Spectral Assignments and Reference Data

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NMR and conformational studies of new 5-phenylpyrrole-carboxamide derivatives

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The ^{1}H and ^{13}C NMR resonances of 22 5-(5-substituted-2-nitrophenyl)-1*H*-pyrrole-2-carboxamides, 22 5-(5-substituted-2-aminophenyl)-1*H*-pyrrole-2-carboxamides, and 9 5-phenyl-1*H*-pyrrole-2-carboxamides were assigned completely using the concerted application of one- and two-dimensional experiments (DEPT, gs-HMQC and gs-HMBC). NOE studies and conformational analysis confirm the preferred conformations of such compounds.

Keywords: NMR; ^{1}H; ^{13}C; HMQC; HMBC; NOEDIFF; 5-phenyl-1*H*-pyrrole-2-carboxamides

Introduction

Nitric oxide synthase (NOS), the enzyme responsible of the transformation of L-arginine in nitric oxide, is an interesting target in the development of new compounds with potential therapeutic interest. In particular, the inducible isoform of this enzyme, inducible nitric oxide synthase (iNOS), is implicated in some diseases such us septic shock[1] and rheumatoid arthritis.[2] In a recent paper, the synthesis and biological evaluation of some 5-phenyl-1*H*-pyrrole-2-carboxamide derivatives **26–47** as new inhibitors of the iNOS have been described.[3]

Although the structures of these derivatives have been determined by means of standard spectroscopic techniques (^{1}H and ^{13}C NMR, MS), a detailed NMR study has been performed in some of them, in order to unequivocally corroborate their structures.

In this paper, we describe the assignment of each signal in the ^{1}H and ^{13}C NMR spectra in compounds **26–47**, using one- and two-dimensional NMR techniques. The spectra of nitro derivatives **4–25**, the direct precursors in the synthetic pathway, are also included. Conformational analysis and NOEDIFF experiments performed on some of these compounds allow determination of their preferred conformations. Finally, the ^{1}H and ^{13}C NMR spectra of 9 new 5-phenyl-1*H*-pirrole-2-carboxamides **48–56**, described herein for the first time, are also included.

Synthesis

Scheme 1 represents the previously reported synthetic pathway followed in the preparation of compounds **26–47.**[3] The synthesis begins with the reaction of 2-nitro-cinnamaldehyde derivatives **1a–c** with ethyl azidoacetate, followed by a thermolysis, to yield the corresponding nitrophenylpyrrole derivatives **2a–c.** Compound **2c** was treated with CH_3I under basic conditions and in the presence of 18-crown-6 ether to yield compound **2d.**[4]

Two alternative procedures were employed in the synthesis of nitrocarboxamide derivatives **4–25** from compounds **2a–d**. Compounds **9**, **14**, **19,** and **20** were directly obtained from **2a–d**, respectively, by treatment with NH_4Cl/NH_4OH.[5] In all other cases, the ester moiety of compounds **2a–c** was previously hydrolyzed (NaOH, then AcOH),[6] transformed into the corresponding acyl chloride ($SOCl_2$),[7] and treated with the appropriated amine (R^2NH_2/TEA)[8] to yield the corresponding *N*-substituted carboxamide. Finally, compounds **26–47** were obtained by reduction of the nitro group in the corresponding derivative **4–25**, performed by treatment with $Fe/FeSO_4$.[9]

A similar procedure was used in the synthesis of compounds **48–56,** starting from cinnamaldehyde **1d,** which was converted into 5-phenyl-1*H*-pyrrole-2-carboxylic acid **3.** Reaction of **1d** with ethyl azidoacetate followed by a pyrolysis yielded ethyl 5-phenyl-1*H*-pyrrole-2-carboxylate which was further hydrolyzed (NaOH, then AcOH) to give compound **3**. Treatment of **3** with $SOCl_2$ and R^2NH_2/TEA yields the final compounds **48–56**.

NMR Techniques

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer, operating at 300.160 MHz for ^{1}H and 75.479 MHz for ^{13}C, respectively, with a 5 mm ^{13}C/^{1}H dual Wilmad probe (No. 528-PP), and the sample temperature was maintained constant at 297 K. In almost all cases, samples were dissolved in $CDCl_3$ at concentrations of *ca* 27 mg ml^{-1}, and the central peak of $CDCl_3$ signals [7.26 ppm (^{1}H) and 77.0 ppm (^{13}C)] was used as internal standard. In some cases, samples were dissolved in $(CD_3)_2CO$, CD_3OD, and DMSO at concentrations of *ca* 27 mg ml^{-1}. The following parameters were used in DEPT experiments: PW (135°), 9.0 μs; recycle time, 1 s; $1/2J(CH) = 4$ ms; 65 536 data points acquired and transformed from 1024 scans; spectral width, 15 KHz; and line broadening, 1.3 Hz.

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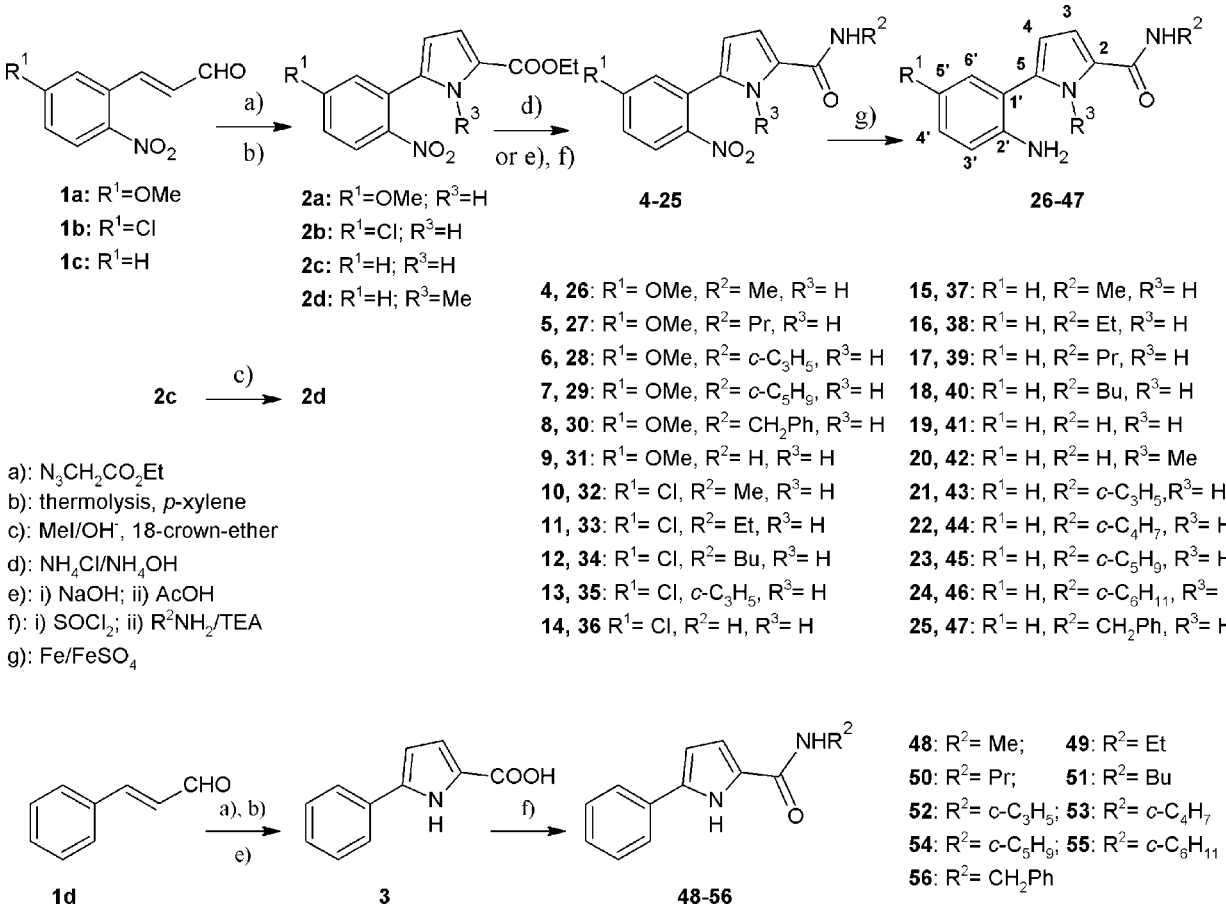

Scheme 1. General synthetic pathway for compounds **4–56**.

The HMQC spectra were recorded using the standard Bruker software, and resulted from a 256 × 1024 data matrix size with 16–64 scans for t_1, depending on the sample concentration, an inter-pulse delay of 3.2 ms, and a 5 : 3:4 gradient combination.[10]

The long-range ^{1}H-^{13}C HMBC was recorded using the sequence described by Bax and Morris,[11] with delay values optimized for ^3J(CH) of 5.5 Hz; 16 scans were measured for 512 values of t_1 to give a total data matrix of 512 × 2048 complex points. The carbon and proton spectral widths were 20 and 4.2 kHz, respectively.

One-dimensional NOE difference experiments were measured with irradiation time of 4 s in series of eight scans with alternating on- and off-resonance. The irradiating power was set low to achieve selectivity.

Results and Discussion

Structural elucidation of compounds **4–56** has been made by routine ^{1}H and ^{13}C NMR techniques. Nevertheless, a definitive determination of all signals needs the use of several NMR techniques as follows: (i) DEPT experiments to determine the multiplicity of ^{13}C signals; (ii) gs-HMQC spectra to determine the ^{13}C resonances of the tertiary, secondary, and primary carbons; (iii) gs-HMBC sequences to assign the signals of quaternary carbons via two- and three-bond interactions; and (iv) NOE experiments to determine the preferred conformations in solutions.

Tables 1–3 show the ^{1}H NMR signals of each proton for compounds **4–56**, while Tables 4–6 show the corresponding ^{13}C NMR chemical shifts for the same molecules.

^{1}H NMR signals have been identified by means of the above mentioned combined techniques.

In the three series of compounds (nitrophenyl-pyrroles **4–25**, aminophenyl-pyrroles **26–47**, and phenyl-pyrroles **48–56,** respectively) ^{1}H NMR and ^{13}C NMR signals are similar, and small differences are observed when the experiments were performed in different solvents.

HMQC and HMBC experiments were performed on some compounds of each series, and the results of these experiments have been extrapolated to the other compounds.

HMQC experiments performed on compounds **5**, **13** and **22** allowed the unequivocal assignment of the tertiary carbon atoms chemical shifts C-3′, C-4′, C-5′, and C-6′ in the nitrophenyl-pyrrole derivatives. These atoms show signals in ranges of 123.85–127.57 (C-3′), 113.55–130.80 (C-4′), 132.16–162.54 (C-5′), and 115.98–133.55 ppm.

NOEDIFF experiments performed in compound **13** (R^1 = Cl, R^2 = c-C_3H_5) indicate the existence of NOE between both the benzene C_6′–H (δ 7.58 ppm) atom and the pyrrole H-4 proton (δ 6.52 ppm), on the one hand, and between the pyrrole H-3 atom (δ 6.34 ppm) and the amide NH proton, on the other. These NOEs demonstrate the spatial proximity of both pairs of atoms in the preferred conformation of this molecule, and confirm the ^{1}H signals assignment to H-3 and H-4.

Table 1. ^{1}H NMR signal assignments of compounds **4–25** δ (in ppm), in $CDCl_3$. Multiplicities and coupling constants (Hz) are given in parentheses

Compound	H-1	H-3	H-4	H-3′	H-4′	H-5′	H-6′	CONH; OCH_3
4	10.60 (bs)	6.54 (t, 3.7)	6.30 (t, 3.7)	7.90 (d, 9.1)	6.87 (dd, 2.8, 9.1)	–	6.99 (d, 2.8)	6.02 (m); 3.86 (s)
5	10.45 (bs)	6.55 (d, 3.5)	6.32 (d, 3.5)	7.90 (d, 9.0)	6.88 (dd, 2.7, 9.0)	–	6.99 (d, 2.7)	5.94 (bs); 3.87 (s)
6	10.40 (bs)	6.52 (bs)	6.30 (t, 3.0)	7.90 (d, 9.1)	6.87 (dd, 2.7, 9.1)	–	6.98 (d, 2.7)	6.13 (bs); 3.87 (s)
7	10.70 (bs)	6.52 (bs)	*6.30* (bs)	7.89 (d, 9.0)	6.87 (dd, 2.5, 9.0)	–	6.98 (d, 2.5)	5.87 (d, 7.3); 3.86 (s)
8[b]	11.27 (bs)	6.88 (dd, 2.5, 3.8)	6.28 (dd, 2.8, 3.8)	7.92 (d, 9.0)	7.00 (dd, 2.8, 9.0)	–	7.18 (d, 2.8)	7.96 (bs); 3.95 (s)
9[b]	11.98 (bs)	6.87 (dd, 2.4, 3.7)	6.30 (dd, 2.7, 3.7)	7.95 (d, 9.0)	7.05 (dd, 2.8, 9.0)	–	7.20 (d, 2.8)	[a]; 3.99 (s)
10[b]	11.45 (bs)	6.78 (dd, 2.2, 3.7)	6.32 (dd, 2.6, 3.7)	7.92 (d, 8.7)	7.57 (dd, 2.2, 8.7)	–	7.79 (d, 2.2)	7.52 (bs); –
11	10.78 (bs)	6.55 (dd, 2.6, 3.7)	6.35 (dd, 2.8, 3.7)	7.75 (d, 8.7)	7.36 (dd, 2.2, 8.7)	–	7.56 (d, 2.2)	3.91 (bs); –
12	10.40 (bs)	6.58 (d, 3.7)	6.40 (d, 3.7)	7.78 (d, 8.7)	7.41 (dd, 1.7, 8.7)	–	7.60 (d, 1.7)	5.93 (bs); –
13	10.50 (bs)	6.52 (bs)	6.34 (bs)	7.74 (d, 8.7)	7.37 (dd, 1.4, 8.7)	–	7.58 (ps)	6.09 (bs); –
14[b]	11.22 (bs)	6.90 (dd, 2.2, 3.8)	6.30 (dd, 2.8, 3.8)	7.93 (d, 8.7)	7.56 (dd, 2.2, 8.7)	–	7.83 (d, 2.2)	7.36 (bs), 6.56 (bs); –
15[d]	11.86 (bs)	6.77 (dd, 2.3, 3.5)	6.16 (dd, 2.5, 3.5)	7.90 (d, 8.0)	7.51 (ddd, 2.9, 5.7, 8.0)	7.83 (m)	7.83 (m)	8.07 (q, 4.5); –
16[d]	11.86 (bs)	6.80 (t, 3.0)	6.15 (t, 3.0)	7.91 (d, 8.1)	7.51 (dt, 2.7, 8.1)	7.66 (m)	7.66 (m)	8.10 (t, 5.3); –
17[b]	[a]	6.82 (d, 3.8)	6.25 (d, 3.8)	7.83 (d, 8.0)	7.52 (ddd, 2.8, 5.8, 8.0)	7.65 (m)	7.65 (m)	[a]; –
18[b]	11.29 (bs)	6.79 (dd, 2.0, 3.6)	6.24 (dd, 2.4, 3.6)	7.86 (dd, 1.0, 8.0)	7.55 (dt, 1.4, 7.4, 8.0)	7.69 (ddd, 1.0, 7.4, 7.8)	7.77 (dd, 1.4, 7.8)	7.49 (bs); –
19[c]	9.90 (bs)	6.64 (dd, 2.6, 3.6)	6.38 (t, 3.6)	7.80 (d, 8.1)	7.45 (ddd, 1.7, 6.7, 8.1)	7.59 (m)	7.59 (m)	5.68 (bs); –
20[b]	[a]	6.88 (d, 3.9)	6.05 (d, 3.9)	8.05 (dd, 1.2, 8.0)	7.73 (ddd, 1.5, 7.5, 8.0)	7.82 (dt, 1.2, 7.5)	7.59 (dd, 1.5, 7.5)	[a]; –
21[b]	11.50 (bs)	6.76 (d, 3.1)	6.24 (d, 3.1)	7.86 (d, 8.0)	7.54 (m)	7.69 (t, 7.4)	7.77 (d, 7.1)	7.54 (m); –
22	10.53 (bs)	6.56 (t, 3.4)	6.32 (t, 3.4)	7.77 (d, 8.0)	7.44 (dt, 2.2, 8.0)	7.58 (m)	7.58 (m)	6.06 (d, 7.9); –
23	10.52 (bs)	6.53 (d, 3.1)	6.31 (t, 3.1)	7.75 (d, 8.0)	7.41 (dt, 1.4, 8.0)	7.57 (m)	7.57 (m)	5.86 (d, 7.3); –
24	10.55 (bs)	6.54 (d, 3.8)	6.32 (d, 3.8)	7.75 (d, 8.1)	7.41 (ddd, 2.2, 7.8, 8.1)	7.56 (m)	7.56 (m)	5.78 (d, 8.1); –
25[c]	[a]	6.88 (d, 3.8)	6.26 (d, 3.8)	7.82 (d, 8.1)	7.51 (dt, 2.3, 8.1)	7.65 (m)	7.65 (m)	5.78 (bs); –

[a] Not observable. [b] $CO(CD_3)_2$, [c] CD_3OD, [d] DMSO as solvent.
^{1}H signals for the R^2 substituent: **4**, CH_3: 2.85 (d, 4.9); **5**, $CH_2CH_2CH_3$: 3.27 (m), 1,54 (m), 0.91 (t, 7.3); **6**, *c*-C_3H_5: 2.75 (m, 1H), 0.75 (m, 4H); **7**, *c*-C_5H_9: 4.17 (m, 1H), 1.95–1.36 (m, 8H); **8**, H2″–H6″: 7.25 (m, 5H); CH_2: 4.49 (d, 6.1); **10**, CH_3: 2.78 (d, 4.7); **11**, CH_2CH_3: 3.35 (m), 1.16 (t, 7.2); **12,** $CH_2CH_2CH_2CH_3$: 3.39 (m), 1,57 (m), 1.34 (m), 0.96 (t, 7.3); **13**, *c*-C_3H_5: 2.78 (m, 1H), 0.75-0.57 (m, 4H); **15**, CH_3: 2.74 (d, 4.5); **16**, CH_2CH_3: 3.24 (m), 1.10 (t, 7.1); **17**, $CH_2CH_2CH_3$: 3.31 (m), 1,62 (m), 0.98 (t, 7.4); **18**, $CH_2CH_2CH_2CH_3$: 3.27 (m), 1.49 (m), 1.32 (m), 0.87 (t, 7.2); **20**, N–CH_3: 3.71 (s); **21**, *c*-C_3H_5: 2.86 (m, 1H), 0.65 (m, 2H), 0.52 (m, 2H); **22**, *c*-C_4H_7: 4.40 (m, 1H), 2.27 (m, 2H), 1.89 (m. 2H), 1.67 (m, 2H); **23**, *c*-C_5H_9: 4.20 (m, 1H), 1.35–1.99 (m, 8H); **24**, *c*-C_6H_{11}: 3.78 (m, 1H), 1.92–1.58 (m, 5H); 1.38–1.09 (m, 5H); **25**, H2″–H6″: 7.32 (m); CH_2: 4.54 (s).

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Table 2. ^{1}H NMR signal assignments of compounds **26–47** δ (in ppm), in $CDCl_3$. Multiplicities and coupling constants (Hz) are given in parentheses

Compound	H-1	H-3	H-4	H-3′	H-4′	H-5′	H-6′	CONH; OCH_3, NH_2
26	10.05 (bs)	6.58 (dd, 2.4, 3.6)	6.42 (dd, 2.7, 3.6)	6.72 (m)	6.72 (m)	–	6.87 (d, 1.5)	5.98 (bs); 3.75 (s);[a]
27	10.00 (bs)	6.58 (t, 3.6)	6.43 (t, 3.6)	6.73 (m)	6.73 (m)	–	6.87 (d, 2.4)	5.93 (bs); 3.75 (s);[a]
28	10.04 (bs)	6.56 (bs)	6.40 (t, 3.5)	6.72 (m)	6.72 (m)	–	6.86 (m)	6.10 (bs); 3.75 (s),; 3.75 (bs)
29[d]	11.30 (bs)	6.83 (d, 3.6)	6.36 (d, 3.6)	6.70 (d, 8.6)	6.62 (dd, 2.8, 8.6)	–	6.89 (d, 2.8)	7.77 (d, 7.4); 3.67 (s); 4.56 (bs)
30[c]	[a]	6.91 (m)	6.43 (d, 3.8)	6.80 (d, 8.7)	6.71 (dd, 2.8, 8.7)	–	6.91 (m)	[a]; 3.74 (s);[a]
31	10.21 (bs)	6.67 (t, 3.3)	6.44 (t, 3.3)	6.90 (m)	6.90 (m)	–	6.70 (bs)	5.83 (bs); 3.73(s);[a]
32[c]	10.05 (bs)	6.58 (dd, 2.6, 3.7)	6.40 (dd, 2.9, 3.7)	6.68 (d, 8.6)	7.05 (dd, 2.4, 8.6)	–	7.24 (d, 2.4)	5.94 (bs); 4.00 (bs); –
33[b]	10.80 (bs)	6.82 (m)	6.43 (t, 3.8)	6.82 (m)	7.02 (dd, 2.4, 8.6)	–	7.32 (d, 2.4)	7.42 (bs); 4.85 (bs); –
34	10.09 (bs)	6.58 (t, 3.4)	6.40 (t, 3.4)	6.66 (d, 8.5)	7.03 (dd, 2.3, 8.5)	–	7.22 (d, 2.3)	5.92 (bs); 4.00 (bs); –
35[b]	11.95 (bs)	6.82 (m)	6.41 (dd, 2.8, 3.6)	6.82 (m)	7.00 (dd, 2.5, 8.5)	–	7.30 (6, 2.5)	7.47 (bs); 4.81 (bs); –
36[b]	9.95 (bs)	6.69 (t, 3.4)	6.46 (t, 3.4)	6.70 (d, 8.5)	7.08 (dd, 2.4, 8.5)	–	7.31 (d, 2.4)	5.70 (bs); 3.98 (bs); –
37	9.83 (bs)	6.61 (t, 3.1)	6.42 (t, 3.1)	6.76 (d, 8.0)	7.12 (dt, 1.0, 7.5, 8.0)	6.82 (dd, 7.5, 7.7)	7.28 (d, 7.7)	5.97 (bs); 4.00 (bs); –
38	10.85 (bs)	6.61 (t, 3.1)	6.41 (t, 3.1)	6.75 (d, 8.0)	7.11 (t, 7.5, 8.0)	6.80 (t, 7.5, 7.7)	7.27 (d, 7.7)	5.95 (bs);[a]; –
39	10.00 (bs)	6.62 (dd, 2.7, 3.6)	6.40 (dd, 2.9, 3.6)	6.73 (dd, 1.0, 8.0)	7.09 (dt, 1.5, 7.7, 8.0)	6.78 (dt, 1.0, 7.7, 7.8)	7.26 (dd, 1.5, 7.8)	6.03 (s); 3.98 (bs); –
40	9.79 (bs)	6.59 (t, 3.5)	6.41 (t, 3.5)	6.75 (d, 8.0)	7.11 (dt, 1.4, 7.7, 8.0)	6.80 (t, 7.7, 7.8)	7.27 (dd, 1.4, 7.8)	5.90 (s); 4.10 (bs); –
41	9.75 (bs)	6.69 (t, 3.5)	6.43 (t, 3.5)	6.74 (d, 8.0)	7.11 (dt, 1.3, 7.5, 8.0)	6.80 (t, 7.5, 7.6)	7.27 (dd, 1.2, 7.6)	5.80 (bs); 4.00 (bs); –
42[c]	[a]	6.92 (d, 3.9)	6.12 (d, 3.9)	7.00 (d, 8.0)	7.22 (t, 7.5, 8.0)	6.85 (t, 7.1, 7.5)	7.10 (d, 7.1)	[a]; [a]; –
43	9.90 (bs)	6.60 (bs)	6.38 (t, 3.5)	6.73 (d, 8.0)	7.09 (dt, 1.5, 7.6, 8.0)	6.78 (dt, 1.1, 7.6, 7.7)	7.27 (dd, 1.5, 7.7)	6.22 (bs); 4.00 (bs); –
44	9.85 (bs)	6.61 (dd, 2.7, 3.6)	6.40 (t, 3.6)	6.75 (d, 8.0)	7.11 (dt, 1.5, 7.7, 8.0)	6.80 (dt, 0.9, 7.6, 7.7)	7.26 (dd, 1.5, 7.6)	6.05 (d, 7.7); 3.93 (bs); –
45	9.85 (bs)	6.58 (dd, 2.6, 3.6)	6.40 (t, 3.6)	6.75 (dd, 1.0, 8.0)	7.11 (dt, 1.5, 7.7, 8.0)	6.80 (dt, 1.0, 7.6, 7.7)	7.27 (d, 7.6)	5.83 (d, 7.6); 4.00 (bs); –
46	9.98 (bs)	6.60 (dd, 2.5, 3.6)	6.40 (dd, 2.7, 3.6)	6.76 (dd, 1.0, 8.3)	7.10 (dt, 1.5, 7.5, 8.3)	6.78 (dt, 1.0, 7.5, 7.6)	7.26 (d, 7.6)	5.83 (d, 8.1); 3.85 (bs); –
47[b]	11.40 (bs)	6.89 (d, 3.5)	6.35 (d, 3.5)	6.82 (d, 8.2)	7.27 (dt, 1.4, 7.5, 8.0)	6.68 (t, 7.5, 77)	7.26 (m)	8.55 (t, 5.9); 5.75 (bs); –

[a] Not observable. [b] $CO(CD_3)_2$, [c] CD_3OD, [d] DMSO as solvent.
^{1}H signals for the R^2 substituents: **26**, CH_3: 2.95 (d, 5.3); **27**, $CH_2CH_2CH_3$: 3.56 (m), 1.60 (m), 0.96 (t, 7.3); **28**, *c*-C_3H_5: 2.81 (m, 1H), 0.82 (m, 2H), 0.60 (m, 2H); **29**, *c*-C_5H_9: 4.17 (m, 1H), 1.93–1.38 (m, 8H); **30**, H2″-H6″: 7.28 (m, 5H), CH_2: 4.53 (s); **32**, CH_3: 2.95 (d, 4.9); **33**, CH_2CH_3: 3.34 (m), 1.12 (t, 7.2); **33,** $CH_2CH_2CH_2CH_3$: 3.38 (m), 1.55 (m), 1.37 (m), 0.93 (t, 7.2); **35**, *c*-C_3H_5: 2.82 (m, 1H), 0.68–0.49 (m, 4H); **37**, CH_3: 2.97 (d, 4.9); **38**, CH_2CH_3: 3.44 (m), 1.22 (t, 7.2); **39**, $CH_2CH_2CH_3$: 3.83 (m), 1.58 (m), 0.94 (t, 7.4); **40**, $CH_2CH_2CH_2CH_3$: 3.40 (m), 1.56 (m), 1.39 (m), 0.95 (t, 7.3); **42**, N(1)–CH_3: 3.61 (s); **43**, *c*-C_3H_5: 2.81 (m, 1H), 0.81 (m, 2H), 0.59 (m, 2H); **44**, *c*-C_4H_7: 4.52 (m, 1H), 2.37 (m, 2H), 1.92 (m, 2H), 1.73 (m, 2H); **45**, *c*-C_5H_9: 4.33 (m, 1H), 2.04 (m, 4H), 1.66 (m, 2H), 1.45 (m, 2H); **46**, *c*-C_6H_{11}: 3.88 (m, 1H), 1.99–1.14 (m, 5H); **47**, H2″-H6″: 7.26 (m); CH_2: 4.38 (d, 6.0).

HMBC experiment performed on compound **13** indicates that H-4 signal (δ 6.34 ppm) is correlated with the ^{13}C signal at δ 129.82 ppm, while H-3 signal (δ 6.52 ppm) is correlated with the ^{13}C signal at δ 129.42 ppm, and consequently these signals can be assigned to C-5 and C-2, respectively. HMBC spectrum of compound **13** also indicates a correlation between the ^{13}C signal at δ 148.07 ppm and the signals of H-3′ (δ 7.74 ppm), on the one hand, and between the ^{13}C signal at δ 139.86 ppm and the signals of H-4′ (δ 7.37 ppm) and H-6′ (δ 7.58 ppm), on the other. These correlations indicate that these signals can be assigned to C-2′ and C-5′, and that the signal at δ 129.51 ppm should be assigned to C-1′.

HMQC experiments performed on compounds **28**, **32,** and **46** allowed the unequivocal assignment of the tertiary carbon atoms chemical shifts C-3′, C-4′, C-5′, and C-6′ in the aminophenyl-pyrrole derivatives. These atoms resonate in ranges of 119.60–116.57 (C-3′), 114.91–132.15 (C-4′), 118.43–154.46 (C-5′), and 113.64–132.07 (C-6′) ppm.

NOEDIFF experiments performed on compound **32** (R^1 = Cl, R^2 = CH_3) indicate the spatial proximity of both H-4 and H-6′ and of H-3 and the NH amide group. The similarity of the NOEs observed in compounds **13** and **32** indicates that the preferred conformations in both molecules should be very similar.

Finally, in the phenyl-pyrrole derivatives HMQC experiments performed on compound **50** allowed the unequivocal assignment of the tertiary carbon atoms chemical shifts C-2′, C-3′, C-4′, C-5′, and C-6′. These atoms show signals in ranges of 128.42–129.10 (C-3′, C-5′), 126.89–128.17 (C-4′), and 124.49–127.74 (C-2′, C-6′) ppm. The quaternary carbons have been perfectly identified with HMBC experiment performed on compound **50**. In this experiment it can be observed that the ^{13}C signal at δ 135.77 ppm is correlated with the signals of H-3 (δ 6.54 ppm), H-2′, and H-6′ (δ 7.53 ppm), indicating that this carbon should be C-5. On the other hand, H-3′ and H-5′ signals (δ 7.29 ppm) are correlated with the ^{13}C signal at δ 131.98 ppm, and this carbon should be C-1′. Consequently, the other quaternary carbon C-2 resonates at δ 126.90 ppm.

Tripos force field[12] implemented in the Sybyl program[13] was employed in the conformational analysis of compounds **41** and **43**. In both compound, the phenyl-pyrrole and the pyrrole-carboxamide bonds were scanned using an interval of 10°. In compound **43** the NH–cyclopropyl bond was also scanned using the same interval. The so obtained conformations were minimized and compared with each other in order to identify the more stable conformers of these molecules.

In order to get more insight into the relative stability of each conformer, the more stable conformations were optimized by means of Gaussian 98 program[14] using the Hartree–Fock Hamiltonian at a 6–31G** level. Both methodologies give similar geometries and energy values for the more stable conformers.

Figure 1 shows the four conformations found for compound **41**. It can be observed that the expected coplanarity of the benzene and pyrrole moieties as a result of the conjugation between both rings is broken (the dihedral angle defined by both rings is about 40°) by the presence of the 2′-NH_2. The energy differences between conformations **I** and **II** or **III** and **IV** are small, indicating that the nonbonding interactions between the 2′-NH_2 and the pyrrole NH (conformers **I** and **III**) are quite similar to that of 2′NH2 and pyrrole C_4-H (conformers **II** and **IV**). Finally, s-*cis* configuration is preferred for the bond between the pyrrole ring and the carboxamide moiety (conformers **I** and **III**), probably because of higher interactions between the pyrrole NH and the terminal NH_2 group in conformations **II** and **IV**.

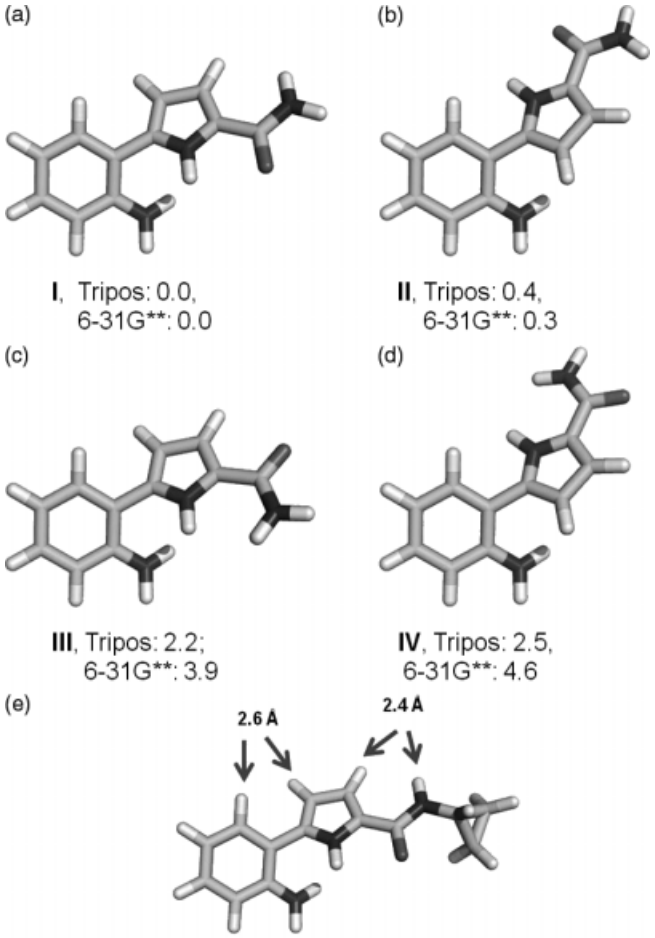

Figure 1. (a–d) The four more stable conformers found for compound **41**. Relative energies are expressed in kcal/mol. (e) The most stable conformer found for compound **43**. Distances (expressed in Angstrom) are compatibles with the NOE observed in compounds **13** and **32**.

Neither the *N*-Alkylation of the amide moiety nor the substitution in C5′ modifies significantly the conformational behavior of these series of compounds. In this sense, the *N*-alkylation only increases the number of rotamers around the N–R bond, and all the resulting conformations can be classified into four families similar to those of the conformers found for compound **41**. Figure 1 also shows, as an example, the most stable conformer of compound **43**, which is similar to conformation **I** obtained for compound **41**. It can be observed that the calculated distances between the benzene C_6′–H and the pyrrole H-4 atoms (2.6 Å), and between the pyrrole H-3 and the amide NH atoms (2.4 Å) are compatible with the observed NOE above described for compounds **13** and **32**, indicating that this type of conformation is the preferred one of these molecules in solution.

Compounds **20** and **42** bear a N1-methyl substituent and, consequently, the existence of a higher rotational barrier around the bond linking the pyrrole and the phenyl moieties can be expected. These molecules have been optimized by means of Gaussian 98 program, and the rotational barriers have been studied by scanning the angle formed by both rings ($\omega_{151'2'}$), using the Hartree–Fock Hamiltonian at a 6–31G** level.

Table 3. ^{1}H NMR signal assignments for compounds **48–56** δ (in ppm), in $CDCl_3$. Multiplicities and coupling constants (Hz) are given in parentheses

Compound	H-1	H-3	H-4	H-2′	H-3′	H-4′	H-5′	H-6′	CONH
48[b]	11.22 (bs)	7.49 (m)	6.87 (d, 1H, 3)	7.86 (m)	7.49 (m)	7.38 (m)	7.49 (m)	7.86 (m)	7.60 (bs)
49[b]	11.58 (bs)	7.50 (m)	6.92 (d, 3.5)	7.86 (m)	7.50 (m)	7.38 (m)	7.50 (m)	7.86 (m)	7.74 (bs)
50	10.08 (bs)	6.54 (d, 4.5)	6.44 (d, 4.5)	7.53 (m)	7.29 (m)	7.17 (m)	7.29 (m)	7.53 (m)	5.92 (bs)
51[c]	10.59 (bs)	6.66 (d, 3.0)	6.51 (d, 3.0)	7.63 (m)	7.35 (m)	7.25 (m)	7.35 (m)	7.63 (m)	6.18 (m)
52[c]	9.83 (bs)	6.53 (d, 3.0)	6.05 (d, 3.0)	7.70 (m)	7.44 (m)	7.34 (m)	7.44 (m)	7.70 (m)	6.18 (m)
53[c]	[a]	7.43 (m)	6.67 (dd, 3.0)	7.71 (m)	7.43 (m)	7.33 (m)	7.43 (m)	7.71 (m)	[a]
54	9.71 (bs)	6.46 (d, 3.0)	6.39 (d, 3.0)	7.63 (m)	7.27 (m)	7.27 (m)	7.27(m)	7.63 (m)	5.67 (d,7.0)
55[b]	10.32 (bs)	7.31 (m)	6.51 (d, 3.0)	7.64 (m)	7.31 (m)	7.31 (m)	7.31 (m)	7.64 (m)	5.73 (bs)
56[b]	11.27 (bs)	7.88–6.99 (m)	7.88–6.99 (m)	7.88–6.99(m)	7.88–6.99 (m)	7.88–6.99 (m)	7.88–6.99 (m)	7.88–6.99(m)	8.06 (bs)

[a] Not observable. [b] $CO(CD_3)_2$, [c] CD_3OD as solvent. ^{1}H signals for the R^2 substituents: **48**, CH_3: 2.85 (d, 6.0); **49**, CH_2CH_3: 3.33 (m), 1,14 (t, 6.0); **50**, $CH_2CH_2CH_3$: 3.33 (m, 2H), 1.54 (m, 2H); 0.89 (t, 6.0); **51**, $CH_2CH_2CH_2CH_3$: 3.39 (m, 2H), 1.56 (m, 2H); 1.35 (m, 2H); 0.92 (t, 6.0); **52**, *c*-C_3H_5: 2.82 (m, 1H), 0.84–0.60 (m, 4H); **53**, *c*-C_4H_7: 4.40 (m, 1H), 2.32, 2.08, 1.76 (3m, 6H), **54**, *c*-C_5H_9: 4.23 (m, 1H), 1.99–1.30 (m, 8H), **55**, *c*-C_6H_{11}: 3.75 (m, 1H), 1.97–1.50 (m, 5H); 0.92–0.65 (m, 5H); **56**, H2″-H6″: 7.88–6.99 (m); CH_2: 4.54 (d, 2.6).

Table 4. ^{13}C NMR chemical shifts of compounds **4–25** δ (in ppm), in $CDCl_3$

Compound	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	CONH	OCH_3
4	127.47	109.71	111.12	130.37	129.55	141.68	127.26	113.55	162.50	116.39	161.72	56.05
5	127.57	109.49	111.16	130.29	129.49	141.73	127.27	113.63	162.51	116.23	160.99	56.05
6	127.31	109.98	111.26	130.49	129.41	141.68	127.31	113.63	162.54	116.29	162.54	56.07
7	127.59	109.62	111.03	130.40	129.55	141.66	127.20	113.63	162.48	116.18	160.69	56.04
8[a]	128.23	110.15	110.42	130.49	129.56	141.82	127.57	113.60	162.49	116.30	160.72	55.71
9[a]	128.16	110.12	111.07	130.32	129.36	141.73	126.80	113.70	162.47	115.98	162.09	55.67
10[a]	129.28	111.96	111.60	130.70	129.69	148.51	127.12	129.37	138.77	132.17	162.47	–
11	128.30	111.67	109.92	128.46	128.36	146.74	125.83	128.10	138.47	131.04	160.82	–
12	128.22	111.83	109.73	130.48	128.36	148.69	125.90	128.17	138.57	130.88	160.72	–
13	129.42	113.17	111.53	129.82	129.51	148.07	127.18	129.51	139.86	132.25	163.53	–
14[a]	126.62	112.23	111.41	129.62	128.92	147.87	126.62	128.92	138.28	131.56	162.69	–
15[c]	128.48	109.15	110.66	128.83	126.00	147.83	123.84	128.15	132.29	131.22	160.72	–
16[c]	128.57	109.13	110.77	128.85	126.02	147.86	123.85	128.17	132.31	131.22	160.01	–
17[a]	127.83	109.59	111.14	129.33	126.27	148.73	124.34	128.41	132.34	130.84	160.79	–
18[a]	128.94	109.88	110.18	129.30	126.48	148.90	123.89	128.34	132.18	131.32	160.55	–
19[b]	128.72	110.74	114.23	132.92	127.81	149.99	124.80	128.72	133.05	131.32	169.51	–
20[a]	127.73	108.99	113.37	134.39	127.73	151.14	124.84	130.80	134.25	133.55	164.13	–
21[a]	129.49	110.65	111.24	130.16	127.17	149.65	124.63	129.12	132.92	132.03	162.49	–
22	127.64	109.91	110.98	129.73	126.44	148.73	124.21	128.27	132.18	131.08	159.90	–
23	127.94	109.74	110.91	129.56	126.42	148.73	124.18	128.20	132.16	131.08	160.56	–
24	128.03	109.66	110.90	129.53	126.46	148.70	124.21	128.19	132.17	131.01	160.04	–
25[b]	128.16	109.24	111.21	129.20	125.96	147.86	123.87	128.26	132.34	131.26	160.20	–

[a] $CO(CD_3)_2$, [b] CD_3OD, [c] DMSO as solvent.
^{13}C signals for the R^2 substituent: **4**, CH_3: 26.21; **5**, $CH_2CH_2CH_3$: 41.23, 23.08, 11.42; **6**, *c*-C_3H_5: C-1″: 22.72, C-2″–C-3″, 6.86; **7**, *c*-C_5H_9: C-1″: 51.27, C-2″,C-5″: 33.25, C-3″,C-4″: 23.81; **8**, CH_2Ph: C-1″: 139.90, C-2″, C-6″: 128.34; C-4″: 127.57; C-3″, C5″: 126.86, CH_2: 42.72; **10**, CH_3: 26.55; **11**, CH_2CH_3: 34.51, 15.04; **12,** $CH_2CH_2CH_2CH_3$: 39.36, 31.36, 20.17, 13.84; **13**, *c*-C_3H_5: C-1″: 24.07, C-2″, C-3″; 8.24; **15**, CH_3: 25.46; **16**, CH_2CH_3: 33.28, 14.98; **17**, $CH_2CH_2CH_3$: 41.27, 23.15, 11.49; **18**, $CH_2CH_2CH_2CH_3$: 38.66, 31.89, 19.92, 13.30; **20**, N–CH_3: 34.06; **21**, *c*-C_3H_5: C1″: 23.21, C-2″, C-3″: 6.40; **22**, *c*-C_4H_7: C-1″: 44.69, C-2″, C-4″: 31.45, C-3″: 15.18; **23** *c*-C_5H_9: C-1″: 51.24, C-2″, C-5″: 33.27; C-3″, C-4″: 23.80; **24**, *c*-C_6H_{11}: C-1″: 48.22, C-2″, C-6″: 33.35; C-3″, C5″: 25.57, C-4″: 24.96; **25**, CH_2Ph: C-1″: 139.77, C-3″, C-5″: 128.16; C-4″: 127.10; C-2″, C6″: 126.63, CH_2: 41.84.

Figure 2 shows the more stable conformers obtained for each compound, and it can be observed that the higher steric interactions originated by the N–Me substituent increase the angle formed by the benzene and the pyrrole rings (90° and 70° in compounds **20** and **74**, respectively). Figure 2 also shows the energy variation during the rotation around the torsional angle $\omega_{151'2'}$. Both molecules show two minima and two maxima during the rotation. The minima correspond to the more stable conformers with the pyrrole ring almost perpendicular to the benzene ring, while the maxima correspond to conformations with both rings almost coplanar. When the value of the torsional angle $\omega_{151'2'}$ is 360° the *N*-methyl substituent is orientated toward the 2′-NO_2 or 2′-NH_2 groups, and the energy barrier is higher and similar in both compounds. A value of about 180° for the torsional angle $\omega_{151'2'}$ indicates a conformation with the pyrrole H-4 near to the 2′-NO_2 or 2′-NH_2 groups, and in this case the energy barrier is smaller.

Table 5. ^{13}C NMR chemical shifts of compounds **26–47** δ (in ppm), in $CDCl_3$

Compound	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	CONH	OCH_3
26	126.07	109.97	109.03	133.28	119.98	136.77	118.96	114.94	153.51	113.64	161.79	55.90
27	126.24	109.73	109.04	133.19	119.13	136.00	119.13	114.91	153.64	113.66	161.13	55.87
28	125.87	110.41	109.49	133.50	119.90	136.85	118.99	114.96	153.50	113.69	158.85	55.89
29[c]	127.26	112.18	108.56	132.99	118.73	139.23	117.96	114.88	151.75	113.84	160.47	55.92
30[b]	127.09	113.33	109.92	135.03	121.14	139.05	119.60	115.89	154.46	114.70	163.58	56.21
31	124.98	111.86	109.27	134.33	119.68	136.99	118.94	115.05	153.36	113.72	162.83	55.87
32[a]	127.51	110.15	108.75	131.48	119.37	144.20	117.29	127.67	121.37	128.28	161.29	–
33[a]	127.46	110.23	108.66	131.47	119.30	144.13	117.20	127.60	121.28	128.19	160.60	–
34	126.63	109.66	109.40	131.80	119.93	141.95	118.02	128.46	124.02	128.46	160.98	–
35[a]	127.37	110.64	108.75	131.68	119.42	144.18	117.32	127.70	121.47	128.28	161.91	–
36[a]	127.07	111.56	108.86	131.97	119.29	144.19	117.40	127.76	121.94	128.24	162.29	–
37	126.01	109.74	108.95	133.16	118.35	143.67	116.72	128.86	119.22	128.86	161.76	–
38	126.10	109.68	108.90	133.19	118.38	143.70	116.67	128.81	119.16	128.87	161.03	–
39	126.11	109.69	108.87	133.19	118.35	143.73	116.57	128.76	119.06	128.82	161.12	–
40	126.18	109.52	108.88	133.20	118.42	143.78	116.71	128.85	119.18	128.89	161.09	–
41	119.56	106.42	103.84	128.79	112.81	138.35	111.41	123.54	113.84	123.65	157.35	–
42[b]	126.91	113.45	108.82	135.40	118.08	145.56	118.08	132.15	120.01	132.07	163.84	–
43	125.81	110.25	108.99	133.46	118.31	143.73	116.67	128.87	119.14	128.87	162.55	–
44	125.99	109.79	108.94	133.36	118.41	143.71	116.69	128.84	119.17	128.89	160.12	–
45	126.24	109.52	108.87	133.12	118.41	143.72	116.68	128.82	119.17	128.85	160.73	–
46	126.36	109.63	108.91	133.08	118.62	143.36	116.79	128.77	119.32	128.92	160.24	–
47[a]	126.56	111.88	108.32	132.45	118.43	140.00	116.68	128.00	118.43	129.06	160.63	–

[a] $CO(CD_3)_2$, [b] CD_3OD, [c] DMSO as solvent.
^{13}C signals for the R^2 substituents: **26**, CH_3: 26.27; **27**, $CH_2CH_2CH_3$: 41.26, 23.17, 11.45; **28**, *c*-C_3H_5: C-1″: 22.71, C-2″, C-3″: 7.01; **29**, *c*-C_5H_9: C-1″: 50.89, C-2″,C-5″: 32.84, C-3″,C-4″: 24.11; **30**, CH_2Ph: C-1″: 140.50, C-2″, C6″: 129.50; C-4″: 128.10; C-3″, C5″: 128.47, CH_2: 43.93; **32**, CH_3: 25.21; **33**, CH_2CH_3: 33.70, 14.53; **34,** $CH_2CH_2CH_2CH_3$: 39.32, 31.99, 20.19, 13.87; **35**, *c*-C_3H_5: C-1″: 22.56, C-2″,C-3″: 5.59; **37**, CH_3: 26.27; **38**, CH_2CH_3: 34.40, 15.18, **39**, $CH_2CH_2CH_3$: 41.17, 23.17, 11.46; **40**, $CH_2CH_2CH_2CH_3$: 39.29, 31.97, 20.18, 13.85; **42**, N–CH_3: 33.92; **43**, *c*-C_3H_5: C1″: 22.67, C-2″, C-3″: 6.94; **44**, *c*-C_4H_7: C-1″: 44.76, C-2″, C-4″: 31.76, C-3″: 15.20; **45**, *c*-C_5H_9: C-1″: 51.25, C-2″, C-5″: 33.40; C-3″, C-4″: 23.85″; **46**, *c*-C_6H_{11}: C-1″: 48.23, C-2″, C-6″: 33.40; C-3″, C-4″, C5″: 25.00; **47**, CH_2Ph: C-1″: 140.00, C-2″, C6″: 128.31; C-4″: 126.76; C-3″, C5″: 127.27, CH_2: 41.98.

Table 6. ^{13}C NMR chemical shifts for compounds **48–56** δ (in ppm), in $CDCl_3$

Compound	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	CONH
48[a]	125.93	110.88	109.66	133.91	130.72	127.56	128.64	127.81	128.64	127.56	160.72
49[a]	126.11	111.22	109.82	135.63	130.70	127.61	128.63	127.85	128.63	127.61	160.30
50	126.90	110.35	107.49	135.77	131.98	124.94	129.10	127.46	129.10	124.94	161.46
51[b]	128.43	112.56	106.89	135.83	132.28	124.49	128.71	126.89	128.71	124.49	162.47
52[b]	129.93	112.21	110.47	136.15	130.62	127.05	128.42	127.64	128.42	127.05	160.50
53[b]	128.38	112.23	111.24	134.10	130.67	127.02	128.43	127.61	128.43	127.02	160.50
54	129.70	110.34	108.28	135.05	130.68	127.01	128.99	128.17	128.99	127.01	160.13
55[a]	125.13	112.26	110.06	135.04	130.70	126.98	128.43	127.58	128.43	126.98	160.60
56[a]	128.79	111.31	105.97	139.83	130.67	127.74	128.56	127.87	128.56	127.74	160.12

[a] $CO(CD_3)_2$, [b] CD_3OD as solvent.
^{13}C signals for the R^2 substituents: **48**, CH_3: 25.40; **49**, CH_2CH_3: 34.18, 14.98; **50**, $CH_2CH_2CH_3$: 41.47, 23.39, 11.66; **51**, $CH_2CH_2CH_2CH_3$: 39.04, 31.76, 20.05, 13.05, **52**, *c*-C_3H_5: C-1″: 21.24, C-2″–C-3″: 5.44; **53,** *c*-C_4H_7: C-1″: 44.89, C-2″, C-4″: 30.64, C-3″: 14.80; **54**, *c*-C_5H_9: C-1″: 51.56, C-2″, C-5″: 33.52; C-3″, C-4″: 23.89″, **56**, *c*-C_6H_{11}: C-1″: 48.85, C-2″, C-6″: 32.81; C-3″, C5″: 25.28, C-4″: 25.28; **56**, CH_2Ph: C-1″: 143.48, C-3″, C5″: 128.68; C-4″: 127.13; C-2″, C6″: 127.52, CH_2: 42.67.

These data indicate that the rotation around the bond linking the benzene and pyrrole rings is not free and that the value of energy barrier is about 20 kcal/mol.

Rotation around the benzene–pyrrole bond also implies the rotation of the 2′-NO_2 or 2′-NH_2 groups in order to allow both rings to be almost coplanar. Consequently, the conjugation between these groups and the benzene ring is broken, and this is another reason for the high energy barrier calculated for both molecules.

Experimental

Preparation of α-azido-5-phenyl-2,4-pentadienoic acid ethyl ester

To a stirred solution of ethyl azidoacetate (69.12 mmol) and cinnamadehyde **1d** (13.43 mmol) in dry ethanol, a solution of sodium ethanolate (70 mmol of Na in 60 ml of dry ethanol) was added dropwise. The reaction mixture was stirred under

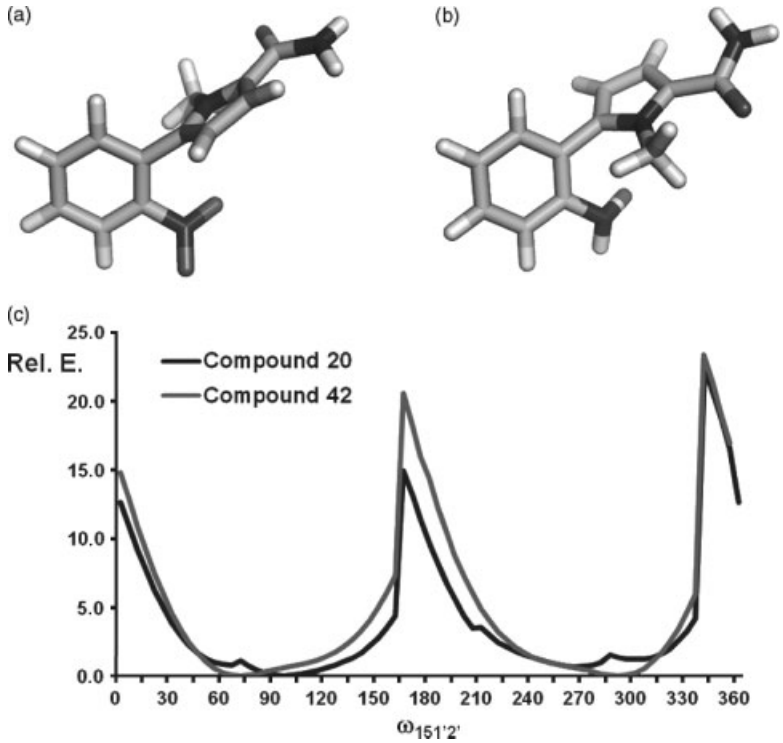

Figure 2. (a, b) The more stable conformers found for compound **20** and **42**, respectively; (c) Variation of the energy (kcal/mol) during the rotation of the torsional angle $\omega_{151'2'}$ in both compounds **20** and **42**.

argon atmosphere at −20 °C for 4.5 h, and then poured into water. The aqueous mixture was extracted with ethyl acetate (3 × 50 ml), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to yield a crude material, which was recrystallized from methanol/diethyl ether or ethyl acetate/hexane. This compound is unstable and spontaneously tends to cyclize to yield 5-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester, and **f**or this reason was not isolated.

Preparation of 5-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester

The α-azido-5-phenyl-2,4-pentadienoic acid ethyl ester was suspended in *p*-xylene and heated at 100 °C for 24 h. Evaporation of the solvent allows the isolation of 5-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester as a white solid after recrystallization from ethyl acetate/hexane.

Preparation of 5-phenyl-1*H*-pyrrole-2-carboxylic acid 3

Ethyl 5-phenyl-1*H*-pyrrole-2-carboxylate (2.04 mmol) was stirred and dissolved in 1 N NaOH solution (4.08 mmol) at 100 °C, glacial AcOH (4.08 mmol) was then added, and the solution was stirred at room temperature for 1 h. The solution was extracted with ethyl acetate (3 × 50 ml), and the combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated to yield a crude material that was recrystallized from ethyl acetate/hexane.

Preparation of 5-phenyl-1*H*-pyrrole-2-carboxylic acid alkylamide 48–51

$SOCl_2$ (11 mmol) was added to a solution of 5-phenyl-1*H*-pyrrole-2-carboxylic acid **3** (1 mmol) in dry CH_3CN (30 ml), and the reaction mixture was stirred at 65–80 °C for 5 h. After this period, the mixture was concentrated to dryness, yielding a brown solid (the acyl chloride) that was dissolved in CH_2Cl_2 (10 ml), and a solution of the appropriated amine (R^3NH_2, 2 mmol) and TEA (3 mmol) in CH_2Cl_2 (3 ml) was added dropwise. The reaction mixture was stirred for 3 h at room temperature, washed with H_2O several times, and the combined aqueous layers extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and the residue recrystallized or purified by flash chromatography.

5-Phenyl-1H-pyrrole-2-carboxylic acid methylamide (48)

(17%); mp 207 °C; MS (LSIMS) *m/z* 201.3546. $(M + H)^+$, Calcd. Mass for $C_{12}H_{13}N_2O$ 201.0923

5-Phenyl-1H-pyrrole-2-carboxylic acid ethylamide (49)

(22%); mp 172 °C; MS (LSIMS) *m/z* 237.1010 $(M + Na)^+$, Calcd. Mass for $C_{13}H_{14}N_2ONa$ 237.1003.

5-Phenyl-1H-pyrrole-2-carboxylic acid propylamide (50)

(62%); mp 135–137 °C; MS (LSIMS) *m/z* 251.1162 $(M + Na)^+$, Calcd. Mass for $C_{14}H_{16}N_2ONa$ 251.1160.

5-Phenyl-1H-pyrrole-2-carboxylic acid butylamide (51)

(22%); mp 115 °C; MS (LSIMS) *m/z* 265.1311$(M + Na)^+$, Calcd. Mass for $C_{15}H_{18}N_2ONa$ 265.1317

5-Phenyl-1H-pyrrole-2-carboxylic acid cyclopropylamide (52)

(12%); mp 197 °C; MS (LSIMS) *m/z* 249.7465 $(M + Na)^+$, Calcd. Mass for $C_{14}H_{14}N_2O$ Na 249.1192

5-Phenyl-1H-pyrrole-2-carboxylic acid cyclobutylamide (53)

(23%); mp 250 °C; MS (LSIMS) *m/z* 263.2437 $(M + Na)^+$, Calcd. Mass for $C_{15}H_{16}N_2ONa$ 263.1385

5-Phenyl-1H-pyrrole-2-carboxylic acid cyclopentylamide (54)

(18%), mp 239 °C; MS (LSIMS) *m/z* 255.1498 $(M + H)^+$, Calcd. Mass for $C_{16}H_{19}N_2O$ 255.1497

5-Phenyl-1H-pyrrole-2-carboxylic acid cyclohexylamide (55)

(20%); mp 213–215 °C; MS (LSIMS) *m/z* 291.6500 $(M + Na)^+$, Calcd. Mass for $C_{17}H_{20}N_2ONa$ 291.1600.

5-Phenyl-1H-pyrrole-2-carboxylic acid bencylamide (56)

(21%); mp 57 °C; MS (LSIMS) *m/z* 299.6856 $(M + Na)^+$, Calcd. Mass for $C_{18}H_{16}N_2ONa$ 299.1356.

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