expected signals, the ^{1}H NMR spectrum of compound **5** exhibited a singlet at δ_H 6.62 ppm related to the dihydro pyrimidine CH together with another singlet at δ_H 7.06 ppm relative to the pyrrole CH. The signals for the corresponding carbon atoms in the ^{13}C NMR spectrum were found at δ_C 65.51 and 103.81 ppm, respectively.

In an attempt to introduce heteroaryl moieties on position 1, commercial 3-amino-5-methyl pyrazole was reacted with triketone **1b** (Scheme 4). Upon heating under reflux in acetic acid, a major compound (60% yields) with a peak *m*/*z* of 324 in the mass spectrum was isolated from the reaction mixture. NMR data of this product excluded the expected 1-pyrazol-2-yl pyrrole derivative **2g**. In fact, besides the signals for the (2-nitrophenyl) group, ^{1}H NMR spectrum showed a singlet at δ_H 6.36 ppm related to one proton, with a signal for the corresponding carbon atom at δ_C 94.30 ppm in the ^{13}C NMR spectrum, attributable to a pyrazole CH. Furthermore, the presence of a methylene group was also evidenced by a singlet at δ_H 4.57 ppm integrated for two protons in the ^{1}H NMR spectrum and by the corresponding carbon atom signal at δ_C 41.22 ppm in the ^{13}C NMR spectrum, confirmed by DEPT experiments.

Usually, 1,4-diketones and 2-amino-azoles give rise to 4+1 cyclo-condensation.[12b] In the case of triketone **1b**, other types of cyclo-condensation (3+3 or 4+3) could be envisaged. So, compounds **6** or **7** could be formed, respectively.



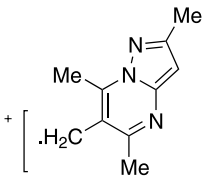
Reagents and conditions: (v) AcOH under reflux, 8h; (vi) H_2, PdC 10%, EtOH, rt, 12h.

Scheme 4. Competitive 3+3 cyclo-condensation in the attempted preparation of **2g**.

Analysis of the NMR data allowed us to assign the structure **6** to the isolated product. Unequivocal assignment of the signals was performed by 2D NMR experiments showing both one-bond and long-range heteronuclear C–H correlations. In addition to the one-bond correlation with the CH_2 carbon atom, the methylene protons exhibited ^2J connections with C-6 and carbonyl carbon atoms and ^3J connections with C-5 and C-7 carbon atoms. Analogously, besides the one-bond correlations, methyl protons exhibited ^2J correlations with the related C-*ipso* carbon atoms and ^3J correlations with the C-*ortho* carbon atoms. Therefore, C-6 carbon atom showed correlations with 5-Me and 7-Me protons, whereas C-3 carbon atom correlated with 2-Me protons. Correlations of pyrazole proton with C-2 and C-3a quaternary carbon atoms were also detected. Finally, the signals of the (2-nitrophenyl) group showed the appropriate correlations either interannular and to carbonyl carbon atom.

The same correlations were found in the 2D NMR spectra of the amino derivative **8** in turn obtained by hydrogenation of **6**. In this case, chemical shift variations $|\Delta\delta| \leq 0.68$ were detected for ^{13}C NMR signals of pyrazolo[1,5-*a*]pyrimidine ring carbon atoms, with the exception of C-6 ($\Delta\delta = +2.40$) and exocyclic methylene ($\Delta\delta = -3.41$) carbon atoms. As expected, the (2-aminophenyl) group showed in the ^1H and ^{13}C NMR spectra the appropriate signals of the reduction product of **6**.

Additional support was furnished by the fragmentation pattern as pointed out in the mass spectra of compound **6**, in which the base peak fragment at *m/z* 174, relative to the stable pyrazolopyrimidine scaffold, was detected (Fig. 1).



m/z 174

Figure 1. Base peak fragment observed at GC–MS (EI 70 eV) for compound **6**.

The above example indicates that the hetero-functionalization onto position 1 of the ring is strictly dependent on the nature and the reactivity of the heteroaryl amino species involved in the first reaction step. Thus, the simultaneous presence of supplementary nucleophilic site can divert from the expected 4+1 cyclo-condensation. Anyway, suitable hetero-aromatic amines could be employed at this purpose.[12a,b]

3. Conclusions

In summary, the above presented study allows easy access to fully aromatic pyrrolo[3,2-*c*]quinoline derivatives. This new approach is operationally simple and makes use of commercial available starting materials such as alkyl, aryl or heteroaryl amines concerned in step (i) and aryl or heteroaryl aldehydes[25] involved in step (iii). In contrast to previous methods, this new pathway allows convenient introduction onto position 1, 3 and 4 of the title ring system a variety of selected functional groups, which in turn are useful for structure–activity relationships studies or may be susceptible of further synthetic development. Although some limitation could be encountered, as observed for the cyclo-condensation of 3-aminopyrazole, the ready availability of the starting materials and ease of this procedure make this method ideal for an alternative new access to fully aromatic pyrrolo[3,2-*c*]quinoline derivatives.

4. Experimental

4.1. Materials and general methods

Unless otherwise specified, materials were purchased from commercial suppliers (Aldrich) and used without further purification. Acetic acid was distilled from acetic anhydride (3%, w/v) under argon Analytical thin layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates and column chromatography was accomplished on Merck silica gel 230–400 mesh (ASTM). Melting points were determined with a Buchi-Tottoli capillary apparatus and are uncorrected. IR spectra were determined in bromoform with a Jasco FT-IR 5300 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer operating in FT mode in DMSO-d_6 solutions at 250.13 and 62.89 MHz, respectively. ^1H and ^{13}C chemical shift values are given in ppm relative to TMS (as internal standard) and DMSO-d_6 (centered at 39.50 ppm downfield from TMS), respectively. Coupling constants values are in Hz. ^{13}C chemical shift values were measured from proton fully decoupled spectra. Signals assignment was made on the basis both of known substituent effects and of one-bond multiplicities (indicated in parentheses) determined by DEPT-135 and confirmed by 2D C,H correlation experiments, using the standard Bruker pulse sequences XHDEPT.AUR and COLOC.AUR, for one-bond and long-range C,H interactions, respectively. Mass spectra (EI) were collected on a GC-MS-QP5050A Shimadzu mass spectrometer with ionization energy of 70 eV. Elemental analyses were performed on a Perkin–Elmer 240 °C elemental analyzer and the results were within ±0.3% of the theoretical values. Yields refer to purified products and are not optimized.

Analytical and spectroscopic data for compounds **1a**,**b** were consistent to those previously reported.[13,14] The yield of compound **1b** was optimized to 92% with respect to the reported 50%[13] by using the following modified procedure. To a solution of sodium ethoxide (80 mmol) in absolute ethanol (100 ml), acetylacetone (80 mmol) was added dropwise cooling with an ice-bath. After 1 h, the mixture was allowed to rt and the 2-nitrophenacyl bromide was added in small portions within 40 min. The reaction mixture was stirred at rt for 3 days and then quenched with 150 ml of water. A white solid was formed and was recrystallized from ethanol.

4.2. General method for the preparation of 5-(*o*-nitrophenyl)-1,3-substituted pyrroles (2a–e)

According to the procedure described[13] for **2a**–**e**, to a

solution of **1a**,**b** (10 mmol) in acetic acid (40 ml), the corresponding amine (10 mmol) was added. The mixture was heated under reflux for 3–8 h until disappearance of reactants (TLC monitorage). After cooling, the resultant solution was poured onto crushed ice. The so formed solid was filtered off, air-dried and recrystallized from ethanol.

Analytical and spectroscopic data for compounds **2a**–**c**,**e** were coincident to those previously reported.[13,14,20,21] Most detailed ^{1}H and ^{13}C NMR data, together with MS data, not previously reported, are now described.

4.2.1. 3-Acetyl-2-methyl-5-(2-nitrophenyl)-1*H*-pyrrole 2b. Yield 80%; white crystals, mp 206–207 °C [lit.[13] mp 208 °C]; δ_H 11.75 (1H, s, exchangeable with D_2O, N*H*), 7.92 (1H, d, *J* 7.5 Hz, H-3′), 7.74–7.64 (2H, m, H-5′ and -6′), 7.51 (1H, t, *J*=7.5 Hz, H-4′), 6.60 (1H, s, H-4), 2.49 (3H, s, 2-*Me*), 2.32 (3H, s, CO*Me*); δ_C 193.28 (s, CO), 147.52 (s, C-2′), 136.56 (s, C-2), 132.50 (d, C-5′), 130.32 (d, C-6′), 127.94 (d, C-4′), 125.62 (s, C-1′), 124.03 (d, C-3′), 123.80 (s, C-5), 121.76 (s, C-3), 110.33 (d, C-4), 28.30 (q, CO*Me*), 13.41 (q, 2-*Me*); *m*/*z* (EI) 244 (100, M^+), 229 (43), 183 (55), 77 (39), 43 (70%).

4.2.2. 3-Acetyl-1,2-dimethyl-5-(2-nitrophenyl)-1*H*-pyrrole 2c. Yield 87%; orange crystals, mp 115–116 °C [lit.[20] mp 116–117 °C]; δ_H 8.07 (1H, d, *J*=8.1 Hz, H-3′), 7.79 (1H, t, *J*=7.4 Hz, H-5′), 7.69 (1H, dd, *J*=8.1, 7.4 Hz, H-4′), 7.57 (1H, d, *J*=7.4 Hz, H-6′), 6.52 (1H, s, H-4), 3.27 (3H, s, N*Me*), 2.52 (3H, s, 2-*Me*), 2.28 (3H, s, CO*Me*); δ_C 193.36 (s, CO), 149.45 (s, C-2′), 135.97 (s, C-2), 133.46 (d, C-6′), 133.01 (d, C-5′), 129.85 (d, C-4′), 127.02 (s, C-5), 126.05 (s, C-1′), 124.08 (d, C-3′), 120.34 (s, C-3), 110.26 (d, C-4), 31.06 (q, N*Me*), 28.23 (q, CO*Me*), 11.41 (q, 2-*Me*); *m*/*z* (EI) 258 (96, M^+), 243 (80), 196 (81), 77 (64), 56 (100), 43 (86%).

4.2.3. 3-Acetyl-1-ethyl-2-methyl-5-(2-nitrophenyl)-1*H*-pyrrole 2d. Yield 60%; white crystals, mp 133–134 °C; [found: C, 66.29; H, 5.94; N, 10.27. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.29%]; ν_{max} 1643 (CO), 1527 and 1348 (NO_2) cm^{-1}; δ_H 8.05 (1H, d, *J*=7.8 Hz, H-3′), 7.78 (1H, t, *J*=7.2 Hz, H-5′), 7.69 (1H, dd, *J*=7.8, 7.2 Hz, H-4′), 7.60 (1H, d, *J*=7.2 Hz, H-6′), 6.46 (1H, s, H-4), 3.77 (2H, q, *J*=7.1 Hz, CH_2Me), 2.55 (3H, s, 2-*Me*), 2.26 (3H, s, CO*Me*), 1.04 (3H, t, *J*=7.1 Hz, CH$_2$*Me*); δ_C 193.37 (s, CO), 149.93 (s, C-2′), 135.02 (s, C-2), 133.48 (d, C-6′), 132.68 (d, C-5′), 129.99 (d, C-4′), 126.02 (s, C-1′), 125.92 (s, C-5), 123.91 (d, C-3′), 120.60 (s, C-3), 110.55 (d, C-4), 38.64 (t, *C*H$_2$Me), 28.21 (q, CO*Me*), 15.09 (q, CH$_2$*Me*), 11.28 (q, 2-*Me*); *m*/*z* (EI) 272 (100, M^+), 257 (33), 210 (25), 77 (21), 70 (71), 43 (70), 42 (91%).

4.2.4. 3-Acetyl-2-methyl-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrrole 2e. Yield 80%; yellow crystals, mp 137–138 °C [lit.[20] mp 138 °C]; δ_H 7.82 (1H, d, *J*=8.0 Hz, H-3′), 7.61 (1H, t, *J*=7.3 Hz, H-5′), 7.49 (1H, dd, *J*=8.0, 7.3 Hz, H-4′), 7.45 (1H, d, *J*=7.3 Hz, H-6′), 7.39–7.33 (3H, m, N*Ph* H-3,5 and -4), 7.14 (2H, dd, *J*=7.9, 1.6 Hz, N*Ph* H-2,6), 6.79 (1H, s, H-4), 2.39 (3H, s, CO*Me*), 2.33 (3H, s, 2-*Me*); δ_C 193.81 (s, CO), 148.72 (s, C-2′), 136.35 (s, C-2),135.84 (s, N*Ph* C-1), 133.43 (d, C-6′), 132.71 (d, C-5′), 129.30 (d, C-4′), 129.16 (d, N*Ph* C-3,5), 128.45 (d, N*Ph*C-4), 128.02 (d, N*Ph* C-2,6), 128.02 (s, C-5), 126.23 (s, C-1′), 123.84 (d, C-3′), 121.29 (s, C-3), 111.07 (d, C-4), 28.53 (q, CO*Me*), 12.55 (q, 2-*Me*); *m*/*z* (EI) 320 (59, M^+), 305 (15), 261 (49), 228 (72), 186 (44), 118 (91), 77 (100), 51 (42), 43 (78%).

4.3. General method for the preparation of 5-(2-aminophenyl)-1-substituted-pyrroles (3a–e)

According to the procedure described[19] for **2a**–**c**,**e** compound **2d** was reduced overnight with hydrogen (50 psi) over 10% Pd–C in ethanol in a Parr apparatus at room temperature. The catalyst was filtered off and the solvent evaporated under reduced pressure. The obtained solid was recrystallized from ethanol.

Analytical and spectroscopic data for compounds **3a**–**c**,**e** were coincident to those previously reported.[13,14,20,21] Most detailed ^{1}H and ^{13}C NMR data, together with MS data, not previously reported, are now described.

4.3.1. 5-(2-Aminophenyl)-3-ethylester-2-methyl-1-phenyl-1*H*-pyrrole 3a. Yield 95%; orange crystals, mp 154–155 °C [lit.[21] mp 153 °C]; δ_H 7.35–7.30 (3H, m, N*Ph* H-3,5 and -4), 7.24 (2H, dd, *J*=7.8, 2.2 Hz, N*Ph* H-2,6), 6.86 (1H, ddd, *J*=8.0, 7.6, 1.3 Hz, H-4′), 6.69 (1H, dd, *J*=7.6, 1.3 Hz, H-6′), 6.54 (1H, dd, *J*=8.0, 0.8 Hz, H-3′), 6.49 (1H, s, H-4), 6.31 (1H, td, *J*=7.6, 0.8 Hz, H-5′), 4.81 (2H, s, exchangeable with D_2O, NH_2), 4.22 (2H, q, *J*=7.1 Hz, CH_2Me), 2.30 (3H, s, 2-*Me*), 1.28 (3H, t, *J*=7.1 Hz, CH$_2$*Me*); δ_C 164.56 (s, CO), 147.14 (s, C-2′), 137.26 (s, N*Ph* C-1), 136.36 (s, C-2), 131.50 (d, C-6′), 130.52 (s, C-5), 128.71 (d, N*Ph* C-3,5), 128.61 (d, C-4′), 128.05 (d, N*Ph* C-2,6 and -4), 116.04 (s, C-1′), 115.26 (d, C-5′), 114.29 (d, C-3′), 111.61 (s, C-3), 109.52 (d, C-4), 58.82 (t, *C*H$_2$Me), 14.45 (q, CH$_2$*Me*), 12.35 (q, 2-*Me*); *m*/*z* (EI) 320 (100, M^+), 275 (31), 274 (44), 130 (44), 118 (57), 77 (33), 51 (12%).

4.3.2. 3-Acetyl-5-(2-aminophenyl)-2-methyl-1*H*-pyrrole 3b. Yield 97%; white crystals, mp 130–131 °C [lit.[13] mp132 °C]; δ_H 11.39 (1H, s, exchangeable with D_2O, N*H*), 7.20 (1H, dd, *J*=7.5, 1.3 Hz, H-6′), 7.00 (1H, ddd, *J*=7.9, 7.5, 1.3 Hz, H-4′), 6.78 (1H, dd, *J*=7.9, 1.0 Hz, H-3′), 6.69 (1H, s, H-4), 6.63 (1H, td, *J*=7.5, 1.0 Hz, H-5′), 5.02 (2H, s, exchangeable with D_2O, NH_2), 2.49 (3H, s, 2-*Me*), 2.34 (3H, s, CO*Me*); δ_C 193.61 (s, CO), 144.90 (s, C-2′), 134.77 (s, C-2), 127.92 (d, C-6′), 127.49 (d, C-4′), 127.12 (s, C-5), 121.14 (s, C-3), 116.94 (s, C-1′), 116.50 (d, C-5′), 115.56 (d, C-3′), 108.52 (d, C-4), 28.40 (q, CO*Me*), 13.35 (q, 2-*Me*); *m*/*z* (EI) 214 (100, M^+), 199 (85), 172 (69), 171 (73), 100 (82), 77 (31), 43 (32%).

4.3.3. 3-Acetyl-5-(2-aminophenyl)-1,2-dimethyl-1*H*-pyrrole 3c. Yield 91%; white crystals, mp 134–135 °C [lit.[21] mp 135 °C]; δ_H 7.09 (1H, ddd, *J*=8.0, 7.3, 1.1 Hz, H-4′), 6.95 (1H, dd, *J*=7.3, 1.1 Hz, H-6′), 6.76 (1H, d, *J*=8.0 Hz, H-3′), 6.59 (1H, t, *J*=7.3 Hz, H-5′), 6.44 (1H, s, H-4), 4.81 (2H, exchangeable with D_2O, NH_2), 3.26 (3H, s, N*Me*), 2.51 (3H, s, 2-*Me*), 2.30 (3H, s, CO*Me*); δ_C 193.45 (s, CO), 147.19 (s, C-2′), 135.19 (s, C-2), 131.46 (d, C-6′), 130.00 (s, C-5), 129.15 (d, C-4′), 120.12 (s, C-3), 116.17 (s, C-1′), 115.83 (d, C-5′), 114.55 (d, C-3′), 109.49 (d, C-4), 30.63 (q, N*Me*), 28.28 (q, CO*Me*), 11.63 (q, 2-*Me*); *m*/*z* (EI) 228 (90,

M^+), 213 (100), 185 (52), 106 (64), 77 (23), 56 (51), 43 (26%).

4.3.4. 3-Acetyl-5-(2-aminophenyl)-1-ethyl-2-methyl-1*H*-pyrrole 3d. Yield 82%; yellow crystals, mp 88–89 °C; [found: C, 74.25; H, 7.51; N, 11.58. $C_{15}H_{18}N_2O$ requires C, 74.35; H, 7.49; N, 11.56%]; ν_{max} 3464 (NH_2), 3366 (NH_2), 1643 (CO) cm^{-1}; δ_H 7.10 (1H, ddd, *J*=7.9, 7.5, 1.3 Hz, H-4′), 6.97 (1H, dd, *J*=7.5, 1.3 Hz, H-6′), 6.75 (1H, d, *J*=7.9 Hz, H-3′), 6.60 (1H, t, *J*=7.5 Hz, H-5′), 6.42 (1H, s, H-4), 4.73 (2H, exchangeable with D_2O, N*H*$_2$), 3.70 (2H, q, *J*=7.1 Hz, C*H*$_2$Me), 2.53 (3H, s, CO*Me*), 2.30 (3H, s, 2-*Me*), 0.98 (3H, t, *J*=7.1 Hz, CH_2*Me*); δ_C 193.71 (s, CO), 147.26 (s, C-2′), 134.44 (s, C-2), 131.64 (d, C-6′), 129.39 (d, C-4′), 129.04 (s, C-5), 120.50 (s, C-3), 116.39 (s, C-1′), 115.99 (d, C-5′), 114.58 (d, C-3′), 110.16 (d, C-4), 38.29 (t, *C*H$_2$Me), 28.41 (q, CO*Me*), 15.57 (q, CH_2*Me*), 11.52 (q, 2-*Me*); *m*/*z* (EI) 242 (100, M^+), 227 (98), 199 (43), 99 (33), 77 (18), 43 (32%).

4.3.5. 3-Acetyl-5-(2-aminophenyl)-2-methyl-1-phenyl-1*H*-pyrrole 3e. Yield 85%; yellow crystals, mp 151–152 °C [lit.[21] mp 153 °C]; δ_H 7.40–7.32 (3H, m, N*Ph* H-3,5 and -4), 7.24 (2H, dd, *J*=7.5, 1.9 Hz, N*Ph* H-2,6), 6.88 (1H, ddd, *J*=8.0, 7.3, 1.3 Hz, H-4′), 6.71 (1H, dd, *J*=7.3, 1.3 Hz, H-6′), 6.70 (1H, s, H-4), 6.59 (1H, dd, *J*=8.0, 1.0 Hz, H-3′), 6.33 (1H, td, *J*=7.3, 1.0 Hz, H-5′), 4.93 (2H, s, exchangeable with D_2O, N*H*$_2$), 2.41 (3H, s, CO*Me*), 2.32 (3H, s, 2-*Me*); δ_C 193.97 (s, CO), 147.03 (s, C-2′), 137.02 (s, N*Ph* C-1), 135.36 (s, C-2), 131.53 (d, C-6′), 130.18 (s, C-5), 128.70 (d, N*Ph* C-3,5), 128.60 (d, C-4′), 128.02 (d, N*Ph* C-4), 127.98 (d, N*Ph* C-2,6), 120.77 (s, C-3), 116.13 (s, C-1′), 115.33 (d, C-5′), 114.36 (d, C-3′), 110.52 (d, C-4), 28.56 (q, CO*Me*), 12.74 (q, 2-*Me*); *m*/*z* (EI) 290 (100, M^+), 275 (98), 247 (40), 130 (61), 118 (42), 77 (83), 51 (49%).

4.4. General method for the preparation of 1,3,4-substituted-pyrrolo[3,2-*c*]quinoline derivatives (4a–f)

To a solution of aminopyrroles **3a**–**e** (0.57 mmol), in DMF (5 ml) commercial aldehydes (0.63 mmol) and catalytic amount of *p*-TsOH (15 mol%) were added. After stirring at 100 °C for 1–3 h, (TLC monitorage) the mixture was allowed to reach room temperature. Evaporation of the solvent under reduced pressure gave rise a dark residue which was dissolved in dichloromethane (30 ml) and washed with 3×10 ml of 5% aqueous $NaHCO_3$ solution. The organic extracts dried with $MgSO_4$ and evaporated in vacuo afforded a solid which was purified by column chromatography (eluant dichloromethane/ethyl acetate, 9:1, followed by recrystallization from ethanol).

In the case of aminopyrrole **3b**, along with the compound **4b** obtained in 85% of yield, compound **5** was isolated in 2% of yield.

4.4.1. 3-Ethylester-2-methyl-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinoline 4a. Yield 84%; white crystals, mp 273–274 °C; [found: C, 79.62; H, 5.48; N, 6.87. $C_{27}H_{22}N_2O_2$ requires C, 79.78; H, 5.46; N, 6.89%]; ν_{max} 1709 (CO) cm^{-1}; δ_H 8.08 (1H, dd, *J*=8.0, 1.3 Hz, H-6), 7.78–7.74 (3H, m, N*Ph* H-3,5 and -4), 7.71–7.61 (4H, m, N*Ph* H-2,6 and *Ph* H-2,6), 7.58–7.46 (4H, m, H-7 and *Ph* H-3,5 and -4), 7.22 (1H, ddd, *J*=8.1, 7.4, 1.3 Hz, H-8), 6.88 (1H, dd, *J*=8.1, 1.1 Hz, H-9), 3.58 (2H, q, *J*=7.2 Hz, C*H*$_2$Me), 2.31 (3H, s, 2-*Me*), 0.74 (3H, t, *J*=7.2 Hz, CH_2*Me*); δ_C 163.01 (s, CO), 151.86 (s, C-4), 144.07 (s, C-5a), 141.89 (s, *Ph* C-1), 137.88 (s, C-2 and N*Ph* C-1), 135.33 (s, C-9b), 130.66 (d, N*Ph* C-3,5), 130.45 (d, N*Ph* C-4), 129.97 (d, C-6), 128.75 (d, N*Ph* C-2,6), 128.29 (d, *Ph* C-4), 128.05 (d, *Ph* C-2,6 and -3,5), 126.95 (d, C-7), 125.58 (d, C-8), 119.91 (d, C-9), 116.70 (s, C-3a), 115.97 (s, C-9a), 115.62 (s, C-3), 60.00 (t, *C*H$_2$Me), 13.33 (q, CH_2*Me*), 11.65 (q, 2-*Me*); *m*/*z* (EI) 406 (92, M^+), 377 (100), 361 (61), 333 (46), 255 (13), 180 (19), 165 (34), 77 (20%).

4.4.2. 3-Acetyl-2-methyl-4-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline 4b. Yield 85%; yellow crystals, mp 157–158 °C; [found: C, 80.15; H, 5.39; N, 9.30. $C_{20}H_{16}N_2O$ requires C, 79.98; H, 5.37; N, 9.33%]; ν_{max} 3225 (NH), 1647 (CO) cm^{-1}; δ_H 12.89 (1H, s, exchangeable with D_2O, N*H*), 8.39 (1H, dd, *J*=7.6, 1.5 Hz, H-9), 8.06 (1H, dd, *J*=8.0,1.3 Hz, H-6), 7.70–7.60 (4H, m, H-7, H-8, and *Ph* H-2,6), 7.51–7.48 (3H, m, *Ph* H-3,5 and -4), 2.55 (3H, s, 2-*Me*), 1.58 (3H, s, CO*Me*); δ_C 196.85 (s, CO), 153.66 (s, C-4), 143.25 (s, C-5a), 142.08 (s, *Ph* C-1), 138.98 (s, C-2), 135.26 (s, C-9b), 129.25 (d, C-6), 128.75 (d, *Ph* C-4), 128.59 (d, *Ph* C-3,5), 128.42 (d, *Ph* C-2,6), 127.22 (d, C-7), 125.99 (d, C-8), 120.84 (d, C-9), 117.74 (s, C-3), 116.14 (s, C-3a), 116.08 (s, C-9a), 31.24 (q, CO*Me*), 12.83 (q, 2-*Me*); *m*/*z* (EI) 300 (64, M^+), 285 (75), 255 (27), 128 (100), 114 (30%).

4.4.3. 3-Acetyl-1,2-dimethyl-4-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline 4c. Yield 77%; yellow crystals, mp 184–185 °C; [found: C, 80.31; H, 5.75; N, 8.93. $C_{21}H_{18}N_2O$ requires C, 80.23; H, 5.77; N, 8.91%]; ν_{max} 1651 (CO) cm^{-1}; δ_H 8.56 (1H, dd, *J*=8.0, 1.1 Hz, H-9), 8.11 (1H, dd, *J*=7.8, 1.1 Hz, H-6), 7.70–7.55 (4H, m, *J* H-7, H-8 and *Ph* H-2,6), 7.51–7.47 (3H, m, *Ph* H-3,5 and -4), 4.13 (3H, s, N*Me*), 2.47 (3H, s, 2-*Me*), 1.51 (3H, s, CO*Me*); δ_C 197.76 (s, CO), 153.22 (s, C-4), 144.02 (s, C-5a), 141.73 (s, *Ph* C-1), 139.26 (s, C-2), 134.70 (s, C-9b), 129.66 (d, C-6), 128.76 (d, *Ph* C-4), 128.54 (d, *Ph* C-3,5), 128.40 (d, *Ph* C-2,6), 126.59 (d, C-7), 125.73 (d, C-8), 121.25 (d, C-9), 117.51 (s, C-3), 116.71 (s, C-9a), 115.70 (s, C-3a), 34.15 (q, N*Me*), 31.46 (q, CO*Me*), 10.94 (q, 2-*Me*); *m*/*z* (EI) 314 (89, M^+), 299 (100), 283 (47), 255 (53), 127 (65), 114 (31%).

4.4.4. 3-Acetyl-1-ethyl-2-methyl-4-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline 4d. Yield 84%; yellow crystals, mp 197–198 °C; [found: C, 80.37; H, 6.16; N, 8.50. $C_{22}H_{20}N_2O$ requires C, 80.46; H, 6.14; N, 8.53%]; ν_{max} 1667 (CO) cm^{-1}; δ_H 8.50 (1H, dd, *J*=8.0, 1.2 Hz, H-9), 8.17 (1H, dd, *J*=8.1, 1.1 Hz, H-6), 7.75–7.65 (4H, m, H-7, H-8, and *Ph* H-2,6), 7.55–7.51 (3H, m, *Ph* H-3,5 and -4), 4.69 (2H, q, *J*=7.2 Hz, C*H*$_2$Me), 2.54 (3H, s, 2-*Me*), 1.52 (3H, s, CO*Me*), 1.50 (3H, t, *J*=7.2 Hz, CH_2*Me*); δ_C 197.83 (s, CO), 152.95 (s, C-4), 142.80 (s, C-5a), 140.47 (s, *Ph* C-1), 139.20 (s, C-2), 133.94 (s, C-9b), 129.20 (d, C-6), 128.88 (d, *Ph* C-4), 128.63 (d, *Ph* C-2,6), 128.58 (d, *Ph* C-3,5), 126.63 (d, C-7), 125.46 (d, C-8), 121.10 (d, C-9), 118.12 (s, C-3), 116.05 (s, C-3a and C-9a), 40.61 (t, *C*H$_2$Me), 31.46 (q, CO*Me*), 14.70 (q, CH_2*Me*), 10.52 (q, 2-*Me*); *m*/*z* (EI) 328 (88, M^+), 313 (100), 285 (56), 255 (41), 128 (19%).

4.4.5. 3-Acetyl-2-methyl-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinoline 4e. Yield 94%; yellow crystals, mp 259–260 °C; [found: C, 83.15; H, 5.37; N, 7.45. $C_{26}H_{20}N_2O$ requires C, 82.95; H, 5.35; N, 7.44%];. ν_{max} 1664 (CO) cm^{-1}; δ_H 8.10 (1H, dd, *J*=8.0, 1.1 Hz, H-6), 7.78–7.72 (5H, m, *Ph* H-2,6 and N*Ph* H-3,5 and -4), 7.63 (2H, dd, *J*=7.2, 1.9 Hz, N*Ph* H-2,6), 7.57–7.53 (4H, m, H-7 and *Ph* H-3,5 and -4), 7.24 (1H, ddd, *J*=8.0, 7.4, 1.1 Hz, H-8), 6.90 (1H, dd, *J*=8.0, 1.3 Hz, H-9), 2.20 (3H, s, 2-*Me*), 1.64 (3H, s, CO*Me*); δ_C 197.72 (s, CO), 153.43 (s, C-4), 143.81 (s, C-5a), 141.32 (s, *Ph*C-1), 139.64 (s, C-2), 137.76 (s, N*Ph* C-1), 135.17 (s, C-9b), 130.59 (d, N*Ph* C-3,5), 130.33 (d, N*Ph* C-4), 129.51 (d, C-6), 128.95 (d, *Ph*C-4), 128.65 (d, N*Ph* C-2,6 and *Ph*C-3,5), 128.47 (d, *Ph*C-2,6), 127.06 (d, C-7), 125.65 (d, C-8), 120.00 (d, C-9), 118.20 (s, C-3), 115.98 (s, C-9a), 115.90 (s, C-3a), 31.43 (q, CO*Me*), 11.55 (q, 2-*Me*); *m*/*z* (EI) 376 (49, M^+), 361 (100), 255 (8), 180 (16), 165 (17), 77 (11%).

4.4.6. 3-Acetyl-2-methyl-4-(5-methylfuran-2yl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline 4f. Yield 72%; yellow crystals, mp 252–253 °C; [found: C, 78.69; H, 5.28; N, 7.38. $C_{25}H_{20}N_2O_2$ requires C, 78.93;H, 5.30; N, 7.36%]; ν_{max} 1672 (CO) cm^{-1}; δ_H 8.02 (1H, dd, *J*=8.1, 1.1 Hz, H-6), 7.76–7.73 (3H, m, N*Ph* H-3,5 and -4), 7.63 (2H, dd, *J*=7.1, 2.3 Hz, N*Ph* H-2,6), 7.53 (1H, ddd, *J*=8.1, 7.0, 1.3 Hz, H-7), 7.19 (1H, ddd, *J*=8.2, 7.0, 1.1 Hz, H-8), 7.13 (1H, d, *J*=3.5 Hz, *Furanyl* H-3), 6.84 (1H, dd, *J*=8.2, 1.3 Hz, H-9), 6.38 (1H, d, *J*=3.5 Hz, *Furanyl* H-4), 2.34 (3H, s, Furanyl-*Me*), 2.20 (3H, s, 2-*Me*), 2.01 (3H, s, CO*Me*); δ_C 197.60 (s, CO), 153.09 (s, *Furanyl* C-5), 152.16 (s, C-4), 143.92 (s, C-5a), 143.16 (s, *Furanyl* C-2), 138.73 (s, C-2), 137.81 (s, N*Ph* C-1), 135.13 (s, C-9b), 130.52 (d, N*Ph* C-3,5), 130.25 (d, N*Ph* C-4), 129.45 (d, C-6), 128.69 (d, N*Ph* C-2,6), 126.98 (d, C-7), 125.28 (d, C-8), 119.93 (d, C-9), 117.99 (s, C-3), 116.09 (s, C-9a), 114.20 (s, C-3a), 111.30 (d, *Furanyl* C-3), 108.71 (d, *Furanyl* C-4), 31.34 (q, CO*Me*), 13.26 (q, Furanyl-*Me*), 11.33 (q, 2-*Me*); *m*/*z* (EI) 380 (98, M^+), 365 (82), 337 (100), 293 (33), 77 (21), 43 (18%).

4.4.7. 2-Acetyl-3-methyl-5-phenyl-5,6-dihydro-pyrrolo[1,2-*c*]quinazoline 5. Yield 2%; yellow crystals, mp 195–196 °C; [found: C, 79.41; H, 5.97; N, 9.18. $C_{20}H_{18}N_2O$ requires C, 79.44; H, 6.00; N, 9.26%]; ν_{max} 3342 (NH), 1641 (CO) cm^{-1}; δ_H 7.52 (1H, d, *J*=7.4 Hz, H-10), 7.33 (1H, s, exchangeable with D_2O, N*H*), 7.27–7.23 (3H, m, H-3′,5′ and -4′), 7.06 (1H, s, H-1), 6.98 (1H, dd, *J*=7.8, 7.4 Hz, H-8), 6.92 (2H, dd, *J*=7.5, 1.1 Hz, H-2′,6′), 6.75 (1H, t, *J*=7.4 Hz, H-9), 6.72 (1H, d, *J*=7.8 Hz, H-7), 6.62 (1H, s, H-5), 2.43 (3H, s, 3-*Me*), 2.40 (3H, s, CO*Me*); δ_C 194.06 (s, CO), 141.29 (s, C-6a), 138.32 (s, C-1′), 132.28 (s, C-3), 128.54 (d, C-3′,5′), 128.01 (d, C-8), 127.23 (d, C-4′), 126.23 (s, C-10b), 125.21 (d, C-2′,6′), 121.88 (d, C-10), 121.59 (s, C-2), 118.55 (d, C-9), 115.95 (s, C-10a), 115.11 (d, C-7), 103.81 (d, C-1), 65.51 (d, C-5), 28.58 (q, CO*Me*), 10.85 (q, 3-*Me*); *m*/*z* (EI) 302 (94, M^+), 287 (17), 259 (20), 225 (100), 77 (10), 43 (15%).

4.4.8. Preparation of substituted pyrazolo[1,5-*a*]pyrimidine derivatives (6 and 8). When 3-amino-5-methyl-1*H*-pyrazole was employed as amine, under conditions specified in Section 4.2, 1-(2-nitro-phenyl)-2-(2,5,7-trimethyl-pyrazolo[1,5-*a*]pyrimidin-6-yl)-1-ethanone **6** was isolated (yield 60%) and crystallized from ethanol as white crystals, mp 149–150 °C; [found: C, 62.84; H, 4.99; N, 17.18. $C_{17}H_{16}N_4O_3$ requires C, 62.95; H, 4.97; N, 17.27%]; ν_{max} 1705 (CO), 1545 and 1350 (NO_2) cm^{-1}; δ_H 8.17 (1H, d, *J*=8.0 Hz, H-3′), 8.00 (1H, d, *J*=7.4 Hz, H-6′), 7.94 (1H, t, *J*=7.4 Hz, H-5′), 7.82 (1H, dd, *J*=8.0, 7.4 Hz, H-4′), 6.36 (1H, s, H-3), 4.57 (2H, s, CH_2), 2.67 (3H, s, 7-*Me*), 2.48 (3H, s, 5-*Me*), 2.41 (3H, s, 2-*Me*); δ_C 198.51 (s, CO), 157.94 (s, C-5), 153.13 (s, C-2), 147.30 (s, C-3a), 145.92 (s, C-2′), 143.94 (s, C-7), 135.41 (s, C-1′), 134.25 (d, C-5′), 131.91 (d, C-4′), 128.27 (d, C-6′), 124.47 (d, C-3′), 110.67 (s, C-6), 94.30 (d, C-3), 41.22 (t, *C*H_2), 23.23 (q, 5-*Me*), 14.30 (q, 2-*Me*), 13.41 (q, 7-*Me*); *m*/*z* (EI) 324 (30, M^+), 174 (100), 81 (53), 53 (34%).

Reduction of **6** under the conditions specified in Section 4.3 gave the 1-(2-amino-phenyl)-2-(2,5,7-trimethyl-pyrazolo[1,5-*a*]pyrimidin-6-yl)-1-ethanone **8**: yield 85%; white crystals, mp 177–178 °C; [found: C, 69.40; H, 6.18; N, 18.99. $C_{17}H_{18}N_4O$ requires C, 69.37; H, 6.16; N, 19.03%]; ν_{max} 3437 and 3350 (NH_2), 1616 (CO) cm^{-1}; δ_H 8.06 (1H, d, *J*=7.4 Hz, H-6′), 7.30 (1H, dd, *J*=8.2, 7.4 Hz, H-4′), 7.16 (2H, s, exchangeable with D_2O, NH_2), 6.80 (1H, d, *J*=8.2 Hz, H-3′), 6.63 (1H, t, *J*=7.4 Hz, H-5′), 6.33 (1H, s, H-3), 4.52 (2H, s, CH_2), 2.58 (3H, s, 7-*Me*), 2.41 (3H, s, 2-*Me*), 2.34 (3H, s, 5-*Me*); δ_C 197.91 (s, CO), 158.04 (s, C-5), 152.68 (s, C-2), 151.26 (s, C-2′), 147.24 (s, C-3a), 143.36 (s, C-7), 134.45 (d, C-4′), 131.33 (d, C-6′), 117.02 (d, C-3′), 116.15 (s, C-1′), 114.47 (d, C-5′), 113.07 (s, C-6), 94.06 (d, C-3), 37.81 (t, *C*H_2), 23.26 (q, 5-*Me*), 14.30 (q, 2-*Me*), 13.38 (q, 7-*Me*); *m*/*z* (EI) 294 (33, M^+), 201 (19), 174 (33), 120 (100), 92 (30), 65 (29).

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References and notes

1. (a) Khan, M. A.; Fereira da Rocha, J. *J. Heterocycl. Chem.* **1978**, *15*, 913–921. (b) Kang, S. K.; Park, S. S.; Kim, S. S.; Choi, J. K.; Yum, E. K. *Tetrahedron Lett.* **1999**, *40*, 4379–4382.
2. Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Piztenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685.
3. Khan, M. A.; Fereira da Rocha, J. *Heterocycles* **1979**, *12*, 857–872.
4. (a) Dudouit, F.; Houssin, R.; Hénichart, J. P. *J. Heterocycl. Chem.* **2001**, *38*, 755–758. (b) Helissey,; Parrot-Lopez, H.; Renault, J.; Cros, S. *Eur. J. Med. Chem.* **1987**, *22*, 366–368. (c) Helissey, P.; Giorgi-Renault, S.; Parrot-Lopez, H.; Renault, J.; Cros, S. *Chem. Pharm. Bull.* **1989**, *37*, 2413–2416. (d) Helissey, P.; Cros, S.; Giorgi-Renault, S. *Anticancer Drug Des.* **1994**, *9*, 51–67.

5. (a) Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem.* **1990**, *33*, 527–533. (b) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951–8955.
6. (a) Wright, G. C.; Watson, E. J.; Ebetino, F. F.; Lougheed, G.; Stevenson, B. F.; Winterstein, A.; Bickerton, R. K.; Halliday, R. P.; Pals, D. T. *J. Med. Chem.* **1971**, *14*, 1060–1066. (b) Shonafinger, K.; Ong, H. U. (Hoechst-Roussel Pharmaceuticals, Inc., USA). Eur. Pat. Appl., 1988, CAN 110:38974 AN 1989:38974.
7. Skonicki, J. S.; Kearney, R. M. US 5, 216, 162, and references cited therein.
8. Lovely, J. C.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079–2082.
9. Helissey, P.; Parrot-Lopez, H.; Renault, J.; Cros, S. *Chem. Pharm. Bull.* **1987**, *35*, 3547–3557.
10. (a) Gurjar, M. K.; Pal, S.; Rama Rao, A. V. *Heterocycles* **1997**, *45*, 231–234. (b) Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627–1638.
11. Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453–1464.
12. (a) Mingoia, F. *Tetrahedron* **2001**, *57*, 10147–10153. (b) Mingoia, F.; Diana, P.; Barraja, P.; Lauria, A.; Almerico, A. M. *Heterocycles* **2000**, *53*, 1975–1985. (c) Almerico, A. M.; Mingoia, F.; Diana, P.; Barraja, P.; Montalbano, A.; Lauria, A.; Loddo, R.; Sanna, L.; Delpiano, D.; Setzu, M. G.; Musiu, C. *Eur. J. Med. Chem.* **2002**, *37*, 3–10. (d) Passannanti, A.; Diana, P.; Mingoia, F.; Barraja, P.; Lauria, A.; Cirrincione, G. *J. Heterocycl. Chem.* **1998**, *35*, 1535–1537. (e) Passannanti, A.; Diana, P.; Barraja, P.; Mingoia, F.; Lauria, A.; Cirrincione, G. *Heterocycles* **1998**, *48*, 1229–1235.
13. Aiello, E.; Dattolo, G.; Cirrincione, G.; Plescia, S.; Daidone, G. *J. Heterocycl. Chem.* **1979**, *16*, 209–211.
14. Aiello, E. *Atti Accad. Sci. Lett., Arti Palermo* **1970**, *30*, 237–241, CA: **1972**, Vol. 77, 152110p.
15. (a) Scindo, H.; Fujishita, T.; Sasatani, T.; Chomei, N.; Takada, S. *Heterocycles* **1989**, *29*, 899–912. (b) Khan, M. A.; Fereira da Rocha, J. *J. Heterocycl. Chem.* **1978**, *15*, 913–921. Kang, S. K.; Park, S. S.; Kim, S. S.; Choi, J. K.; Yum, E. K. *Tetrahedron Lett.* **1999**, *40*, 4379–4382. (c) Dudouit, F.; Houssin, R.; Hénichart, J. P. *J. Heterocycl. Chem.* **2001**, *38*, 755–758. Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem.* **1990**, *33*, 527–533. (d) Helissey, P.; Parrot-Lopez, H.; Renault, J.; Cros, S. *Chem. Pharm. Bull.* **1987**, *35*, 3547–3557. (e) Mekheimer, R. A. *Synthesis* **2000**, *14*, 2078–2084. (f) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2078–2084. (g) JPN. Kokai Tokkyo Koho **2001**, *203*, 855, 28 August, 2001.
16. Burns, G. D.; Coe, P. L.; Andrews, C. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 552–557.
17. Görlitzer, K.; Heinrici, C. *Pharmazie* **1998**, *53*, 847–853.
18. Leach, C. A.; Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem.* **1992**, *35*, 1845–1852.
19. Aiello, E.; Dattolo, G.; Cirrincione, G.; Almerico, A. M.; D'Asdia, I. *J. Heterocycl. Chem.* **1981**, *18*, 1153–1155.
20. Aiello, E.; Dattolo, G.; Cirrincione, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1–3.
21. Dattolo, G.; Cirrincione, G.; Almerico, A.; D'Asdia, I.; Aiello, E. *Heterocycles* **1982**, *19*, 681–686.
22. Dattolo, G.; Cirrincione, G.; Aiello, E. *J. Heterocycl. Chem.* **1980**, *17*, 701–703.
23. Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256–8262.
24. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
25. Aliphatic aldehydes will be considered in further studies.