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DIPYRROLO[1,2-*a*:1',2'-*c*]QUINAZOLINE, A NEW RING SYSTEM OF BIOLOGICAL INTEREST[§]

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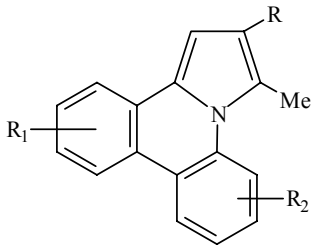
Abstract - Dipyrrolo[1,2-*a*:1',2'-*c*]quinazoline derivatives (**10a-c**) and (**11b,c**) were obtained in moderate to good yields by trifluoromethanesulfonic acid catalyzed decomposition of 2-(3-azidophenyl)-1-(1*H*-pyrrol-2-yl)pyrroles (**8a-c**), through cyclisation of the protosolvated intermediates arylnitrenium ions (**9**).

DNA represents one of the most important molecular cellular targets of several anticancer drugs. Molecular planarity shape is a structural feature commonly required for the DNA-intercalating agents,[1] which are able to insert between the stacked base paired oligonucleotides. Increasing interest towards the phenanthridine portion, which has been proposed as an effective pharmacophore in the classes of DNA-interactive compounds[2] and the current clinical success of natural fagaridine,[3] a benzo[*c*]phenanthridine alkaloid, has drawn considerable attention on the synthesis[4] and the biological evaluation of related compounds.[5]

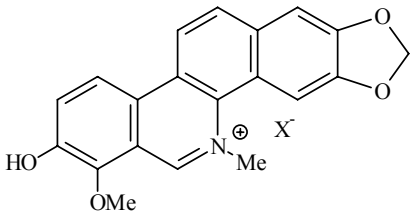
As part of our research program aimed to develop new polycyclic molecules through 1-heteroaryl-pyrroles as key intermediates, and to explore their biological properties, we became interested in the synthesis of the new ring system dipyrrolo[1,2-*a*:1',2'-*c*]quinazoline (**DPQ**) as bioisoster of pyrrolo[1,2-*f*]-phenanthridines (**PPH**), which showed *in vitro* antiproliferative activity against cell lines derived from human tumors in the range 5-50 μM[6] and an *in vitro* anti-HIV-1 activity at noncytotoxic concentrations for MT-4 cells. In particular, amino-methoxy-PPH derivatives proved a moderate but selective anti-HIV-1 activity (targeting the reverse transcriptase) coupled with a stimulation of the multiplication of T lymphocytes.

On the basis of these premises we planned the synthesis of the title compounds and of other related polycondensed heterocycles following a synthetic pathway involving arylnitrenium intermediates of type

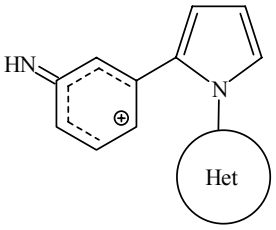
(**1**)**,** analogues of intermediates (**2**) and (**3**) successfully utilized for the preparation of substituted **PPH**,[7,8] which also had the advantage of introducing an amino group in crucial position for a better DNA-intercalation.[2]



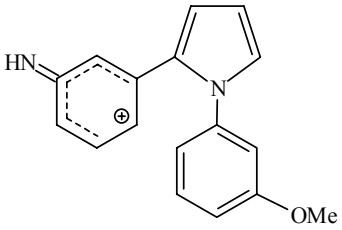
PPH



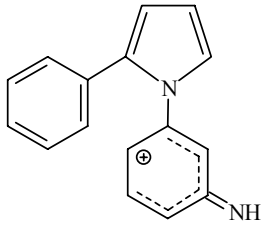
fagaridine



1



2

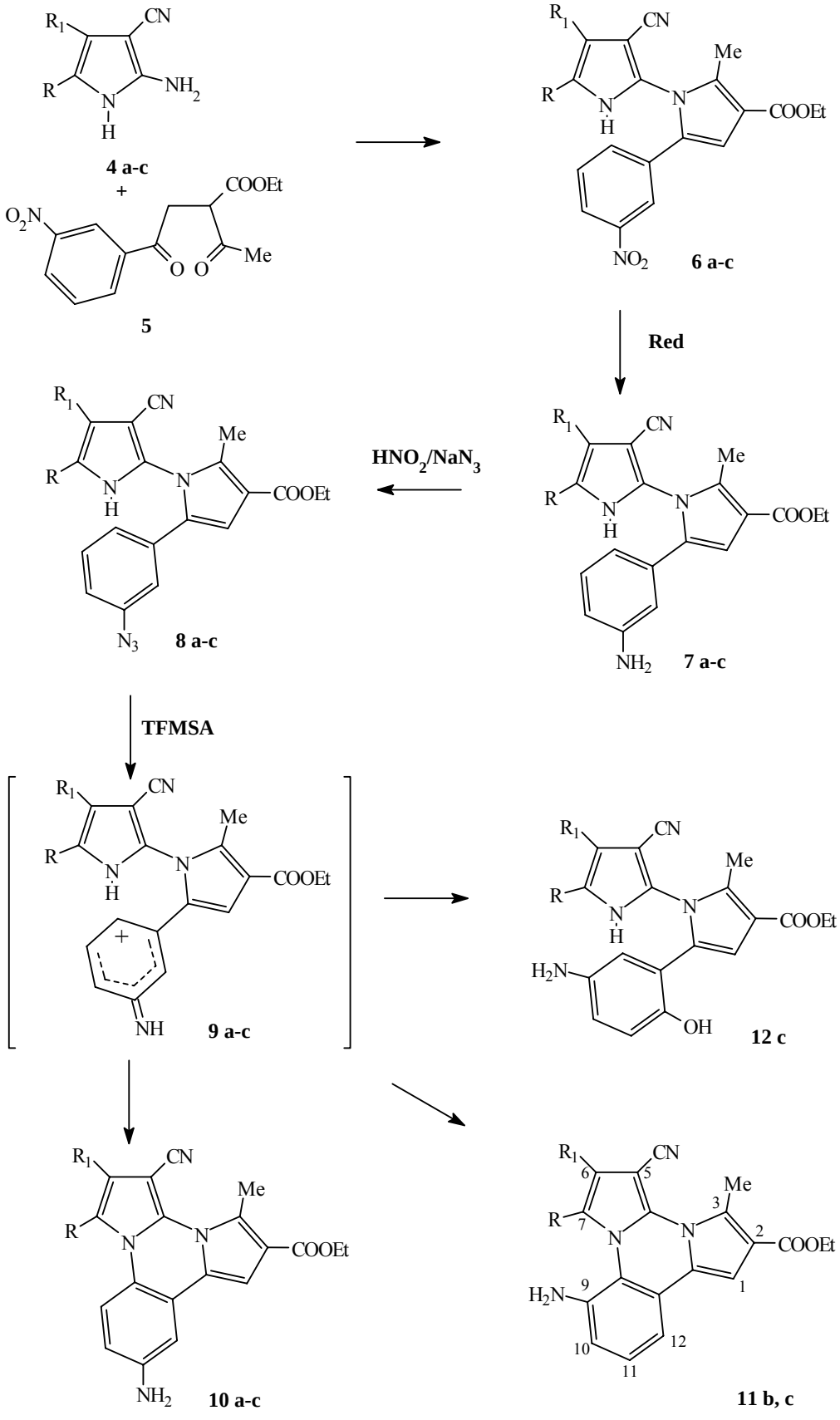


3

In the case of intermediate (**2**), the cyclization did take place only in the presence of an activating methoxy group in the suitable position on the N-linked ring. Such an intermediate, as π-carbocation, needs a sufficient high electron density of the attacking substrates under the reaction conditions. In the intermediate of type (**3**), the same electronic effects exerted by the the pyrrole nitrogen enhanced the electrophilic character of the π-carbocation allowing the cyclization even in the absence of a methoxy group. It has to be expected that the intermediate arylnitrenium ion of type (**1**), in which an electron rich five membered heterocycle replaced the activated 1-phenyl substituent of (**2**)**,** can result more prone to the cyclization reaction.

The synthesis started from the opportune substituted 2-(3-azidophenyl)-1-(1*H*-pyrrol-2-yl)pyrroles (**8**) which were easily obtained as shown in Scheme 1. Reaction of 1,4-diketone (**5**) with 2-amino-3-cyanopyrroles (**4a-c**) in acetic acid at reflux for 4-8 h, afforded the 2-(3-nitrophenyl)pyrroles (**6a-c**) in moderate to good yield (65-94%). Catalytic reduction of the nitro group at room temperature over palladium on charcoal, produced the amino compounds (**7a-c**), which were treated with sodium nitrite in acid solution followed by addition of an excess of sodium azide to give the 2-(3-azidophenyl)pyrroles (**8a-c**) in good yields (81-98%). The structure of these compounds was confirmed by spectroscopic data. In fact, the IR spectra showed bands at *ca.* 2110, 2224 and 3200 cm^{-1}, due to N_3, CN, and NH respectively. The NMR spectra, in addition to all the other expected signals, exhibited a signal at 12.25-12.86 δ, exchangeable with D_2O, relative to N-H.

Scheme 1



a: R = H, R1 = Ph; b: R = R1 = Me; c: R = Ph, R1 = Me.

The azido derivatives (**8a-c**) were decomposed in dichloromethane solution by treatment with a two fold excess of trifluoromethanesulfonic acid (**TFMSA)** from 0 °C to room temperature. From the reaction mixture, it was possible to isolate the 11- and 9-amino-dipyrrolo[1,2-*a*:1',2'-*c*]quinazolines of type (**10**) and (**11**), in moderate to good overall yields. As expected, in fact, the electronic effect that the pyrrole nucleus exerts in the intermediate protosolvated arylnitrenium ions of type (**9**) makes the 1-pyrrolyl moiety nucleophilic enough to allow the cyclization even in the strong acid media. Steric effects play a minor role with this aryl π-carbocation since it was possible to isolate even the derivatives (**11b,c**) originated from cyclization in the *ortho* position. In the case of (**8c**) a little amount of the hydroxyphenyl derivative of type (**12**) was also isolated, probably due to the competing intermolecular nucleophilic reactions with triflate or water, as already observed in previous reports.[7,8] In the case of the azide (**8a**), the fact that was only isolated the 11-amino derivative in low yield has probably to be ascribed to the fact that a pyrrole moiety unsubstituted at the α-position undergoes extensive decomposition under the strong acid reaction conditions.

All structures were confirmed by IR, NMR, MS spectroscopies and elemental analysis. The comparison of the ^{1}H NMR data with those of other related compounds already described,[7-10] and the use of additivity rules for the effect of the substituents allowed us to assign the resonances of all the protons. In particular it is possible to evidence, in the case of derivatives of type (**10**), a moderate downfield shift (0.2 - 0.4 ppm) of the resonances attributable to H-9 and H-12, this last further deshielded (up to 0.6 ppm) in compounds (**11**), with respect to the chemical shifts of the protons in the amines (**7**). Moreover, the H-2 of the pyrrolyl moiety in compound (**7a**, R = H), becomes H-7 in (**10a**, R = H), experienced the largest shift (~ 1.2 ppm) following the ring closure to the polycyclic ring system.

To investigate the potential ability of DPQ compounds of types (**10**) and (**11)** to interact with DNA, we run structure optimization *in vacuo* by using PIMMS V1.47 and VAMP V6.1 softwares supplied by Oxford Molecular.[11] Preliminary results show that the DPQ ring system can be regarded as a pharmacophore as shown by the good fitting between derivative (**10b**) and PPH or fagaridine (R.M.S. in the range 0.0039 – 0.0109).

In summary this synthetic method involving the acid decomposition of suitable 2-(3-azidophenyl)-1-(1*H*-pyrrol-2-yl)pyrroles represents a convenient access to 9-amino and/or 11-aminodipyrrolo[1,2-*a*:1',2'-*c*]-quinazoline in yields depending on the nature of the substituents on the 1-pyrrolyl moiety. The new ring system seems to possess all the requisite for DNA-interaction.

EXPERIMENTAL

All melting points were taken on a Büchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a JASCO FT/IR 5300 spectrophotometer; ^{1}H and ^{13}C NMR spectra were

measured at 200 and 50.3 MHz respectively in DMSO-d_6 solution, using a Bruker AC-E series 200 MHz spectrometer (TMS as internal reference); MS 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.

Substituted 2-aminopyrroles (**4a-c**)[12-14] and ethyl 1-(3-nitrophenacyl)-1,4-pentandione-3-carboxylate **5**[8] were prepared according to literature procedure.

General method for the preparation of 4,5-disubstituted ethyl 1-(3-cyanopyrrol-2-yl)-2-methyl-5-(3-nitrophenyl)pyrrole-3-carboxylate (6a-c).

A solution of ethyl 1-(3-nitrophenacyl)-1,4-pentanedione-3-carboxylate (**5**) (4.4 g 15 mmol) and aminopyrrole (**4a-c**) (15 mmol) in acetic acid (50 mL) was heated under reflux for 6 h. After cooling, the resultant brown mixture was poured onto ice-water. The solid formed was filtered off, air dried, purified by column chromatography (eluant dichloromethane), and recrystallized from ethanol.

Ethyl 1-(3-cyano-4-phenylpyrrol-2-yl)-2-methyl-5-(3-nitrophenyl)pyrrole-3-carboxylate (**6a**): yield 65%, mp 215°C; 3225 (NH), 2222 (CN), 1672 (CO), 1529 and 1346 (NO_2) cm^{-1}; ^1H δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 7.09 (s, 1H, pyrrole H-4), 7.31 (dt, J = 7.8, 1.9 Hz, 1H, H-6'), 7.44 (t, J = 7.8 Hz, 1H, H-5'), 7.53 (s, 1H, pyrrole H-5'), 7.55-7.72 (m, 5H, C_6H_5), 7.79 (d, J = 1.9 Hz, 1H, H-2'), 8.08 (dt, J = 7.8, 1.9 Hz, 1H, H-4'), 11.99 (s, 1H, NH); ^{13}C 11.45 (q), 14.33 (q), 59.59 (t), 111.41 (d), 113.77 (d), 116.79 (s), 120.37 (d), 121.92 (d), 125.30 (s), 125.80 (d), 127.29 (d), 128.92 (d), 128.93 (s), 130.25 (d), 131.39 (s), 131.84 (s), 132.01 (s), 132.24 (s), 132.26 (s), 132.95 (d), 139.96 (s), 147.80 (s), 163.76 (s); MS: m/z 440 (M^+). Anal. Calcd for $C_{25}H_{20}N_4O_4$: C, 68.17; H, 4.58; N, 12.72. Found: C, 68.30 ; H, 4.56; N, 13.10.

Ethyl 1-(3-cyano-4,5-dimethylpyrrol-2-yl)-2-methyl-5-(3-nitrophenyl)pyrrole-3-carboxylate (**6b**): yield 90%, mp 203-204°C; 3248 (NH), 2232 (CN), 1703 (CO), 1533 and 1348 (NO_2) cm^{-1}; ^1H δ 1.34 (t, J = 6.7 Hz, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.29 (q, J = 6.7 Hz, 2H, CH_2), 7.09 (s, 1H, pyrrole H-4), 7.57 (dt, J = 7.3, 1.2 Hz, 1H, H-6'), 7.64 (t, J = 7.3 Hz, 1H, H-5'), 7.84 (d, J = 1.2 Hz, 1H, H-2'), 8.09 (dt, J = 7.3, 1.2 Hz, 1H, H-4'), 12.35 (s, 1H, NH); ^{13}C 9.31 (q), 10.26 (q), 11.47 (q), 14.31 (q), 59.57 (t), 91.75 (s), 111.28 (d), 113.61 (s), 114.48 (s), 116.41 (s), 120.46 (d), 121.71 (d), 124.88 (s), 127.05 (s), 130.08 (d), 132.01 (s), 132.51 (s), 132.76 (d), 140.16 (s), 147.89 (s), 163.87 (s); MS: m/z 392 (M^+). Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.02; H, 5.15; N, 14.33.

Ethyl 1-(3-cyano-4-methyl-5-phenylpyrrol-2-yl)-2-methyl-5-(3-nitrophenyl)pyrrole-3-carboxylate (**6c**): yield 94%, mp 203-205°C; 3231 (NH), 2216 (CN), 1678 (CO), 1533 and 1346 (NO_2) cm^{-1}; ^1H: δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.29 (q, J = 7.1 Hz, 2H, CH_2), 7.11 (s, 1H, pyrrole H-4), 7.30-7.79 (m, 5H, C_6H_5), 7.43 (d, J = 8.2 Hz, 1H, H-6'), 7.63 (t, J = 8.2 Hz, 1H, H-5'), 7.82 (s, 1H, H-2'), 8.09 (d, J = 8.2 Hz, 1H, H-4'), 12.94 (s, 1H, NH); ^{13}C 10.94 (q), 11.60 (q), 14.34 (q), 59.64 (t), 93.64 (s), 111.43 (d), 113.86 (s), 114.05 (s), 117.79 (s), 120.51 (d), 121.83 (d), 127.25 (d), 127.59 (d), 128.63 (s), 128.82 (d), 129.22 (s), 130.17 (d), 130.82 (s), 132.19 (s), 132.47 (s), 133.02 (s), 140.21 (d), 147.87 (s), 163.88 (s); MS: m/z 454 (M^+). Anal. Calcd for $C_{26}H_{22}N_4O_4$: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.84; H, 4.86; N, 12.37.

General method for the preparation of 4,5-disubstituted ethyl 5-(3-aminophenyl)-1-(3-cyano-pyrrol-2-yl)-2-methylpyrrole-3-carboxylate (7a-c).

A solution of nitro derivatives (**6a-c**) (8 mmol) in ethanol (50 mL) was reduced overnight with hydrogen over 10% Pd on charcoal (0.1 g) in a Parr apparatus at 50 psi at rt. Removal of the catalyst and evaporation of the solvent under reduced pressure gave the amino derivatives (**7a-c**) which were purified by recrystallization from ethanol.

Ethyl 5-(3-aminophenyl)-1-(3-cyano-4-phenylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**7a**) yield 91%, mp 217°C; 3425 and 3358 (NH_2), 3213 (NH), 2226 (CN), 1651 (CO) cm^{-1}; ^1H δ 1.31 (t, J = 6.8 Hz, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.26 (q, J = 6.8 Hz, 2H, CH_2), 5.10 (s, 2H, NH_2), 6.18 (d, J = 7.6 Hz, 1H, H-4'), 6.46 (d, J = 7.6 Hz, 1H, H-6'), 6.58 (s, 1H, H-2'), 6.67 (s, 1H, pyrrole H-4), 6.90 (t, J = 7.6 Hz, 1H, H-5'), 7.30 (t, J = 6.8 Hz, 1H, H-4''), 7.43 (t, J = 7.6 Hz, 2H, H-3'' and H-5''), 7.45 (s, 1H, pyrrole H-5'), 7.67 (d, 2H, J = 7.6 Hz, H-2'' and H-6''), 12.76 (s, 1H, NH); ^{13}C 11.38 (q), 14.36 (q), 59.38 (t), 88.62 (s) 108.85 (d), 112.79 (d), 113.10 (s), 113.27 (d), 113.92 (d), 115.10 (s), 116.13 (d), 124.75 (s), 125.67 (d), 127.12 (d), 128.89 (d), 128.90 (d), 131.46 (s), 132.53 (2s), 135.64 (s), 138.44 (s), 148.76 (s), 164.10 (s); MS: m/z 410 (M^+). Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.36; H, 5.42; N, 13.67.

Ethyl 5-(3-aminophenyl)-1-(3-cyano-4,5-dimethylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**7b**): yield 70%, mp 208-210°C; 3375 and 3275 (NH_2), 3189 (NH), 2214 (CN), 1692 (CO) cm^{-1}; ^1H δ 1.30 (t, J = 7.0 Hz, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.10 (s, 3H, CH_3) 2.30 (s, 3H, CH_3), 4.23 (q, J = 7.0 Hz, 2H, CH_2), 5.0 7 (s, 2H, NH_2), 6.11 (d, J = 7.3 Hz, 1H, H-4'), 6.44 (d, 1H, J = 7.3 Hz, H-6'), 6.53 (s, 1H, H-2'), 7.09 (s, 1H, pyrrole H-4), 6.88 (t, J = 7.3 Hz, 1H, H-5'), 12.05 (bs, 1H, NH); ^{13}C 9.43 (q), 10.34 (q), 11.36 (q), 14.37 (q), 59.30 (t), 91.28 (s), 108.63 (d), 112.70 (d), 112.72 (s), 113.13 (d), 113.82 (d), 114.89 (s), 115.79 (s),

124.02 (s), 128.07 (s), 128.81 (d), 131.56 (s), 135.50 (s), 138.56 (s), 148.70 (s) 164.12 (s); MS: m/z 362 (M^+). Anal. Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.52; H, 6.10; N, 15.86.

Ethyl 5-(3-aminophenyl)-1-(3-cyano-4-methyl-5-phenylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**7c**): yield 90%, mp 215-216°C; 3373 and 3275 (NH_2), 3192 (NH), 2218 (CN), 1695 (CO) cm^{-1}; ^1H δ 1.31 (t, J = 6.9 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.25 (q, J = 6.9 Hz, 2H, CH_2), 5.10 (s, 2H, NH_2), 6.22 (d, J = 7.6 Hz, 1H, H-4'), 6.47 (d, J = 7.6 Hz, 1H, H-6'), 6.59 (s, 1H, H-2'), 6.66 (s, 1H, pyrrole H-4), 6.90 (t, J = 7.6 Hz, 1H, H-5'), 7.33 (t, 1H, J = 7.6 Hz, H-4"), 7.46 (t, J= 7.6 Hz, 2H, H-3" and H-5"), 7.52 (d, J = 7.6 Hz, 2H, H-2" and H-6"), 12.65 (s, 1H, NH); ^{13}C 11.18 (q), 11.52 (q), 14.40 (q), 59.40 (t), 93.31 (s), 108.83 (d), 112.86 (d), 113.03 (s), 113.28 (d), 114.07 (d), 114.43 (s), 117.34 (s), 127.02 (d), 127.34 (d), 127.76 (s), 128.81 (d), 128.87 (d), 130.32 (s), 130.92 (s), 131.59 (s), 135.73 (s), 138.56 (s), 148.76 (s), 164.17 (s); MS: m/z 424 (M^+). Anal. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.27; H, 5.68; N, 13.25.

General method for the preparation of 4,5-disubstituted ethyl 5-(3-azidophenyl)-2-methyl-1-(3-cyanopyrrol-2-yl)pyrrole-3-carboxylate (8a-c).

To a solution of the amines **(7a-c**) (10 mmol) in acetic acid (20 mL) sodium nitrite (690 mg, 10 mmol) in water (20 mL) was added at 0-5°C. After stirring for 1 h sodium azide (1.3 g, 20 mmol) in small portions was added at rt. The reaction mixture was stirred for further 24 h at rt and then poured onto crushed ice/water. The solid was filtered off, air dried and recrystallized from ethanol.

Ethyl 5-(3-azidophenyl)-1-(3-cyano-4-phenylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**8a**): yield 98%, mp 173-175°C; 3202 (br NH), 2222 (CN), 2099 (N_3), 1672 (CO) cm^{-1}; ^1H δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 6.75 (s, 1H, H-2'), 6.95 (s, 1H, pyrrole H-4), 6.97 (d, J = 8.3 Hz, 1H, H-4'), 7.05 (d, J = 8.3 Hz, 1H, H-6'), 7.31 (t, J = 8.3 Hz, 1H, H-5'), 7.33 (t, J = 7.6 Hz, 1H, H-4"), 7.44 (t, J = 7.6 Hz, 2H, H-3" and H-5"), 7.51 (s, 1H, pyrrole H-5'), 7.65 (d, J= 7.6 Hz, 2H, H-2" and H-6"), 12.87 (bs, 1H, NH); ^{13}C (ppm): 11.38 (q), 14.36 (q), 59.38 (t), 88.62 (s) 108.85 (d), 112.79 (d), 113.10 (s), 113.27 (d), 113.92 (d), 115.10 (s), 116.13 (d), 124.75 (d), 125.67 (d), 127.11 (s), 128.89 (d), 131.46 (s), 132.53 (s), 135.64 (s), 138.44 (s), 148.76 (s), 132.95 (d), 139.96 (s), 147.80 (s), 164.10 (s); MS: m/z 410 (M^+-26). Anal. Calcd for $C_{25}H_{20}N_6O_2$: C, 68.79; H, 4.62; N, 19.26. Found: C, 68.99; H, 4.68; N, 19.27.

Ethyl 5-(3-azidophenyl)-1-(3-cyano-4,5-dimethylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**8b**): yield 81%, mp 188-190°C; 3173 (NH), 2218 (CN), 2105 (N_3), 1664 (CO) cm^{-1}; ^1H δ 1.31 (t, J = 7.1 Hz, 3H,

CH_3), 2.02 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.26 (q, J = 7.1 Hz, 2H, CH_2), 6.61 (brs, 1H, H-2'), 6.92 (s, 1H, pyrrole H-4), 6.94 (d, J = 7.9 Hz, 1H, H-4'), 7.09 (d, 1H, J = 7.9 Hz, H-6'), 7.34 (t, J = 7.9 Hz, 1H, H-5'), 12.25 (bs, 1H, NH); ^{13}C 9.37 (q), 10.31 (q), 11.42 (q), 14.36 (q), 59.47 (t), 91.54 (s), 110.23 (d), 113.23 (s), 114.54 (s), 115.71 (d), 116.27 (s), 118.04 (d), 123.41 (d), 124.56 (s), 127.41 (s), 130.25 (d), 132.63 (s), 133.09 (s), 139.45 (s), 139.54 (s) 169.18 (s); MS: m/z 362 (M^+-26). Anal. Calcd for $C_{21}H_{20}N_6O_2$: C, 64.94; H, 5.19; N, 21.64. Found: C, 64.74; H, 5.20; N, 21.72.

Ethyl 5-(3-azidophenyl)-1-(3-cyano-4-methyl-5-phenylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**8c**): yield 86%, mp 170-172°C; 3225 (NH), 2224 (CN), 2105 (N_3), 1672 (CO) cm^{-1}; ^{1}H: δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 6.72 (br s, 1H, H-2'), 6.90-6.99 (m, 2H, H-4' and pyrrole H-4), 7.12 (d, 1H, J = 7.5 Hz, H-6'), 7.30-7.40 (m, 2H, H-5' and H-4"), 7.41-7.58 (m, 4H, H-2", H-3", H-5", and H-6"), 12.80 (s, 1H, NH); ^{13}C 11.07 (q), 11.53 (q), 14.37 (q), 59.52 (t), 93.40 (s), 110.38 (d), 113.46 (s), 114.11 (s), 116.03 (d), 117.60 (s), 118.14 (d), 123.54 (d), 127.05 (d), 127.34 (s), 127.50 (d), 128.19 (s), 128.82 (d), 129.60 (s), 130.28 (d), 130.68 (s), 132.60 (s), 133.28 (s), 139.50 (s), 163.94 (s); MS m/z 424 (M^+-26). Anal. Calcd for $C_{26}H_{22}N_6O_2$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.52; H, 4.89; N, 18.68.

Decomposition of the azido compounds (8a-c) in TFMSA.

To a solution of the azido derivatives (**8a-c**) (6 mmol) in dry dichloromethane (50 mL) trifluoromethanesulfonic acid (1.8 g, 12 mmol) was added dropwise at 0°C. The reactants were allowed to stand at rt and stirred for further 24 h. The reaction mixture was evaporated under reduced pressure, treated with a saturated solution of sodium bicarbonate (150 mL), and extracted with dichloromethane (4 x 100 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a brown residue which was chromatographed.

In the case of the decomposition of derivative **(8a**) elution with dichloromethane/ethyl acetate (95:05) gave ethyl 11-amino-5-cyano-3-methyl-6-phenyldipyrrolo[1,2-*a*:1',2'-*c*]quinazoline-2-carboxylate (**10a**) (30%), which was recrystallized from ethanol, mp 213-214°C; 3474 and 3354 (NH_2), 2226 (CN), 1688 (CO) cm^{-1}; ^{1}H δ 1.38 (t, J = 6.9 Hz, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.28 (q, J = 6.9 Hz, 2H, CH_2), 5.59 (s, 2H, NH_2), 6.38 (dd, J = 7.2, 1.3 Hz, 1H, H-10), 6.78 (d, J = 8.7 Hz, 1H, H-9), 7.00 (d, J = 1.3 Hz, 1H, H-12), 7.06 (s, 1H, H-1), 7.48-7.58 (m, 3H, H-3, H-4' and H-5'), 7.81 (dd, J = 7.7, 1.0 Hz, 2H, H-2' and H-6'), 7.90 (s, 1H, H-7); ^{13}C 12.01 (q), 14.23 (q), 59.86 (t), 108.45 (d), 109.71 (d), 110.66 (s), 113.09 (d), 116.12 (s), 116.83 (s), 126.55 (d), 126.88 (d), 127.72 (s), 128.97 (d), 129.33 (d), 129.65 (s), 131.03 (s),

132.88 (s), 136.43 (s), 143.64 (d), 150.49 (2s), 162.35 (s), 163.41 (s); MS: m/z 408 (M^+). Anal. Calcd for $C_{25}H_{20}N_4O_2$: C, 73.51; H, 4.94; N, 13.72. Found: C, 73.33; H, 4.96; N, 13.75.

In the case of the decomposition of derivative **(8b**) elution with dichloromethane/ethyl acetate (95:05) gave a first fraction (25%) which was identified as a mixture (5:1) of (**10b**) and ethyl 9-amino-5-cyano-3,6,7-trimethyldipyrrolo[1,2-*a*:1',2'-*c*]quinazoline-2-carboxylate (**11b**): ^{1}H δ 1.06 (t, J = 7.0 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 4.32 (q, J = 7.0 Hz, 2H, CH_2), 5.51 (s, 2H, NH_2), 6.61 (dd, J = 8.4, 1.5 Hz, 1H, H-10), 6.96 (s, 1H, H-1), 6.98-7.00 (m, 1H, H-11), 7.22 (dd, J = 8.4, 1.5 Hz, 1H, H-12); MS: m/z 360 (M^+).
Further elution with dichloromethane/ethyl acetate (95:05) gave ethyl 11-amino-5-cyano-3,6,7-trimethyldipyrrolo[1,2-*a*:1',2'-*c*]quinazoline-2-carboxylate (**10b**) (40%), which was recrystallized from ethanol, mp 168-170°C; 3482 and 3399 (NH_2), 2226 (CN), 1688 (CO) cm^{-1}; ^{1}H δ 1.32 (t, J = 7.0 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.26 (q, J = 7.0 Hz, 2H, CH_2), 5.56 (s, 2H, NH_2), 6.56 (dd, J = 8.5, 1.9 Hz, 1H, H-10), 6.96 (s, 1H, H-1), 7.00 (d, J = 1.9 Hz, 1H, H-12), 7.35 (d, J = 8.5 Hz, 1H, H-9); ^{13}C 10.99 (q), 12.06 (q), 12.84 (q), 14.22 (q), 59.78 (t), 107.70 (d), 109.79 (d), 111.74 (s), 113.90 (d), 114.53 (s), 115.28 (s), 115.92 (s), 121.87 (s), 126.61 (d), 126.99 (s), 129.76 (s), 136.00 (s), 150.25 (s), 151.19 (s), 159.97 (s), 163.52 (s); MS: m/z 360 (M^+). Anal. Calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 69.84; H, 5.57; N, 15.61.

In the case of the decomposition of derivative **(8c**) elution with dichloromethane/ethyl acetate (95:05) gave ethyl 9-amino-5-cyano-3,6-dimethyl-7-phenyldipyrrolo[1,2-*a*:1',2'-*c*]quinazoline-2-carboxylate (**11c**) (10%), which was recrystallized from ethanol, mp 111-113°C; 3461 and 3383 (NH_2), 2222 (CN), 1691 (CO) cm^{-1}; ^{1}H δ 1.27 (t, J = 7.2 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 4.66 (s, 2H, NH_2), 6.58 (d, J = 8.2 Hz, 1H, H-10), 6.67 (s, 1H, H-1), 6.92 (d, J = 8.2 Hz, 1H, H-12), 7.19 (t, J = 8.2 Hz, 1H, H-11), 7.50-7.66 (m, 3H, H-3', H-4', and H-5'), 7.95-8.00 (m, 2H, H-2' and H-6'); ^{13}C 9.54 (q), 14.34 (q), 15.21 (q), 59.12 (t), 95.39 (s), 100.43 (d), 108.08 (d), 112.50 (s), 115.09 (d), 116.06 (s), 116.48 (s), 126.38 (s), 128.68 (d), 128.85 (d), 131.31 (d), 131.57 (s), 131.80 (d), 133.56 (s), 133.66 (s), 136.02 (s), 143.79 (s), 156.52 (s), 164.24 (s), 175.23 (s); MS: m/z 422 (M^+). Anal. Calcd for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.69; H, 5.23; N, 13.31.
Further elution with dichloromethane/ethyl acetate (9:1) gave ethyl 5-(5-amino-2-hydroxyphenyl)-1-(3-cyano-4-methyl-5-phenylpyrrol-2-yl)-2-methylpyrrole-3-carboxylate (**12c**) (10%), which was recrystallized from ethanol, mp 169-170°C; 3499-3383 (NH_2, OH, and NH), 2224 (CN), 1697 (CO) cm^{-1}; ^{1}H δ 1.34 (t, J = 7.0 Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.60 (bs, 1H, OH), 4.28 (q, J = 7.0 Hz, 2H, CH_2), 5.62 (s, 2H, NH_2), 6.62 (dd, J = 8.2, 2.5 Hz, 1H, H-4'), 7.01 (s, 1H, pyrrole H-4), 7.05

(d, J = 2.5 Hz, 1H, H-6'), 7.42-7.59 (m, 4H, H-3', H-3", H-4", and H-5"), 7.79 (dd, J = 7.0, 1.2 Hz, 2H, H-2" and H-6"), 12.33 (s, 1H, NH); ^{13}C 12.07 (q), 12.95 (q), 14.25 (q), 59.80 (t), 107.94 (d), 109.00 (d), 111.56 (s), 113.91 (d), 115.68 (s), 116.69 (s), 122.42 (s), 126.66 (d), 127.09 (d), 128.21 (d), 128.61 (d), 129.04 (s), 129.72 (s), 132.41 (s), 136.29 (s), 150.43 (s), 151.42 (s), 160.03 (s), 163.50 (s), 171.23 (s); MS: m/z 440 (M^+). Anal. Calcd for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72. Found: C, 70.74; H, 5.50; N, 12.75.

Further elution with dichloromethane/ethyl acetate (9:1) gave ethyl 11-amino-5-cyano-3,6-dimethyl-7-phenyldipyrrolo[1,2-*a*:1',2'-*c*]quinazoline-2-carboxylate (**10c**) (70%), which was recrystallized from ethanol, mp 145-146°C; 3490 and 3374 (NH_2), 2222 (CN), 1689 (CO) cm^{-1}; ^{1}H δ 1.28 (t, J = 6.9 Hz, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.20 (q, J = 6.9 Hz, 2H, CH_2), 5.54 (s, 2H, NH_2), 6.42 (dd, J = 8.1, 1.5 Hz, 1H, H-10), 6.64 (s, 1H, H-1), 6.80 (d, J = 8.1 Hz, 1H, H-9), 6.83 (d, J = 1.5 Hz, 1H, H-12), 7.50-7.65 (m, 3H, H-3', H-4', and H-5'), 7.91 (d, J = 7.3 Hz, 2H, H-2' and H-6'); ^{13}C 9.82 (q), 14.38 (q), 14.81 (q), 59.11 (t), 95.24 (s), 100.47 (d), 104.82 (d), 112.28 (d), 112.68 (s), 116.19 (s), 121.08 (s), 122.57 (d), 128.20 (s), 128.54 (d), 128.85 (d), 131.58 (d), 131.66 (s), 133.55 (s), 134.34 (s), 135.93 (s), 151.01 (s), 154.33 (s), 164.25 (s), 174.90 (s); MS: m/z 422 (M^+). Anal. Calcd for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.69; H, 5.23; N, 13.29.

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