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Reactivity of 5-(3-azidophenyl)-1-(1*H*-pyrrol-3-yl)pyrroles in TFMSA. A route for new ring systems as DNA-interactive agents

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Abstract—Acid catalyzed decomposition of 5-(3-azidophenyl)-1-(1*H*-pyrrol-3-yl)pyrroles did not afford the expected dipyrrolo[2,1-*a*:3,4-*c*]-isoquinoline derivatives, but the planar dipyrrolo[2,1-*a*:3,2-*c*]isoquinoline derivatives and related non planar derivatives 11b*H*-dipyrrolo[2,1-*a*:3,2-*c*]isoquinoline derivatives. In strong acid media (trifluoromethanesulfonic acid) the α-(1-pyrrol-3yl) position even if blocked, was more prone to undergo cyclization with respect to the free β one. Despite the steric hindrance, these compounds were obtained in moderate to good overall yields, depending on the nature and position of the substituents on the 1-(1*H*-pyrrolyl) moiety.

Among DNA-interactive agents, involving intercalation as binding mode, the planar geometry of the molecule represents one of the most important structural features required for the adequate insertion between the stacked base paired oligonucleotides.[1] Such compounds are of interest both for the development of new therapeutics and in targeting specific DNA sequences.[2] To better clarify the structural features that contribute to the DNA binding, an approach may involve modifications and functionalizations of the ligand which in turn may lead from subtle to substantial changes in the binding mode, location and affinity towards DNA.[3] Moreover, the proposal of the phenanthridine moiety as an effective pharmacophore in the classes of DNA-interactive compounds[4] and the current clinical success of natural fagaridine, a phenanthro-fused alkaloid,[5] has increased the attention on the synthesis[6] and on the biological evaluation of related compounds.[7] As an extension of an ongoing effort aimed to develop new polycyclic molecules, by using 1-heteroaryl-pyrroles as key intermediates and to explore their biological properties, interest was focussed in the synthesis of the new ring system dipyrrolo[2,1-*a*:3,4-*c*]isoquinoline as structural analog of the bioactive pyrrolo[1,2-*f*]-phenanthridines (PPH),[8] and as bioisostere of the benzo-fused isoquinoline derivative (BFI), that showed intercalating ability with specific DNA sequences[9] (Fig. 1).

Previously, some synthetic aspects regarding the utility, scope and limitations of the preparation of substituted PPH,[10,11] and more recently of the dipyrrolo[1,2-*a*:1′,2′-*c*]-quinazoline (DPQ)[12] were described. In all these cases, the synthetic pathway involved arylnitrenium ions of type (**1**)–(**3**) as key intermediates. Such a synthetic strategy provides the opportunity to introduce into the different

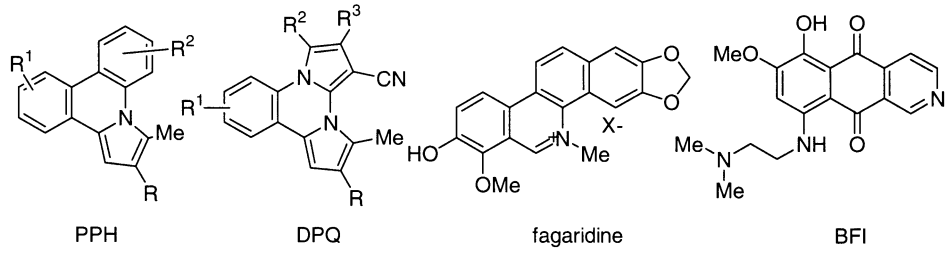

Figure 1.

Keywords: azides; arylnitrenium ions; cyclization; nitrogen heterocycles; pyrroles.
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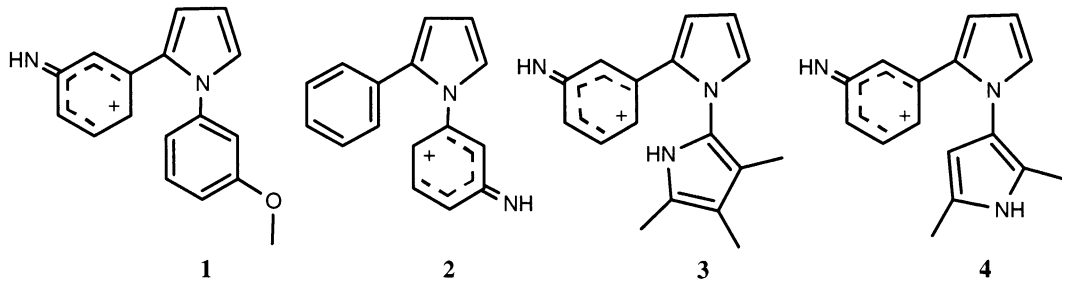


Figure 2.

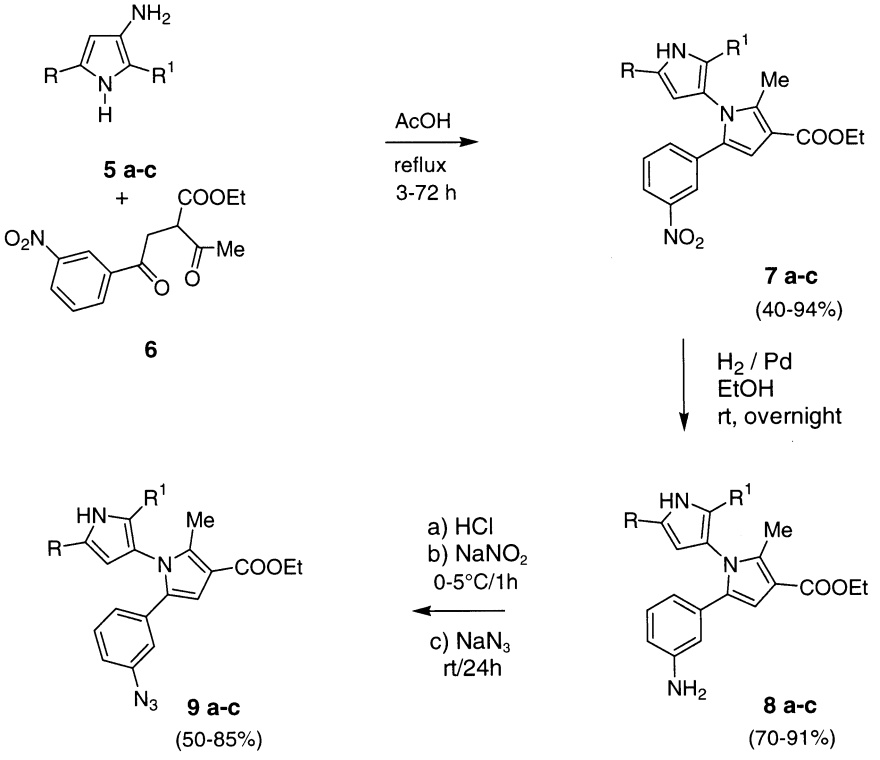
moieties of the molecule an amino group or other groups in crucial positions for better DNA-intercalation[4] by suitable choice of the starting material (Fig. 2).

Since the arylnitrenium ion behaves as a π-carbocation, a sufficiently high electron density for cyclization was required under the reaction conditions. Thus, for intermediates of type (**1**) cyclization took place only in the presence of an activating methoxy group in a suitable position on the N-linked ring. Instead, using the intermediate of type (**2**), the same electronic effects exerted by the pyrrole nitrogen enhanced the electrophilic character of the π-carbocation allowing cyclization even in the absence of a methoxy group. Upon replacement of the activated 1-phenyl substituent of (**1**) with an electron rich five membered heterocycle, as in intermediate of type (**3**), the cyclization reaction proceeded successfully as expected yielding (DPQ) derivatives even in the presence of an electron withdrawing cyano group. Taking these results into account, it was to be expected that intermediate such as (**4**) containing the isomeric pyrrole moiety should also exhibit favorable electronic requirements for cyclization.

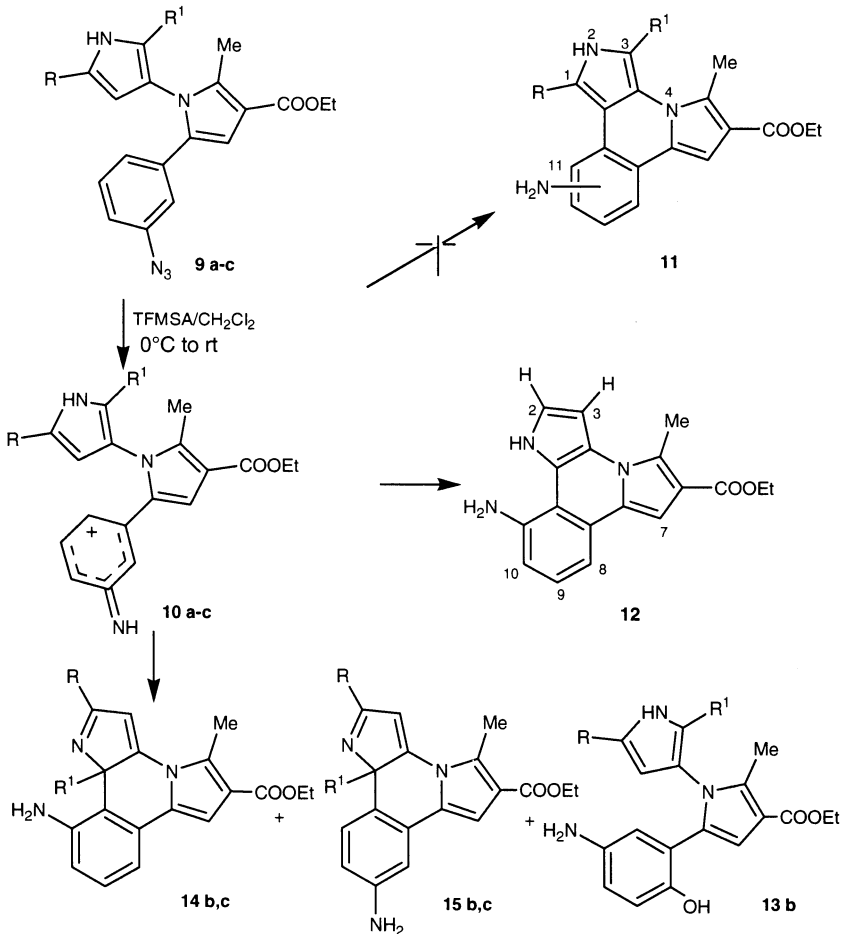
In order to investigate the reactivity of the pyrrole moiety to be attacked either as a function of its position of insertion in the entire molecule or on the nature and the position of functional groups, the behavior of intermediates of type (**4**) towards cyclization was explored, choosing at first derivatives with a simply unsubstituted β′ position.

The synthetic route is outlined in Scheme 1. The substituted ethyl 1-(pyrrol-3-yl)-5-(3-nitrophenyl)pyrrole-3-carboxylates (**7a–c**) were prepared by reacting 1,4-diketone[11] (**6**) with substituted 3-aminopyrroles[13,14] (**5a–c**) in refluxing acetic acid. After 3–72 h, depending on basicity of the amine, the nitro derivatives (**7a–c**) were obtained in moderate to good yield (40–94%). Catalytic reduction of the nitro group, at room temperature over palladium on charcoal, gave the amino compounds (**8a–c**). Diazotization at 0–5°C with sodium nitrite in acid solution followed by addition of an excess of sodium azide provided the azido derivatives (**9a–c**) in moderate to good yields (50–85%).

The spectroscopic data obtained from the IR spectra, ^{1}H and ^{13}C NMR spectra, and GC–MS furnished all the expected



Scheme 1. (a) R=H, R^1=COOEt; (b) R=Me, R^1=Ph; (c) R=R^1=Ph.



Scheme 2. (a) R=H, R^1=COOEt; (b) R=Me, R^1=Ph; (c) R=R^1=Ph.

signals for the structural characterization of all these derivatives. The pyrrole NH was detected for all derivatives. In particular, the IR spectra showed a broad peak in the range 3200–3600 cm^{-1} and in addition to all the other expected signals, the ^1H NMR spectrum, exhibited a signal at δ_H 11.12–12.29 ppm, exchangeable with D_2O. These data are in agreement with a 1*H*-pyrrole form for all derivatives.

Treatment of the azido derivative (**9a**) in dichloromethane solution from 0°C to room temperature with a two-fold excess of trifluoromethanesulfonic acid (TFMSA) within 6 h, allowed the isolation of a stable compound for which the mass spectra furnished the molecular ion at *m/z* 307 and a peak of comparable intensity at *m/z* 278 relative to the lost of an ethyl group. These data were compatible with a cyclized mono-decarboxylated structure of type (**11**, R=R^1=H) or (**12**) (Scheme 2). On the basis of the multiplicity and the coupling constants of the protons of the benzene portion, the ^1H NMR spectrum suggested the 11-amino structure (**12**). In fact the more deshielded proton H-8 appeared as a doublet coupling with H-9 (*J*=7.1 Hz) and the upfield signal relative to H-10 appeared as a doublet and coupled with the latter with *J*=8.3 Hz. The two protons H-2 and H-3 appeared as doublets at δ_H 7.2 and 6.89 ppm, respectively, with *J*=2.5 Hz. This *J* value, even if solvent dependent, results in the typical range for the α,β coupling rather than the α,α one. Therefore the cyclized product is a derivative of the dipyrrolo[2,1-*a*:3,2-*c*]isoquinoline ring system (**12**) and the expected dipyrrolo[2,1-*a*:3,4-*c*]isoquinoline (**11**) has to be ruled out.

Table 1. Representative ^{13}C NMR signals (ppm) of cyclized compounds

Carbons	Compounds				
	12	**14b**	**15b**	**14c**	**15c**
C-11b	97.15	84.93	83.67	85.21	84.13
5-Me	14.43	14.28	14.24	13.94	14.29
CO	164.96	174.03	172.81	171.74	171.62
–OCH2–	59.09	59.36	59.35	59.10	59.43
–CH3	12.97	11.41	11.47	11.38	11.62
C-2	101.68	163.84	163.85	163.86	163.89

These findings could be explained supposing that the low pH value of the medium, favored the hydrolysis and successive decarboxylation of the R^1 group (COOEt). The resulting free α 1-pyrrol-3yl position competes with the β one for the cyclization reaction giving rise to derivative (**12**) rather than (**11** R=R^1=H). In this way the cyclization reaction, that occurs in a following step, on the α position was preferred with respect to β one as it can be expected for the electrophilic attack in pyrrole series when there is competition between α and β positions.

It has to be noticed that in the reaction conditions only the

ethyl carboxylate group in the β position of the 1-pyrrolyl moiety (NH pyrrole) easily hydrolyses and has been lost, whereas the one in the β position of the pyrrole moiety (*N*-substituted) remains unaffected.

As previously observed for derivatives unsubstituted at the α,β position of the 1-pyrrolyl moiety,[12] the 11-amino derivative (**12**) was isolated in low yield (15%). This fact has probably to be ascribed to the extensive decomposition or formation of unstable by-products under the strong acid reaction conditions.

Replacing the ethyl carboxylate group with an non-hydrolizable (and bulky group), such as methyl or phenyl, it was to be expected that the free β position could be the preferable site for cyclization leading to compounds of type (**11**). Thus, azido derivatives (**9b**,**c**) were subjected to the same experimental conditions specified above.

The GC–MS analysis of the reaction mixtures revealed the presence of pairs of isomers, with molecular ions at *m*/*z* 397 and 459, respectively, in agreement with the expected cyclized compounds. In addition the peaks relative to the loss of the ethyl chain (M−29) and the phenyl group (M−77) were detected. However, no evidence for the presence of the NH was found in the IR spectrum or in the ^{1}H NMR spectra. Moreover in the ^{1}H NMR spectra, a sharp singlet at δ_H 5.75–6.82 ppm indicated that the β proton of the pyrrolyl moiety was still present together with another singlet in the range δ_H 6.66–7.30 ppm due to the pyrrole β proton *ortho* to the 3-ethyl carboxylate group. Additionally, these cyclized derivatives showed, in the ^{13}C NMR spectra, a well distinguishable quaternary carbon signal in the range δ_C 83.67–85.21 ppm as confirmed in the DEPT. This fact together with the appearance of a carbon signal in the range δ_C 163.84–163.89 ppm typical of a C=N and attributable to C-2 confirms the presence of a carbon with sp^3 hybridization and therefore a 2*H*-pyrrole like structure is proposed. In Table 1, some representative values of ^{13}C NMR signals are reported, that indicate the different pattern of signals obtained for the cyclized compounds derived from the reaction of azides (**9a**) and (**9b**,**c**).

Thus, on the basis of the spectroscopic data, the compounds isolated from the decomposition of the azido compounds (**9b**) and (**9c**), were assigned as 11- and 9-amino-11b*H*-dipyrrolo[2,1-*a*:3,2-*c*]isoquinolines of type (**14**) and (**15**), respectively. In spite of the steric hindrance due to the bulky phenyl group in the intermediate arylnitrenium ions (**10b**,**c**), the two stable isomers can be isolated in good yields including those (derivatives of type **14**) deriving from *ortho–ortho* cyclization. As evidenced from the limited side reactions, a considerably cleaner behavior was observed for intermediate (**10b**) in which the favorable electronic effects (Ph and Me group as substituents) allowed the isolation of the two possible isomers in high yields (90%), together with a little amount of the hydroxyphenyl derivative (**13**) and traces of the amine (**8b**), probably due to the competing intermolecular nucleophilic reactions with triflate or water, or by hydrogen abstraction, respectively, as already observed in previous reports.[10,11] In the case of intermediate (**10c**), the presence of two phenyl groups in the α′ and β′ positions, reduces the overall yield of the stable cyclized products to 60%. To our knowledge, the decomposition of azides (**9b**,**c**) represent the first examples of a ring closure leading to a non aromatic structure instead of the expected planar derivatives of dipyrrolo[2,1-*a*:3,4-*c*]isoquinoline of type (**11**). Although, in several examples the β pyrrolyl position has proved to be nucleophilic enough to undergo both facile protonation[15] and to undergo electrophilic attack by a weak electrophile such as –N=N$^+$, as demonstrated in the case of the synthesis of the pyrrolocinnoline ring.[16] In this cyclization, steric effects and thermodynamic aspects do not seem to play a decisive role. In fact, the ring closure occurs easily even at expense of the loss of planarity.

In summary, depending on the nature and the effect of the substituents located on the 1-pyrrol-3-yl moiety, this method represents an efficient and reproducible access to the planar 11-amino-1*H*-dipyrrolo[2,1-*a*:3,4-*c*]isoquinoline (**12**) and non planar 9- and 11-amino-2*H*-dipyrrolo[2,1-*a*:3,4-*c*]isoquinoline (**14**,**15b**,**c**). Under strong acidic reaction conditions, although blocked, the α 1-pyrrolyl position remains the favorite one to undergo electrophilic attack by arylnitrenium ion. These results indicate that 1-pyrrol-3-yl moiety exhibits nucleophilicity comparable with that of 1-pyrrol-2-yl isomers.[12] Further investigations directed to elucidate some mechanistic aspects are in progress.

1. Experimental

All melting points were taken on a Sanyo–Gallenkamp 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. Flash column chromatography was performed on Kieselgel 60 (Merck) 0.040–0.063 mm.

Substituted 3-aminopyrroles (**5a–c**)[13,14] and ethyl 1-(3-nitrophenacyl)-1,4-pentandione-3-carboxylate (**6**)[11] were prepared according to literature procedure.

1.1. General method for the preparation of 2,5-disubstituted ethyl 1-(pyrrol-3-yl)-5-(3-nitrophenyl)pyrrole-3-carboxylate (7a–c)

A solution of ethyl 1-(3-nitrophenacyl)-1,4-pentanedione-3-carboxylate (**6**) (4.4 g 15 mmol) and aminopyrrole (**5a–c**) (15 mmol) in acetic acid (50 mL) was heated under reflux for 3–72 h (TLC monitorage). 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.

1.1.1. Ethyl 1-(pyrrol-3-yl)-5-(3-nitrophenyl)pyrrole-3,2′-dicarboxylate (7a). Yellow crystals, yield 40%; MS: *m*/*z* 411 (M$^+$) was directly reduced into the amino-derivative (**8a**).

1.1.2. Ethyl 1-(5-methyl-2-phenylpyrrol-3-yl)-5-(3-nitrophenyl)pyrrole-3-carboxylate (7b). Yellow–orange crystals, yield 90%, mp 182–184°C; 3333 (NH), 1682 (CO), 1530 and 1346 (NO_2) cm^{-1}; ^1H δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.25 (q, J=7.1 Hz, 2H, CH_2), 5.99 (s, 1H, pyrrole H-4′), 6.86 (d, J=7.5 Hz, 2H, H-2 and H-6, 2′-Ph), 6.97 (s, 1H, pyrrole H-4), 7.06 (t, J=7.5 Hz, 1H, H-4, 2′-Ph), 7.18 (t, J=7.5 Hz, 2H, H-3 and H-5, 2′-Ph), 7.39 (t, J=8.1 Hz, 1H, H-5′), 7.58 (d, J=8.1 Hz, 1H, H-6′), 7.82 (s, 1H, H-2′), 7.91 (d, J=8.1 Hz, 1H, H-4′), 11.36 (s, 1H, NH); ^{13}C 11.84 (q), 12.73 (q), 14.30 (q), 59.09 (t), 106.75 (d), 110.67 (d), 112.47 (s), 117.31 (s), 120.68 (d), 123.64 (2d), 124.97 (s), 125.89 (d), 128.53 (d), 128.67 (s), 129.25 (d), 130.69 (s), 130.70 (s), 132.97 (d), 133.53 (s), 138.95 (s), 147.44 (s), 164.17 (s); MS: m/z 429 (M^+). Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 70.02; H, 5.44; N, 9.69.

1.1.3. Ethyl 1-(2-5-diphenylpyrrol-3-yl)-5-(3-nitrophenyl)pyrrole-3-carboxylate (7c). Yellow–orange crystals, yield 70%, mp 104–106°C; 3345–3290 (broad NH), 1682 (CO), 1530 and 1346 (NO_2) cm^{-1}; ^1H δ 1.31 (t, J=7.3 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.26 (q, J=7.3 Hz, 2H, CH_2), 6.86 (s, 1H, pyrrole H-4′), 6.94 (d, J=6.8 Hz, 2H, Ph), 6.96 (s, 1H, pyrrole H-4), 7.10–7.30 (m, 4H, Ph), 7.32–7.48 (m, 2H, Ph),7.39 (t, J=7.8 Hz, 1H, H-5′), 7.56 (d, J=7.8 Hz, 1H, H-6′), 7.78–7.90 (m, 2H, Ph), 7.81 (s, 1H, H-2′), 7.90 (d, J=7.3 Hz, 1H, H-4′), 11.68 (s, 1H, NH); ^{13}C 12.00 (q), 14.37 (q), 59.20 (t), 106.78 (d), 110.77 (d), 112.63 (s), 118.95 (s), 120.94 (2d), 124.40 (d), 125.06 (d), 126.67 (d), 126.76 (d), 128.21 (s), 128.45 (d), 128.65 (d), 129.38 (d), 130.14 (s), 130.91 (s), 131.62 (s), 132.03 (s),133.16 (d), 133.45 (s), 138.95 (s), 147.42 (s), 164.217 (s); MS: m/z 491.5 (M^+). Anal. Calcd for $C_{30}H_{25}N_3O_4$: C, 73.30; H, 5.13; N, 8.55. Found: C, 73.10; H, 5.17; N, 8.45.

1.2. General method for the preparation of 2,5-disubstituted ethyl 5-(3-aminophenyl)-2-methyl-1-(pyrrol-3yl)-pyrrole-3-carboxylate (8a–c)

A solution of nitro derivatives (**7a**–**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 (**8a**–**c**) which were purified by recrystallization from ethanol.

1.2.1. Ethyl 5-(3-aminophenyl)-1-(pyrrol-3-yl)-2-methylpyrrole-2′,3-dicarboxylate (8a). Pale-yellow needles, yield 90%, mp 177–178°C; 3387 (NH), 3316 and 3210 (NH_2), 1697 (CO), 1680 (CO) cm^{-1}; ^1H δ 1.02 (t, J=7.1 Hz, 3H, CH_3), 1.28 (t, J=7.1 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.99 (m, 2H, CH_2), 4.20 (q, J=7.1 Hz, 2H, CH_2), 4.93 (s, 2H, NH_2), 6.19 (d, J=7.8 Hz, 1H, H-4′), 6.20 (bs, 1H, H-2′), 6.36 (d, J=7.6 Hz, 1H, H-6′), 6.49 (s, 1H, pyrrole H-4), 6.50 (s, J=2.4 Hz, 1H, pyrrole H-4′), 6.79 (t, J=7.6 Hz, 1H, H-5′), 7.06 (d, J=2.4 Hz, 1H, pyrrole H-5′), 11.65 (s, 1H, NH); ^{13}C 11.89 (q), 13.85 (q), 14.48 (q), 58.82 (t), 59.55 (t), 108.00 (d), 110.54 (d), 111.30 (s), 112.56 (d), 113.50 (d), 115.13 (d), 117.85 (s), 122.55 (d), 126.53 (s), 128.27 (d), 133.00 (s), 135.01 (s), 137.99 (s), 148.26 (s), 159.14 (s), 164.71 (s); MS: m/z 381 (M^+). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.25; H, 6.11; N, 9.95.

1.2.2. Ethyl 5-(3-aminophenyl)-1-(5-methyl-2-phenylpyrrol-3-yl)-2-methylpyrrole-3-carboxylate (8b). Pale-yellow crystals, yield 91%, mp 219–221°C; 3408 (NH), 3327 and 3230 (NH_2), 1686 (CO) cm^{-1}; ^1H δ 1.28 (t, J=7.1 Hz, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.19 (q, J=7.1 Hz, 2H, CH_2), 4.89 (s, 2H, NH_2), 5.82 (s, 1H, pyrrole H-4′), 6.34 (d, J=7.5 Hz, 2H, H-4′ and H-6′), 6.59 (s, 1H, H-2′), 6.60 (s, 1H, pyrrole H-4), 6.76 (t, J=7.5 Hz, 1H, H-5′), 6.96 (d, J=7.1 Hz, 2H, H-2 and H-6, 2′-Ph), 7.07 (t, J=7.1 Hz, 1H, H-4, 2′-Ph), 7.21 (t, J=7.1 Hz, 2H, H-3 and H-5, 2′-Ph), 11.12 (s, 1H, NH); ^{13}C 11.68 (q), 12.83 (q), 14.34 (q), 58.82 (t), 107.48 (d), 108.56 (d), 111.61 (s), 112.51 (d), 113.21 (d), 114.86 (d), 118.36 (s), 123.28 (d), 124.54 (s), 125.60 (d), 127.73 (s), 128.27 (d), 128.59 (d), 131.09 (s), 132.76 (s), 134.33 (s), 137.61 (s), 148.16 (s), 164.43 (s); MS: m/z 399 (M^+). Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 74.85; H, 6.32; N, 10.49.

1.2.3. Ethyl 5-(3-aminophenyl)-1-(2,5-diphenylpyrrol-3-yl)-2-methylpyrrole-3-carboxylate (8c). Yellow–brown crystals, yield 70%, mp 146–148°C; 3445 and 3339 (NH_2), 3200 (NH), 1678 (CO) cm^{-1}; ^1H δ 1.29 (t, J=7.3 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.21 (q, J=7.3 Hz, 2H, CH_2), 4.94 (s, 2H, NH_2), 5.75 (s, 1H, CH, pyrrole H-4′), 6.38 (t, J=7.3 Hz, 2H, H-3 and H-5, Ph), 6.66 (s, 1H, pyrrole H-4), 6.68 (d, J=7.9 Hz, 1H, H-4′), 6.70 (s, 1H, H-2′), 6.78 (t, J=7.9 Hz, 1H, H-5′), 7.10–7.38 (m, 6H, H-2 and H-5, Ph), 7.30 (d, J=7.9 Hz, 1H, H-6′), 11.52 (s, 1H, NH); ^{13}C 11.84 (q), 14.42 (q), 58.99 (t), 107.64 (d), 108.78 (d), 111.87 (s), 112.68 (d), 113.39 (d), 114.96 (d), 120.07 (s), 124.29 (d), 124.77 (d), 126.50 (d), 126.59 (d), 128.01 (s), 128.44 (d), 128.62 (2d), 130.56 (s), 131.28 (s), 131.75 (s), 132.74 (s), 134.60 (s), 137.72 (s), 148.34 (s), 164.52 (s); MS: m/z 461 (M^+). Anal. Calcd for $C_{30}H_{27}N_3O_2$: C, 78.07; H, 5.90; N, 9.10. Found: C, 77.99; H, 5.91; N, 9.04.

1.3. General method for the preparation of 2,5-disubstituted ethyl 5-(3-azidophenyl)-2-methyl-1-(pyrrol-3yl)-pyrrole-3-carboxylate (9a–c)

To a solution of the amines (**8a**–**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.

1.3.1. Ethyl 5-(3-azidophenyl)-1-(pyrrol-3-yl)-2-methylpyrrole-2′,3-dicarboxylate (9a). Yellow–brown crystals, yield 85%, mp 79–81°C; 3431and 3293 (NH), 2105 (N_3), 1686 (CO) cm^{-1}; ^1H: δ 1.00 (t, J=6.7 Hz, 3H, CH_3), 1.29 (t, J=7.1 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.98 (m, J=6.7 Hz, 2H, CH_2), 4.23 (q, J=7.1 Hz, 2H, CH_2), 6.29 (d, J=2.2 Hz, 1H, pyrrole H-4′), 6.70–6.77 (bs, 2H, H-2′ and pyrrole H-4), 6.86 (d, J=8.2 Hz, 1H, H-4′), 7.04 (d, J=8.2 Hz, 1H, H-6′), 7.13 (d, J=2.2 Hz, 1H, pyrrole H-5′), 7.25 (t, J=8.2 Hz, 1H, H-5′), 12.29 (s, 1H, NH); ^{13}C 11.84 (q),

13.79 (q), 14.41 (q), 58.90(t), 59.58 (t), 109.28 (d), 110.36 (d), 111.78 (s), 116.88 (d), 117.12 (d), 117.84 (s), 122.93 (d), 123.92 (d), 126.00 (s), 129.70 (d), 132.70 (s), 134.04 (s), 138.88 (s), 139.00 (s), 158.90 (s), 164.40 (s); MS: *m/z* 381 (M^+-26). Anal. Calcd for $C_{21}H_{21}N_5O_4$: C, 61.91; H, 5.20; N, 17.19. Found: C, 61.78; H, 5.21; N, 17.13.

1.3.2. Ethyl 5-(3-azidophenyl)-1-(5-methyl-2-phenylpyrrol-3-yl)-2-methylpyrrole-3-carboxylate (9b). Pale-yellow, yield 70%, mp 186–188°C; 3330–3600 (br NH), 2102 (N_3), 1684 (CO) cm^{-1}; ^1H δ 1.30 (t, *J*=7.1 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.22 (q, *J*=7.1 Hz, 2H, CH_2), 5.92 (s, 1H, pyrrole H-4′), 6.76 (bs, 1H, H-2′), 6.61 (d, *J*=7.5 Hz, 1H, H-4′), 6.86 (s, 1H, pyrrole H-4), 6.74–6.94 (m, 2H, H-6′ and H-5′), 7.01–7.24 (m, 5H, 2′-Ph), 11.33 (s, 1H, NH); ^{13}C 11.79 (q), 12.77 (q), 14.33 (q), 58.99 (t), 107.06 (d), 109.83 (d), 112.14 (s), 11.35 (d), 117.04 (d), 117.78 (s), 123.43 (d), 123.69 (d), 124.76 (s), 125.78 (d), 128.39 (s), 128.57 (d), 129.53 (d), 130.80 (s), 131.88 (s), 133.79 (s), 138.52 (s), 138.88 (s), 164.28 (s); MS: *m/z* 399 (M^+-26). Anal. Calcd for $C_{25}H_{23}N_5O_2$: C, 70.57; H, 5.45; N, 16.46. Found: C, 70.45; H, 5.47; N, 16.42.

1.3.3. Ethyl 5-(3-azidophenyl)-1-(2,5-diphenylpyrrol-3-yl)-2-methylpyrrole-3-carboxylate (9c). Pale-yellow crystals, yield 50%, mp 59–60°C; 3323 (NH), 2102 (N_3), 1678 (CO) cm^{-1}; ^1H δ 1.31 (t, *J*=6.8 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 4.24 (q, *J*=6.8 Hz, 2H, CH_2), 6.79 (s, 1H, pyrrole H-4′), 6.78 (m, 1H, H-4′), 6.85 (bs, 1H, H-2′), 6.90 (s, 1H, pyrrole H-4), 7.04–7.48 (m, 8H, 2′-Ph and 5′-Ph), 7.12–7.20 (m, 2H, H-5′ and H-6′), 7.86 (d, *J*=6.8 Hz, 2H, 5′-Ph), 11.63 (s,1H, NH); ^{13}C 11.92 (q), 14.36 (q), 59.10 (t), 107.06 (d), 110.01 (d), 112.38 (s), 116.77 (d), 117.10 (d), 119.49 (s), 123.82 (d), 124.33 (d), 124.91 (d), 126.56 (d), 126.65 (d), 128.13 (s), 128.51 (d), 128.59 (d), 129.56 (d) 130.32 (s), 131.64 (s), 131.79 (s), 132.21 (s), 133.80 (s), 138.55 (s), 138.99 (s), 164.34 (s); MS: *m/z* 461 (M^+-26). Anal. Calcd for $C_{30}H_{25}N_5O_2$: C, 73.90; H, 5.17; N, 14.36. Found: C, 74.19; H, 5.19; N, 14.42.

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

To a solution of the azido derivatives (**9a–c**) (6 mmol) in dry dichloromethane (50 mL) TFMSA (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 (4×100 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 (**9a**) elution with dichloromethane/ethyl acetate (95:05) gave *ethyl 11-amino-5-methyl-1H-dipyrrolo[2,1-a:3,2-c]isoquinoline-6-carboxylate* (**12**): white flake, yield 15%, mp 212–214°C; 3403 and 3362 (NH_2), 3297 (NH), 1682 (CO) cm^{-1}; ^1H δ 1.34 (t, *J*=7.1 Hz, 3H, CH_3), 3.04 (s, 3H, CH_3), 4.27 (q, *J*=7.1 Hz, 2H, CH_2), 5.23 (bs, 2H, NH_2), 6.86 (d, *J*=8.3 Hz, H-10), 6.90 (d, *J*=2.5 Hz, 1H, H-3), 7.12 (d, *J*=7.1 Hz, 1H, H-9), 7.16 (d, *J*=2.5 Hz, 1H, H-2), 7.26 (s, 1H, H-7), 7.53 (d, *J*=7.1 Hz, 1H, H-8); ^{13}C 12.97 (q), 14.43 (q), 59.09 (t), 97.15 (d), 101.68 (d), 110.51 (s), 112.82 (s), 113.03 (d), 114.93 (d), 118.33 (s), 119.53 (d), 121.22 (s), 124.18 (s), 125.88 (d), 127.53 (s), 128.36 (s), 142.08 (s), 164.96 (s); MS: *m/z* 307. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.26; H, 5.59; N, 13.65.

In the case of the decomposition of derivative (**9b**) elution with dichloromethane/ethyl acetate (95:05) gave *ethyl 11-amino-2,5-dimethyl-11bH-11b-phenyl-dipyrrolo[2,1-a:3,2-c]isoquinoline-6-carboxylate* (**14b**) brown powder, yield 19%, mp 174–176°C; 3466 and 3310 (NH_2), 1695 (CO) cm^{-1}; ^1H δ 1.25 (t, *J*=6.9 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.19 (q, *J*=6.9 Hz, 2H, CH_2), 6.16 (bs, 2H, NH_2), 6.52 (s, 1H, H-3), 6.57 (d, *J*=8.1 Hz, H-10), 6.88 (s, 1H, H-7), 6.90–6.97 (m, 2H, H-2 and H-6, 11b-Ph), 6.92 (d, *J*=8.1 Hz, 1H, H-8), 7.06 (t, *J*=8.1 Hz, 1H, H-9), 7.12–7.22 (m, 3H, H-3, H-5 and H-4, 11b-Ph); ^{13}C 11.41 (q), 14.28 (q), 19.32 (q), 59.36 (t), 84.93 (s), 106.74 (d), 101.46 (d), 113.08 (d), 114.33 (d), 114.96 (s), 115.34 (s), 125.52 (d), 127.63 (d), 127.94 (s), 128.52 (d), 129.07 (d), 130.13 (s), 133.79 (s), 137.42 (s), 147.80 (s), 161.32 (s), 163.84 (s), 174.03 (s); MS: *m/z* 397. Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.84; H, 5.86; N, 10.52.

Further elution with dichloromethane/ethyl acetate (95:05) gave *ethyl 9-amino-2,5-dimethyl-11bH-phenyl-dipyrrolo-[2,1-a:3,2-c]isoquinoline-6-carboxylate* (**15b**): yellow powder, yield 68%, mp 235–236°C; 3476 and 3337 (NH_2), 1697 (CO) cm^{-1}; ^1H δ 1.27 (t, *J*=6.7 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.19 (q, *J*=6.7 Hz, 2H, CH_2), 5.24 (bs, 2H, NH_2), 6.45 (s, 1H, H-3), 6.58 (dd, *J*=8.1, 1.9 Hz, H-10), 6.89 (s, 1H, H-7), 6.70–6.90 (m, 2H, H-2 and H-6, 11b-Ph), 6.91 (d, *J*=1.9 Hz, 1H, H-8), 7.08–7.22 (m, 3H, H-3, H-5 and H-4, 11b-Ph), 7.43 (d, *J*=8.1 Hz, 1H, H-11); ^{13}C 11.47 (q), 14.24 (q), 19.27 (q), 59.35 (t), 83.67 (s), 105.89 (d), 108.26 (d), 113.40 (d), 113.78 (d), 114.88 (s), 121.09 (s), 125.54 (d), 127.13 (d), 127.24 (s), 128.12 (d), 128.28 (d), 129.92 (s), 134.01 (s), 140.31 (s), 148.55 (s), 161.12 (s), 163.85 (s), 172.81 (s); MS: *m/z* 397. Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.31; H, 5.86; N, 10.52.

Compound (**13b**) due to its instability was only characterized by GC–MS and presented a pattern of fragments in agreement to analogous compounds previously reported.[8,10–11] Dark powder, yield 7%, MS *m/z* 415.

In the case of the decomposition of derivative (**9c**) elution with dichloromethane/ethyl acetate (95:05) gave a first fraction (25%) which was identified as *ethyl 11-amino-5-methyl-2-phenyl-11bH-phenyl-dipyrrolo[2,1-a:3,2-c]isoquinoline-6-carboxylate* (**14c**): yellow-pale powder, yield 25%, mp 212–213°C from DMSO; 3430 and 3326 (NH_2), 1696 (CO) cm^{-1}; ^1H δ 1.34 (t, *J*=7.0 Hz, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.25 (q, *J*=7.0 Hz, 2H, CH_2), 5.93 (bs, 2H, NH_2), 6.60 (d, *J*=8.2 Hz, H-10), 6.86 (s, 1H, H-3), 6.89 (s, 1H, H-7), 6.90–7.10 (m, 5H, Ph), 7.10 (t, *J*=8.2 Hz, 1H, H-9), 7.13 (d, *J*=8.2 Hz, 1H, H-8), 7.48–7.58 (m, 3H, Ph), 8.05–8.15 (m, 2H, Ph); ^{13}C 11.38 (q), 13.94 (q), 59.10 (t), 85.21

(s), 106.62 (d), 108.47 (d), 111.55 (d), 114.32 (d), 115.16 (s), 115.65 (s), 125.29 (d), 127.30 (d), 127.43 (d), 127.87 (s), 128.11 (d), 128.29 (d), 128.73 (d), 129.89 (s), 130.88 (d), 132.51 (s), 133.63 (s), 136.85 (s), 147.12 (s), 162.84 (s), 163.86 (s), 171.74 (s); MS: *m/z* 459. Anal. Calcd for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14. Found: C, 78.25; H, 5.50; N, 9.11.

Further elution with dichloromethane/ethyl acetate (95:05) gave *ethyl 9-amino-5-methyl-2-phenyl-11bH-phenyl-dipyrrolo[2,1-a:3,2-c]isoquinoline-6-carboxylate* (**15c**): yellow–brown powder, yield 35%, mp 158–160°C; 3464 and 3379 (NH_2), 1694 (CO) cm^{-1}; ^1H: δ 1.29 (t, J= 7.0 Hz, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.22 (q, J=7.0 Hz, 2H, CH_2), 5.28 (bs, 2H, NH_2), 6.63 (d, J=8.8 Hz, H-10), 6.82 (s, 1H, H-3), 6.88–6.97 (m, 2H, Ph), 6.93 (d, J=8.8 Hz, 1H, H-11), 6.96 (s, 1H, H-8), 7.12–7.22 (m, 3H, Ph), 7.30 (s, 1H, H-7), 7.50–7.62 (m, 4H, Ph), 8.17–8.22 (m, 2H, Ph); ^{13}C 11.62 (q), 14.29 (q), 59.43 (t), 84.13 (s), 106.06 (d), 108.39 (d), 110.85 (d), 113.49 (d), 115.01 (s), 121.00 (s), 125.62 (d), 127.32 (s), 127.36 (d), 127.81 (d), 128.22 (d), 128.49 (d), 128.78 (d), 129.94 (s), 131.14 (d), 133.37 (s), 134.36 (s), 140.22 (s), 148.75 (s), 162.27 (s), 163.89 (s), 171.62 (s); MS: *m/z* 459. Anal. Calcd for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14. Found: C, 78.26; H, 5.49; N, 9.11.

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