New tri- and tetra-substituted pyrroles *via* quinazolinium N1-ylides

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Abstract

New tri- and tetra-substituted *N*-arylpyrroles were synthesized by one-pot reaction of 3,7-disubstituted quinazolinonium bromides with substituted alkynes having at least one electron-withdrawing substituent in 1,2-epoxybutane acting both as solvent and hydrogen bromide scavenger. Structural characterization of the new compounds was based on IR and NMR spectroscopy as well as on single crystal X-ray analysis.

Keywords: *N*-Arylpyrrole, 3,7-disubstituted quinazolinium N1-bromides, 1,3-dipolar cycloaddition reaction

Introduction

Tri- and tetra-substituted pyrroles are known to possess a broad range of biological activity that includes antimycobacterial action, inhibition of both neuronal and inducible nitric oxide synthases (nNOS and iNOS respectively), antifungal activity, and inhibition of oxidosqualene cyclase (OSC).¹ For this reason, efforts are constantly being directed towards finding new synthetic pathways or improving known synthetic strategies.²

Our interest in obtaining new *N*-bridgehead heterocycles by the 1,3-dipolar cycloaddition reaction of the heteroaromatic *N*-ylides³ led us to investigate the reaction between quinazolinonium N1-ylides and acetylenic dipolarophiles with the aim of obtaining pyrrolo[1,2-*a*]quinazoline derivatives. Surprisingly, instead of the expected pyrrolo[1,2-*a*]quinazolines, highly substituted pyrroles were obtained in moderate to good yields.⁴ The new tri- and tetra-substituted pyrroles were obtained starting only from unsubstituted 4(3*H*)-quinazolinone and thus the possibility of extending the reaction to substituted 4(3*H*)-quinazolinones was considered.

Herein we present the one-pot synthesis of new tri- and tetra-substituted pyrroles starting from 7-chloro-4(3*H*)-quinazolinone with different acetylenic dipolarophiles, which afford structural variety to the new series of compounds.

Results and Discussion

The new substituted pyrroles were synthesized starting from quinazolinonium *N*1 bromides **3**, which were obtained in good yields by the reaction of 3-methyl-7-chloro-4(3*H*)-quinazolinone **1** with 2-bromoacetophenones **2** according to Scheme 1.

Scheme 1

The structures of the quinazolinonium *N*1 bromides **3** were assigned by IR and NMR spectroscopy.

The IR spectra of the compounds **3** present as main characteristics the bands of the carbonyl group in COAr at 1645-1658 cm⁻¹ and at 1707-1730 cm⁻¹ for the CO group in the pyrimidine ring.

The characteristic ¹H NMR data are for the protons attached to the quinazoline moiety. The H-2 atom appears strongly deshielded as a singlet at around 10 ppm due to its vicinity to the two nitrogen atoms from the pyrimidine ring. The three protons H-5, H-6 and H-8 from the quinazoline moiety appear as follows: the atoms H-6 appears as a double doublet with the coupling constants of *J*₅₆ = 8.8 Hz and *J*₆₈ = 1.6 Hz, due to its coupling with the protons H-5 and H-8 which have the multiplicity of doublet. The ¹³C NMR spectra present the signals of the carbon atoms in the carbonyl groups in the range 156-159 ppm for the carbonyl group in the amide and 188-190 ppm for the carbonyl group in the aroyl moiety. Also characteristic of the spectra of the salts **3** are the carbon C-2, which appears at around 155 ppm (strongly deshielded due to its direct bonding to the two nitrogen atoms) and the carbon C-7 which appears at ~145 ppm due to its direct bonding with the chlorine atom.

The substituted pyrroles **5** were obtained by one-pot reaction between quinazolinonium bromides **3** and acetylenic dipolarophiles **4** in 1,2-epoxybutane as reaction medium and acid acceptor (Scheme 2, Table 1).

Scheme 2

Table 1. Tri- and tetra-substituted *N*-arylpyrroles **5a-l**

Compound	R ¹	R ²	E	Mp (°C)	Yield (%)
5a	H	H	COMe	230-232	85
5b	3-NO ₂	H	COMe	197-198	76
5c	4-Br	H	COMe	195-196	61
5d	4-MeO	H	COMe	208-210	52
5e	H	H	CO ₂ Et	182-184	67
5f	3-NO ₂	H	CO ₂ Et	193-195	43
5g	4-Cl	H	CO ₂ Et	171-173	58
5h	4-Br	H	CO ₂ Et	161-163	65
5i	4-MeO	H	CO ₂ Et	160-162	66
5j	3-NO ₂	CO ₂ Me	CO ₂ Me	199-200	58
5k	4-Br	CO ₂ Me	CO ₂ Me	222-224	47
5l	4-Cl	CO ₂ Me	CO ₂ Me	232-234	45

The reaction mechanism implies the attack of bromide ion on the 1,2-epoxypropane ring leading to its opening with formation of an alkoxide that generates the ylide **6** by its action on the quinazolinon bromide **3** (Scheme 3). The 1,3-dipolar cycloaddition reaction between the *N*-ylide **6** and acetylenic dipolarophiles gives the primary cycloadduct **7** which, under the reaction conditions, suffers a pyrimidine ring opening to the corresponding pyrroles **5**.

Scheme 3

The structures of the new pyrroles were determined by IR, NMR spectroscopy and X-ray analysis of a representative compound of this series, namely *N*-arylpyrrole **5a**. In the IR spectra of *N*-aryl pyrroles **5** the band located in the region 3244-3399 cm^{-1} is strong evidence for the presence of the NH bond in the secondary amide group.

In the ^1H NMR spectra of compounds **5** of tri-substituted pyrroles **5a-i** the protons H-3 and H-5 of the pyrrole ring appear as two doublets with a coupling constant of 1.6 Hz. The pyrrole structure of the compounds is also emphasized by the signal of Me in the MeNH group which has the multiplicity of a doublet in the range 2.65-2.80 ppm with the coupling constant of $J_{\text{MeNH}} = 4.9$ Hz. In the case of ethyl esters **5e-i** the signal for methylenic protons in the ethyl group is a multiplet instead of a quartet. The multiplicity of methylenic protons in the ^1H NMR spectrum could be attributed to hindered rotation about the N-Ar bond, as proposed earlier in the case of *N*-arylpyrazole.⁵

The X-ray structure of the representative compound **5a**⁶⁻¹⁰ is shown in Figure 1 (left). Primary torsion angles describing the overall conformation include C2-N1-C9-C14 -52.8° , C3-C4-C6-O7 3.3° , C9-C14-C16-O17 -41.3° , N1-C2-C20-O21 -19.0° and C2-C20-C22-C23 -45.3° (all e.s.d.s 0.2°). In this conformation, the bonds N18-H18 and C20=O21 adopt nearly parallel orientations, enabling two molecules of **5a** to form a centrosymmetric hydrogen-bonded dimer (Figure 1, right), in which the unique H-bond is N18-H18 $\cdots$ O21ⁱ ($i = 1/2-x, 1/2-y, 1-z$), N $\cdots$ O is 2.987(2) Å and the angle subtended at H18 is 149° . Weaker, but significant C-H $\cdots$ O hydrogen bonds complement the former hydrogen bonds in stabilizing the crystal structure.

Thus, the dimers of **5a** are in turn hydrogen bonded to one another to form infinite ribbons parallel to the crystal *b*-axis *via* a pair of inversion-related C-H $\cdots$ O hydrogen bonds. Specifically, the unique H-bond is C25-H25 $\cdots$ O7ⁱⁱ ($ii = 1/2-x, 3/2-y, 1-z$) with C $\cdots$ O 3.160(2) Å and C-H $\cdots$ O angle 142° . Additional C-H $\cdots$ O bonding with C $\cdots$ O in the range 3.304(2)-3.407(2) Å occurs, involving atom O17 as acceptor. Thus, all three oxygen atoms of **5a** engage in hydrogen bonds, stabilizing the crystal structure. Similar hydrogen bonding motifs are likely to occur in the crystals of **5b-5l**. Only one significant π -stacking interaction was evident for **5a**, namely that between the chorophenyl rings of two molecules related by the crystallographic twofold rotation axis, with centroid $\cdots$ centroid distance 3.789(1) Å. All other ring centroid $\cdots$ centroid distances exceed 4 Å.

Figure 1. Structure of **5a** with thermal ellipsoids drawn at the 50% probability level (left) and hydrogen bonded dimer of **5a** (right).

Conclusions

In conclusion, a library of highly substituted pyrroles was synthesized by a simple one-pot reaction. The structure of the new compounds was established by IR and NMR spectroscopy and was confirmed by X-ray analysis, which also provided information regarding their stereochemistry and possible intermolecular interactions in their crystals.

Experimental Section

General. Melting points were measured on Boëtius hot plate microscope and are uncorrected. IR spectra from samples prepared as KBr pellets were recorded on a Nicolet Impact 410 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Varian Gemini 300 BB instrument with CDCl_3 as solvent and TMS as internal standard. Elemental analyses for C, H and N were obtained using a COSTECH Instruments EAS32. 3-Methyl-7-chloro-4(3*H*)-quinazolinone was obtained from 4-chloroanthranilic acid and *N*-methylformamide according to the known method.¹¹ Activated acetylenic esters, 3-butyne-2-one, 2-bromoacetophenones and 4-chloroanthranilic acid were purchased from Aldrich and used further without purification.

General synthetic procedure, exemplified by 7-chloro-3-methyl-1-(2-phenyl-2-oxoethyl)-4(3H)-quinazolinon-1-ium bromide (3a)

A mixture of 3-methyl-7-chloro-4(3H)-quinazolinone **1** (1.95 g, 10 mmol) and 2-bromoacetophenone **2** (1.99 g, 10 mmol) in 40 ml methyl ethyl ketone was heated at reflux for 20 h. The obtained precipitate was filtered and recrystallized from methanol.

(3a). Colorless crystals with mp 236-8 °C, yield 75%; FT-IR ($\nu_{\max}$, cm^{-1}): 1600, 1647, 1711, 2915, 3054. $^1\text{H-NMR}$ (300 MHz, CDCl_3+TFA) δ : 3.87 (s, 3H, MeN); 6.28 (s, 2H, CH_2); 7.39 (d, 1H, $J = 1.6$ Hz, H-8); 7.55-7.61 (m, 2H, H-3', H-5'); 7.73-7.79 (m, 2H, H-6, H-4'); 8.09-8.13 (m, 2H, H-2', H-6'); 8.43 (d, 1H, $J = 8.8$ Hz, H-5); 10.08 (s, 1H, H-2). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3+TFA) δ : 36.8 (MeN); 58.7 (CH_2); 117.5, 130.8, 131.3 (C-5, C-6, C-8); 117.9, 138.7, 144.7 (C-4a, C-7, C-8a); 132.6 (C-4') 128.8, 129.5 (C-2', C-3', C-5', C-6'); 155.2 (C-2); 156.8 (CONH); 189.6 (COAr). Anal. Calcd. $\text{C}_{17}\text{H}_{14}\text{BrClN}_2\text{O}_2$: C 51.87, H 3.58, N 7.12; Found: C 51.62, H 3.40, N 7.41.

7-Chloro-3-methyl-1-[2-(3-nitrophenyl)-2-oxoethyl]-4(3H)-quinazolinon-1-ium bromide (3b).

Colorless crystals with mp 247-9 °C, yield 77%; FT-IR (cm^{-1}): 1347, 1522, 1605, 1658, 1722, 2940, 3076. $^1\text{H-NMR}$ (300 MHz, CDCl_3+TFA) δ : 3.90 (s, 3H, MeN); 6.55 (s, 2H, CH_2); 7.53 (d, 1H, $J = 1.6$ Hz, H-8); 7.78-7.85 (m, 2H, H-6, H-5'); 8.46-8.57 (m, 3H, H-5, H-4', H-6'); 8.96 (t, 1H, $J = 1.9$ Hz, H-2'); 9.92 (s, 1H, H-2). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3+TFA) δ : 37.1 (MeN); 59.2 (CH_2); 117.7, 131.0, 131.1 (C-5, C-6, C-8); 117.9, 138.7, 145.2 (C-4a, C-7, C-8a); 124.0 (C-2'); 129.8, 131.7 (C-5', C-6'); 134.0 (C-1'); 134.6 (C-4'); 148.6 (C-3'); 155.2 (C-2); 157.1 (CONH); 188.4 (COAr). Anal. Calcd. $\text{C}_{17}\text{H}_{13}\text{BrClN}_3\text{O}_4$: C 46.55, H 2.99, N 9.58; Found: C 46.81, H 3.31, N 10.26.

7-Chloro-3-methyl-1-[2-(4-chlorophenyl)-2-oxoethyl]-4(3H)-quinazolinon-1-ium bromide (3c).

Colorless crystals with mp 238-240 °C, yield 78%; FT-IR (cm^{-1}): 1595, 1649, 1711, 2924, 3082. $^1\text{H-NMR}$ (300 MHz, CDCl_3+TFA) δ : 3.88 (s, 3H, MeN); 6.27 (s, 2H, CH_2); 7.37 (d, 1H, $J = 1.6$ Hz, H-8); 7.98 (d, 2H, $J = 8.8$ Hz, H-3', H-5'); 7.79 (dd, 1H, $J = 8.8, 1.6$ Hz, H-5); 8.16 (d, 2H, $J = 8.8$ Hz, H-2', H-6'); 8.47 (d, 1H, $J = 8.8$ Hz, H-5); 9.84 (s, 1H, H-2). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3+TFA) δ : 37.1 (MeN); 58.6 (CH_2); 116.4, 131.0, 131.7 (C-5, C-6, C-8); 117.9, 130.8, 138.6, 140.0, 145.2 (C-4a, C-7, C-8a, C-1', C-4'); 130.1, 130.2 (C-2', C-3', C-5', C-6'); 155.3 (C-2); 156.9 (CONH); 188.8 (COAr). Anal. Calcd. $\text{C}_{17}\text{H}_{13}\text{BrCl}_2\text{N}_2\text{O}_2$: C 47.69, H 3.06, N 6.54; Found: C 47.91, H 3.40, N 6.28.

1-[2-(4-Bromophenyl)-2-oxoethyl]-7-chloro-3-methyl-4(3H)-quinazolinon-1-ium bromide (3d)

Colorless crystals with mp 250-2 °C, yield 73%; FT-IR (cm^{-1}): 1585, 1645, 1712, 2917, 3017. $^1\text{H-NMR}$ (300 MHz, CDCl_3+TFA) δ : 3.88 (s, 3H, MeN); 6.28 (s, 2H, CH_2); 7.38 (d, 1H, $J = 1.6$ Hz, H-8); 7.75-7.81 (m, 3H, H-6, H-3', H-5'); 7.98 (d, 2H, $J = 8.5$ Hz, H-2', H-6'); 8.47 (d, 1H, $J = 8.8$ Hz, H-5); 9.85 (s, 1H, H-2). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3+TFA) δ : 37.1 (MeN); 58.7 (CH_2); 116.4, 131.1, 131.7 (C-5, C-6, C-8); 117.5, 130.8, 132.2, 138.6, 145.1 (C-4a, C-7, C-8a, C-1', C-4'); 130.2, 133.2 (C-2', C-3', C-5', C-6'); 155.2 (C-2); 157.1 (CONH); 189.1 (COAr). Anal. Calcd. $\text{C}_{17}\text{H}_{13}\text{Br}_2\text{ClN}_2\text{O}_2$: C 43.21, H 2.77, N 5.93; Found: C 43.47, H 3.06, N 6.24.

7-Chloro-1-[2-(4-methoxyphenyl)-2-oxoethyl]-3-methyl-4(3*H*)-quinazolinon-1-ium bromide (3e). Colorless crystals with mp 253-5 °C, yield 65%; FT-IR (cm⁻¹): 1600, 1652, 1707, 2920, 3053. ¹H-NMR (300 MHz, CDCl₃+TFA) δ: 3.88, 3.95 (2s, 6H, 2Me); 6.28 (s, 2H, CH₂); 7.07 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.42 (d, 1H, *J* = 1.6 Hz, H-8); 7.79 (dd, 1H, *J* = 8.8, 1.6 Hz, H-5); 8.10 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.45 (d, 1H, *J* = 8.8 Hz, H-5); 9.61 (s, 1H, H-2). ¹³C-NMR (75 MHz, CDCl₃+TFA) δ: 37.0 (MeN); 56.0 (MeO); 58.5 (CH₂); 115.1 (C-3', C-5'); 116.4, 130.9, 131.6 (C-5, C-6, C-8); 117.9, 130.5, 138.6, 145.0 (C-4a, C-7, C-8a, C-1'); 131.8 (C-2', C-6'); 155.2 (C-2); 156.9 (CONH); 159.7 (C-4'); 188.8 (COAr). Anal. Calcd. C₁₈H₁₆BrClN₂O₃: C 51.03, H 3.81, N 6.61; Found: C 51.34, H 4.05, N 6.93.

General synthetic procedure, exemplified by 4-acetyl-2-benzoyl-1-(5-chloro-2-methylaminocarbonylphenyl)pyrrole (5a)

A suspension of 7-chloro-3-methyl-1-(2-phenyl-2-oxoethyl)-4(3*H*)-quinazolinon-1-ium bromide **3a** (1.97 g, 5 mmol) and 3-buten-2-one (0.51 g, 7.5 mmol) in 30 ml 1,2-epoxybutane is heated under reflux for 60 h. The obtained precipitate was filtered and recrystallized from methanol.

5a. Colorless crystals; FT-IR (cm⁻¹): 1633, 1655, 3066, 3398. ¹H-NMR (300 MHz, CDCl₃) δ: 2.43 (s, 3H, MeCO); 2.65 (d, 1H, *J* = 4.9, MeNH); 6.70 (1H, q, *J* = 4.9, NH); 7.22 (d, 1H, *J* = 2.1 Hz, H-6''); 7.27 (d, 1H, *J* = 1.6, H-5); 7.46 (dd, 1H, *J* = 8.2, 2.1 Hz, H-4''); 7.49-7.54 (m, 2H, H-3', H-5'); 7.59 (d, 1H, *J* = 8.2 Hz, H-3''); 7.60 (d, 1H, *J* = 1.6, H-3); 7.62-7.68 (m, 1H, H-4'); 7.91-7.94 (m, 2H, H-2', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 26.6 (MeNH); 27.4 (COMe); 121.0 (C-3); 126.3 (C-4); 127.4 (C-6''); 128.7, 130.3 (C-2', C-3', C-5', C-6'); 129.7 (C-3''); 129.9 (C-4''); 129.6, 132.9, 133.5, 136.2, 136.9, 137.8 (C-2, C-1', C-4', C-1'', C-2'', C-5''); 133.6 (C-4'); 134.4 (C-5); 166.7 (CONH); 186.5 (COAr); 192.4 (COMe). Anal. Calc. C₂₁H₁₇ClN₂O₃: C 66.23, H 4.50, Cl 9.31, N 7.36; Found: C 66.55, H 4.21, Cl 9.70, N 7.67

4-Acetyl-1-(5-chloro-2-methylaminocarbonylphenyl)-2-(3-nitrobenzoyl)pyrrole (5b).

Colorless crystals; FT-IR (cm⁻¹): 1343, 1529, 1632, 1651, 3084, 3249. ¹H-NMR (300 MHz, CDCl₃) δ: 2.46 (s, 3H, MeCO); 2.73 (d, 1H, *J* = 4.9, MeNH); 6.44 (1H, q, *J* = 4.9, NH); 7.27 (d, 1H, *J* = 2.1 Hz, H-6''); 7.29 (d, 1H, *J* = 1.6, H-5); 7.44 (dd, 1H, *J* = 8.2, 2.1 Hz, H-4''); 7.59 (d, 1H, *J* = 8.2 Hz, H-3''); 7.67 (d, 1H, *J* = 1.6, H-3); 7.74 (t, 1H, *J* = 8.0 Hz, H-5'); 8.22-8.26, 8.46-8.50 (2m, 2H, H-4', H-6'); 8.70 (t, 1H, *J* = 1.8, H-2'). ¹³C-NMR (75 MHz, CDCl₃) δ: 26.7 (MeNH); 27.4 (COMe); 121.5 (C-3); 124.5 (C-2'); 126.6 (C-4); 127.5 (C-6''); 127.6 (C-4'); 129.7 (C-3''); 129.8 (C-4''); 130.0 (C-5'); 132.5, 133.2, 136.5, 137.7, 138.7 (C-2, C-1', C-1'', C-2'', C-5''); 135.3 (C-5, C-6'); 148.4 (C-3'); 166.6 (CONH); 183.6 (COAr); 192.4 (COMe). Anal. Calc. C₂₁H₁₆ClN₃O₅: C 59.23, H 3.79, Cl 8.33, N 9.87; Found: C 59.60, H 3.54, Cl 8.71, N 10.11.

4-Acetyl-1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-bromobenzoyl)pyrrole (5c).

Colorless crystals; FT-IR (cm⁻¹): 1647, 1674, 3106, 3276. ¹H-NMR (300 MHz, CDCl₃) δ: 2.45 (s, 3H, MeCO); 2.66 (d, 1H, *J* = 4.9, MeNH); 6.57 (1H, q, *J* = 4.9, NH); 7.22 (d, 1H, *J* = 2.2 Hz, H-6''); 7.25 (d, 1H, *J* = 1.6, H-5); 7.51 (dd, 1H, *J* = 8.2, 2.2 Hz, H-4''); 7.60 (d, 1H, *J* = 8.2 Hz, H-3''); 7.60 (d, 1H, *J* = 1.6, H-3); 7.67, 7.80 (2d, 4H, *J* = 8.8, H-2', H-3', H-5', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 26.7 (MeNH); 27.4 (COMe); 121.0 (C-3); 126.4 (C-4); 127.4 (C-6''); 129.7 (C-

3''); 129.9 (C-4''); 128.8, 132.9, 133.3, 135.7, 136.4, 137.7 (C-2, C-1', C-4', C-1'', C-2'', C-5''); 134.6 (C-5); 131.4, 132.1 (C-2', C-3', C-5', C-6'); 166.6 (CONH); 185.2 (COAr); 192.4 (COMe). Anal. Calc. C₂₁H₁₆BrClN₂O₃: N 6.09; Found: N 6.31.

4-Acetyl-1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-methoxybenzoyl)pyrrole (5d).

Colorless crystals; FT-IR (cm⁻¹): 1630, 1662, 3112, 3384. ¹H-NMR (300 MHz, CDCl₃) δ: 2.44 (s, 3H, MeCO); 2.66 (d, 1H, *J* = 4.9, MeNH); 3.91 (s, 3H, MeO); 6.92 (1H, q, *J* = 4.9, NH); 7.00 (d, 2H, *J* = 9.1 Hz, H-3', H-5'); 7.17 (d, 1H, *J* = 2.1 Hz, H-6''); 7.25 (d, 1H, *J* = 1.6 Hz, H-5); 7.47 (dd, 1H, *J* = 8.2, 2.1 Hz, H-4''); 7.54 (d, 1H, *J* = 1.6 Hz, H-3); 7.62 (d, 1H, *J* = 8.2 Hz, H-3''); 7.95 (d, 2H, *J* = 9.1 Hz, H-2', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 26.6 (MeNH); 27.4 (COMe); 55.7 (MeO); 114.1 (C-3', C-5'); 119.8 (C-3); 126.2 (C-4); 127.3 (C-6''); 129.7 (C-3''); 129.4, 133.6, 133.7, 136.2, 137.7 (C-2, C-1', C-1'', C-2'', C-5''); 130.1 (C-4''); 133.9 (C-5); 132.5 (C-2', C-6'); 164.4 (C-4'); 166.8 (CONH); 185.2 (COAr); 192.7 (COMe). Anal. Calc. C₂₂H₁₉ClN₂O₄: C 64.32, H 4.66, Cl 8.63, N 6.82; Found: C 64.67, H 4.31, Cl 8.91, N 6.61.

Ethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-benzoylpyrrole-4-carboxylate (5e).

Colorless crystals; FT-IR (cm⁻¹): 1632, 1666, 1710, 2978, 3116, 3396. ¹H-NMR (300 MHz, CDCl₃) δ: 1.33 (t, 3H, *J* = 7.1, Me); 2.67 (d, 1H, *J* = 4.9, MeNH); 4.26-4.34 (m, 2H, CH₂); 6.68 (1H, q, *J* = 4.9, NH); 7.19 (d, 1H, *J* = 2.1 Hz, H-6''); 7.30 (d, 1H, *J* = 1.6, H-5); 7.47 (dd, 1H, *J* = 8.2, 2.1 Hz, H-4''); 7.47-7.56 (m, 2H, H-3', H-5'); 7.60 (d, 1H, *J* = 8.2 Hz, H-3''); 7.61 (d, 1H, *J* = 1.6, H-3); 7.62-7.68 (m, 1H, H-4'); 7.93-7.96 (m, 2H, H-2', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 14.5 (MeCH₂); 26.6 (MeNH); 60.7 (CH₂); 117.8 (C-3); 122.6 (C-4); 127.4 (C-6''); 128.7, 130.3 (C-2', C-3', C-5', C-6', C-4''); 129.6 (C-3''); 132.9, 133.5, 136.3, 137.0, 137.8 (C-2, C-1', C-1'', C-2'', C-5''); 133.6 (C-4'); 134.4 (C-5); 163.4 (COO); 166.8 (CONH); 186.4 (COAr). Anal. Calc. C₂₂H₁₉ClN₂O₄: C 64.32, H 4.66, Cl 8.63, N 6.82; Found: C 64.58, H 4.29, Cl 8.96, N 7.10.

Ethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(3-nitrobenzoyl)pyrrole-4-carboxylate (5f).

Colorless crystals; FT-IR (cm⁻¹): 1347, 1531, 1638, 1665, 1716, 2981, 3095, 3386. ¹H-NMR (300 MHz, CDCl₃) δ: 1.34 (t, 3H, *J* = 7.1, Me); 2.71 (d, 1H, *J* = 4.9, MeNH); 4.20-4.35 (m, 2H, CH₂); 6.36 (1H, q, *J* = 4.9, NH); 7.26 (d, 1H, *J* = 1.9 Hz, H-6''); 7.29 (d, 1H, *J* = 1.6, H-5); 7.51 (dd, 1H, *J* = 8.2, 1.9 Hz, H-4''); 7.61 (d, 1H, *J* = 8.2 Hz, H-3''); 7.67 (d, 1H, *J* = 1.6, H-3); 7.74 (t, 1H, *J* = 8.0 Hz, H-5'); 8.22-8.26, 8.46-8.50 (2m, 2H, H-4', H-6'); 8.72 (t, 1H, *J* = 1.8, H-2'). ¹³C-NMR (75 MHz, CDCl₃) δ: 14.5 (MeCH₂); 26.8 (MeNH); 60.9 (CH₂); 118.3 (C-4); 122.4 (C-3); 124.6 (C-2'); 127.5 (C-6''); 127.6 (C-4'); 129.7 (C-3''); 129.8 (C-4''); 130.0 (C-5'); 132.0, 133.3, 136.6, 137.8, 138.7 (C-2, C-1', C-1'', C-2'', C-5''); 135.3, 135.8 (C-5, C-6'); 148.5 (C-3'); 163.1 (COO); 166.6 (CONH); 183.5 (COAr). Anal. Calc. C₂₂H₁₈ClN₃O₆: C 57.97, H 3.98, Cl 7.78, N 9.22; Found: C 58.31, H 4.29, Cl 8.11, N 9.46.

Ethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-chlorobenzoyl)pyrrole-4-carboxylate (5g).

Colorless crystals; FT-IR (cm⁻¹): 1632, 1665, 1710, 2979, 3115, 3399. ¹H-NMR (300 MHz, CDCl₃) δ: 1.34 (t, 3H, *J* = 7.1, Me); 2.66 (d, 1H, *J* = 4.9, MeNH); 4.26-4.34 (m, 2H, CH₂); 6.59 (1H, q, *J* = 4.9, NH); 7.20 (d, 1H, *J* = 1.9 Hz, H-6''); 7.26 (d, 1H, *J* = 1.6, H-5); 7.47 (dd, 1H, *J* = 8.2, 1.9 Hz, H-4''); 7.50 (d, 2H, *J* = 8.5, H-3', H-5'); 7.59 (d, 1H, *J* = 8.2, H-3''); 7.62 (d, 1H, *J* = 1.6, H-3); 7.88 (d, 2H, *J* = 8.5, H-2', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 14.4

(MeCH₂); 26.6 (MeNH); 60.6 (CH₂); 117.8 (C-4); 122.5 (C-3); 127.4 (C-6''); 129.1, 131.3 (C-2', C-3', C-5', C-6'); 129.6 (C-3''); 129.9 (C-4''); 132.5, 133.3, 135.4, 136.3, 137.8, 140.1 (C-2, C-1', C-4', C-1'', C-2'', C-5''); 135.0 (C-5); 163.2 (COO); 166.6 (CONH); 184.9 (COAr). Anal. Calc. C₂₂H₁₈Cl₂N₂O₄: C 59.34, H 4.07, Cl 15.92, N 6.92; Found: C 59.61, H 4.44, Cl 16.29, N 6.78.

Ethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-bromobenzoyl)pyrrole-4-carboxylate (5h). Colorless crystals; FT-IR (cm⁻¹): 1638, 1661, 1711, 2979, 3058, 3315. ¹H-NMR (300 MHz, CDCl₃) δ: 1.33 (t, 3H, *J* = 7.1, Me); 2.66 (d, 1H, *J* = 4.9, MeNH); 4.09-4.33 (m, 2H, CH₂); 6.62 (1H, q, *J* = 4.9, NH); 7.21 (d, 1H, *J* = 1.9 Hz, H-6''); 7.26 (d, 1H, *J* = 1.6, H-5); 7.46 (dd, 1H, *J* = 8.2, 1.9 Hz, H-4''); 7.58 (d, 1H, *J* = 8.2 Hz, H-3''); 7.62 (d, 1H, *J* = 1.6, H-3); 7.66, 7.80 (2d, 4H, *J* = 8.8, H-2', H-3', H-5', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 14.4 (Me CH₂); 26.8 (MeNH); 60.7 (CH₂); 117.8 (C-4); 122.5 (C-3); 127.4 (C-6''); 128.7 (C-4') 132.5, 133.3, 135.9, 136.3, 137.9 (C-2, C-1', C-1'', C-2'', C-5''); 129.6 (C-3''); 129.9 (C-4''); 135.0 (C-5); 131.4, 132.0 (C-2', C-3', C-5', C-6'); 163.2 (COO); 166.6 (CONH); 185.0 (COAr). Anal. Calc. C₂₂H₁₈BrClN₂O₄: N 7.24; Found: N 7.47.

Ethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-methoxybenzoyl)pyrrole-4-carboxylate (5i). Colorless crystals; FT-IR (cm⁻¹): 1643, 1708, 2987, 3118, 3305. ¹H-NMR (300 MHz, CDCl₃) δ: 1.34 (t, 3H, *J* = 7.1, Me); 2.67 (d, 1H, *J* = 4.9, MeNH); 3.91 (s, 3H, MeO); 4.27-4.33 (m, 3H, NH, CH₂); 7.05 (d, 2H, *J* = 9.1 Hz, H-3', H-5'); 7.11 (1H, q, *J* = 4.9, NH); 7.14 (d, 1H, *J* = 1.9 Hz, H-6''); 7.26 (d, 1H, *J* = 1.6 Hz, H-5); 7.46 (dd, 1H, *J* = 8.2, 1.9 Hz, H-4''); 7.56 (d, 1H, *J* = 1.6 Hz, H-3); 7.63 (d, 1H, *J* = 8.2 Hz, H-3''); 7.95 (d, 2H, *J* = 9.1 Hz, H-2', H-6'). ¹³C-NMR (75 MHz, CDCl₃) δ: 14.4 (Me CH₂); 26.5 (MeNH); 55.7 (MeO); 60.6 (CH₂); 114.1 (C-3', C-5'); 117.5 (C-4); 121.5 (C-3); 127.3 (C-6''); 129.7 (C-3''); 129.5, 133.0, 133.6, 136.1, 137.8 (C-2, C-1', C-1'', C-2'', C-5''); 130.2 (C-4''); 134.3 (C-5); 132.5 (C-2', C-6'); 163.5 (COO); 164.3 (C-4'); 166.8 (CONH); 185.1 (COAr). Anal. Calc. C₂₃H₂₁ClN₂O₅: C 62.66, H 4.80, Cl 8.04, N 6.35; Found: C 62.41, H 4.38, Cl 8.41, N 6.61.

Dimethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(3-nitrobenzoyl)pyrrole-3,4-dicarboxylate (5j). Colorless crystals; FT-IR (cm⁻¹): 1348, 1532, 1650, 1724, 1739, 2955, 3082, 3244. ¹H-NMR (300 MHz, CDCl₃) δ: 2.73 (d, 1H, *J* = 4.9, MeNH); 3.39, 3.83 (2s, 6H, 2MeO); 6.50 (q, 1H, *J* = 4.9, NH); 7.22 (d, 1H, *J* = 1.9 Hz, H-6''); 7.50 (dd, 1H, *J* = 8.2, 1.9 Hz, H-4''); 7.55 (s, 1H, H-5); 7.61 (d, 1H, *J* = 8.2 Hz, H-3''); 7.70 (t, 1H, *J* = 8.0 Hz, H-5'); 8.15-8.19, 8.43-8.49 (2m, 2H, H-4', H-6'); 8.67 (t, 1H, *J* = 1.8, H-2'). ¹³C-NMR (75 MHz, CDCl₃) δ: 26.8 (MeNH); 52.1, 52.4 (2MeO); 116.0 (C-4); 124.9 (C-3); 124.2 (C-2'); 127.7 (C-6''); 127.9 (C-4'); 129.9 (C-3''); 130.1 (C-4''); 130.3 (C-5'); 131.4, 133.3, 136.6, 136.8, 138.7 (C-2, C-1', C-1'', C-2'', C-5''); 133.4 (C-5); 135.1 (C-6'); 148.3 (C-3'); 162.5, 163.7 (2COO); 166.1 (CONH); 185.0 (COAr). Anal. Calc. C₂₃H₁₈ClN₃O₈: C 55.27, H 3.63, Cl 7.09, N 8.41; Found: C 55.53, H 3.89, Cl 7.45, N 8.71.

Dimethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-bromobenzoyl)pyrrole-3,4-dicarboxylate (5k). Colorless crystals; FT-IR (cm⁻¹): 1654, 1719, 1742, 2946, 3077, 3395. ¹H-NMR (300 MHz, CDCl₃) δ: 2.71 (d, 1H, *J* = 4.9, MeNH); 3.39, 3.83 (2s, 6H, 2MeO); 6.75 (1H, q, *J* = 4.9, NH); 7.11 (d, 1H, *J* = 2.2 Hz, H-6''); 7.47 (dd, 1H, *J* = 8.2, 2.1 Hz, H-4''); 7.50 (s, 1H, H-5); 7.61 (d, 1H, *J* = 8.2 Hz, H-3''); 7.65, 7.72 (2d, 4H, *J* = 8.8, H-2', H-3', H-5', H-6'). ¹³C-

NMR (75 MHz, CDCl₃) δ : 26.8 (MeNH); 52.0, 52.3 (2MeO); 115.8 (C-4); 123.9 (C-3); 127.3 (C-6''); 129.6 (C-4'); 130.3, 130.4 (C-3'', C-4''); 131.0, 132.2 (C-2', C-3', C-5', C-6'); 131.4, 133.7, 136.1, 136.4, 136.5 (C-2, C-1', C-1'', C-2'', C-5''); 132.8 (C-5); 162.5, 163.7 (2COO); 166.1 (CONH); 186.7 (COAr). Anal. Calc. C₂₃H₁₈BrClN₂O₆: N 5.25; Found: N 5.58.

Dimethyl 1-(5-chloro-2-methylaminocarbonylphenyl)-2-(4-chlorobenzoyl)pyrrole-3,4-dicarboxylate (5I). Colorless crystals; FT-IR (cm⁻¹): 1660, 1722, 1743, 2945, 3074, 3389. ¹H-NMR (300 MHz, CDCl₃+TFA) δ : 2.71 (d, 1H, *J* = 4.9, MeNH); 3.47, 3.90 (2s, 6H, 2MeO); 7.18 (d, 1H, *J* = 1.9 Hz, H-6''); 7.51-7.57 (m, 3H, H-3', H-5', H-4''); 7.50 (s, 1H, H-5); 7.62 (d, 1H, *J* = 8.2 Hz, H-3''); 7.78 (d, 2H, *J* = 8.5, H-2', H-6'); 7.80 (1H, q, *J* = 4.9, NH). ¹³C-NMR (75 MHz, CDCl₃+TFA) δ : 27.5 (MeNH); 53.1, 52.3 (2MeO); 115.7 (C-4); 123.6 (C-3); 127.8 (C-6''); 129.7, 131.0 (C-2', C-3', C-5', C-6'); 130.9 (C-3'', C-4''); 131.3, 132.6, 134.9, 136.1, 138.1, 142.1 (C-2, C-1', C-4', C-1'', C-2'', C-5''); 134.1 (C-5); 164.1, 165.4 (2COO); 169.0 (CONH); 187.6 (COAr). Anal. Calc. C₂₃H₁₈Cl₂N₂O₆: C 56.46, H 3.71, Cl 14.49, N 5.73; Found: C 56.79, H 3.38, Cl 14.78, N 5.96.

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 6. X-ray reflection intensities for the crystal of **5a** were measured on a Nonius Kappa CCD diffractometer with the crystal cooled in a constant stream of nitrogen vapour at 173(2) K. Lorentz-polarization and absorption corrections⁸ were applied. Programs SHELXS-97⁹ and SHELXL-97¹⁰ were used for structure solution and full-matrix least-squares refinement respectively. All H atoms were located in difference electron density maps and were added in idealized positions in a riding model with isotropic thermal displacement parameters 1.2-1.5 times those of their parent atoms. All non-H atoms were refined anisotropically.
 7. Crystal data for **5a**: C₂₁H₁₇ClN₂O₃, *M* = 380.82, 0.42 × 0.32 × 0.25 mm³, monoclinic, space group *C2/c* (No. 15), *a* = 15.5248(4), *b* = 14.5869(4), *c* = 17.4286(4) Å, *β* = 109.1970(10)°, *V* = 3727.39(16) Å³, *Z* = 8, *D_c* = 1.357 g/cm³, *F*₀₀₀ = 1584, MoKα radiation, *λ* = 0.71073 Å, *μ* = 0.229 mm⁻¹, *T* = 173(2)K, 2*θ*_{max} = 56.6°, 103650 reflections collected, 4627 unique (*R*_{int} = 0.0425). Final *GooF* = 1.048, *R*_I = 0.0370, *wR*₂ = 0.0956, *R* indices based on 3749 reflections with *I* > 2σ(*I*) (refinement on *F*²), 246 parameters, 0 restraints, CCDC deposition no. 809419.
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