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Dedicated to the memory of
Dr. Emilian GEORGESCU (1946-2020)

THE TRANSFORMATION OF BENZIMIDAZOLES INTO FLUORINATED PYRROLES *VIA* CYCLOADDITION REACTIONS OF BENZIMIDAZOLIUM N-YLIDES

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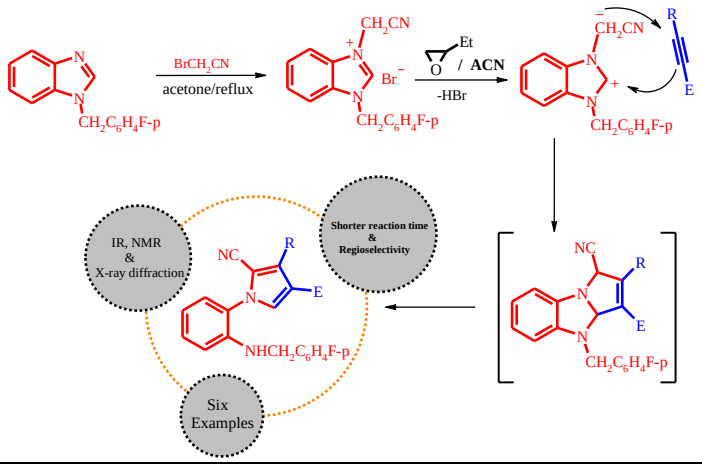
New highly substituted pyrroles with fluorine atoms in their structure were obtained through an improved two-stage procedure starting from 1-(4-fluorobenzyl)benzimidazole, bromoacetonitrile and electron-deficient alkynes *via* 1,3-dipolar cycloaddition of benzimidazolium *N*-ylides. The structures of new fluorine-substituted pyrroles were proved by IR and NMR spectroscopy and confirmed by X-Ray analysis.



INTRODUCTION

The incorporation of fluorine atoms in organic molecules increases their biological activity, bioavailability and bioaccessibility compared to the analogous non-fluorinated structures[1-14] and, as a consequence, over 20% of small molecule drugs contain one or more fluorine atoms. Fluorine-containing molecules are represented among the top best-selling small molecule synthetic drugs[4] and in the last two years, 28 new fluorine-based structures were approved for commercial use by the FDA.[4,5] As a result, new synthetic methods or improved procedures for obtaining new fluorinated compounds have been developed and their biological properties investigated.[3-14]

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Pyrrole is a privileged heterocyclic structure which is widely distributed among natural compounds such as haem, chlorophyll, vitamin B12 and marine alkaloids.[15-20] Lamellarin alkaloids **1-3** represent a large family of marine alkaloids which contain a pyrrole or a condensed pyrrole ring (Figure 1) and show antitumor activity.

It has been found that synthetic pyrroles possessing fluorine atoms in their molecules exhibit significant antitumoral, antibacterial, antiviral, anti-inflammatory and pesticide activities. For example, atorvastatin **5,** known also as Lipitor, is a statin inhibiting HMG-CoA-reductase and was between 1996 and 2012 the best-selling drug in the world. Other commercial fluorine pyrrole derivatives are the antitumoral sunitinib **6**, and the pro-insecticide chlorfenapyr **7**. The high pharmaceutical potential of natural and synthetic pyrroles stimulated new explorations in the field of pyrrole chemistry and biological applications.[1-14, 21-27]

1,3-Dipolar cycloaddition reaction of activated olefinic and acetylenic dipolarophiles with various 1,3-dipoles or masked 1,3-dipoles is one of the key methods for the preparation of pyrroles and condensed pyrroles.[3, 26-32] In particular, the cycloaddition reaction of heteroaromatic *N*-ylides **11** as cyclic azomethine 1,3-dipoles with acetylenic or olefinic dipolarophiles is a readily accessible route to afford pyrroloazoles and pyrroloazines **12**.[30-36] In most cases, *N*-ylides **11** are generated *in situ* by deprotonating cycloimmonium salts **10** resulting from the reaction between aromatic *N*-heterocycles **9** and halogenated derivatives (Scheme 1).

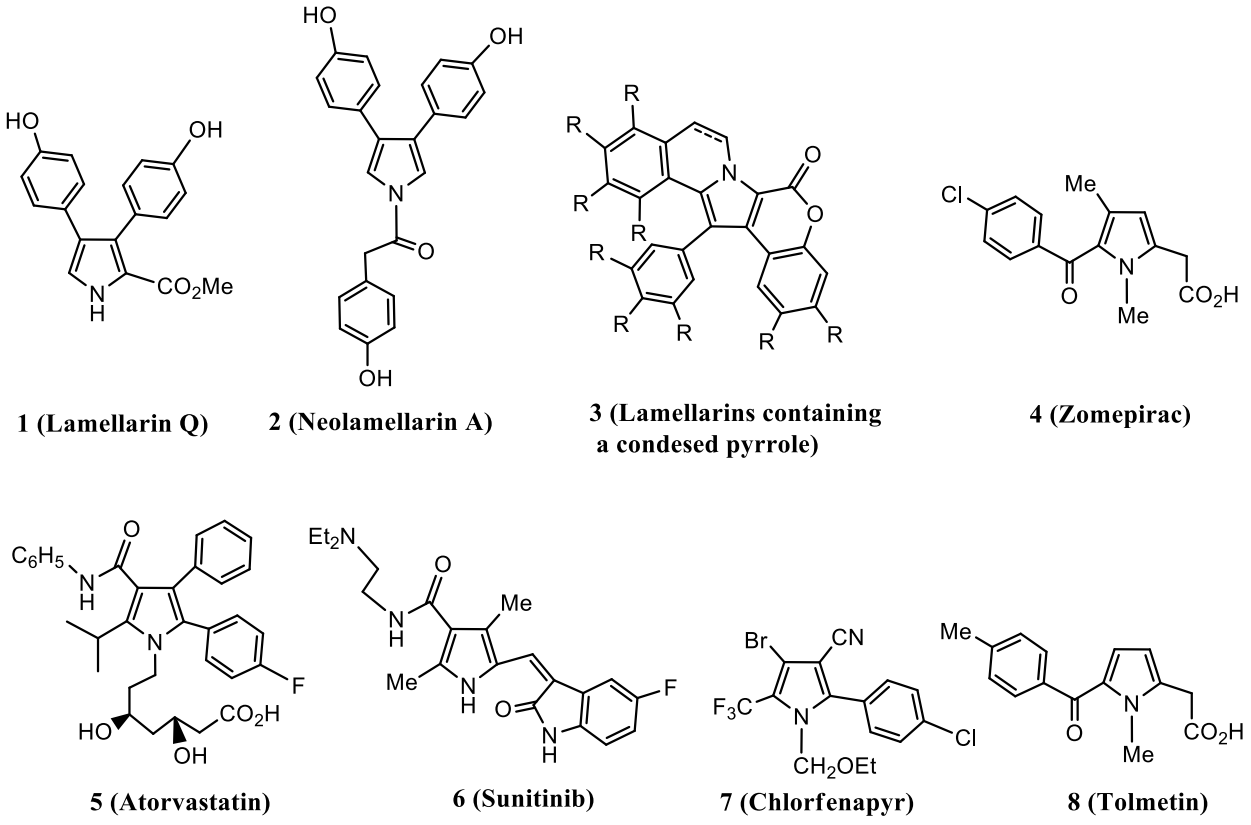
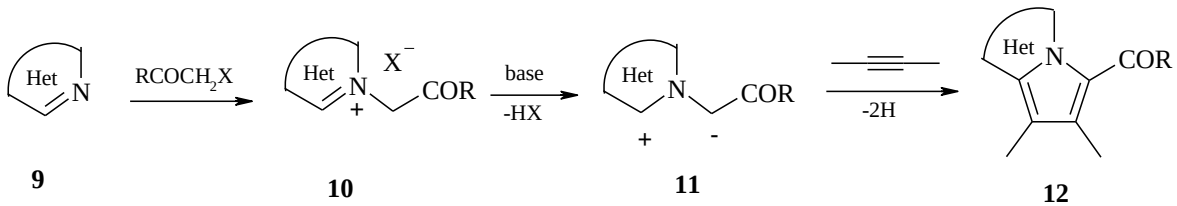
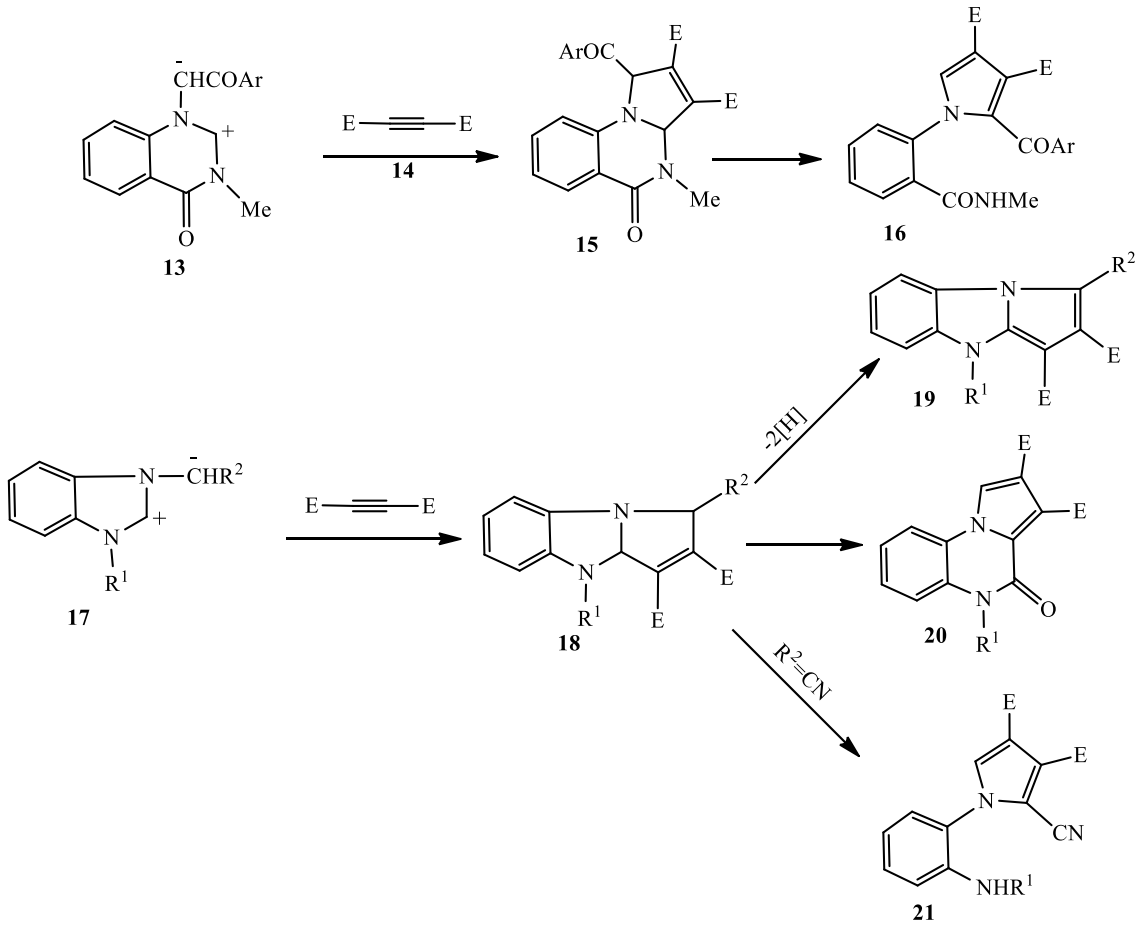


Fig. 1 – Drugs containing a pyrrole ring system.



Scheme 1 – Transformation of aromatic *N*-heterocycles **9** into condensed pyrrolo derivatives **12**, by two-step [3+2] cycloaddition reaction.



Scheme 2 – Quinazolinium or benzimidazolium *N*-ylides as precursors of pyrroles or pyrrolo condensed *N*-heterocycles.

Unexpected formation of pyrroles (Scheme 2) was reported in the reaction of quinazolinium *N1*-ylides **13**[37-39] and benzimidazolium *N3*-ylides **17** with activated acetylenic dipolarophiles **14.**[40,41] From *N1*-quinazolinium ylides **13**, pyrroles **16** were obtained**,** whereas from benzimidazolium *N3*-ylide **17**, a mixture of the expected pyrrolo[1,2-*a*]benzimidazole **19** and/or pyrrolo[1,2-*a*]quinoxaline **20** resulted. By changing the substituent attached to N3 of the benzimidazole salts (R^2=CN), substituted pyrroles **21** were obtained.[40] The formation of pyrroles or condensed pyrroles is caused by the susceptibility of the so-called primary cycloadducts of type **15** and **18** to undergo either dehydrogenation or ring opening, assisted by, among other factors, the nature or the electron withdrawing strength of the R^2 substituent.

The synthesis of condensed pyrroles **12**, isomerisation and aromatization of primary cycloadducts and isolation of the reaction intermediates resulting from [3+2] cycloaddition of heteroaromatic *N*-ylides were exemplified by our group for several cases (Scheme 2).[3, 26-32]

Herein is presented an improved two-step method for the synthesis of fluorine-containing pyrroles starting from 1-(4-fluorophenyl)benzimidazole, bromoacetonitrile and activated acetylenes. The structures of the new pyrroles were deduced by NMR spectroscopy and confirmed by X-ray analysis.

RESULTS AND DISCUSSION

The starting material for the synthesis of fluorine-containing pyrroles was 1-(4-fluorobenzyl)-3-cyanomethylbenzimidazolium bromide **23** (Scheme 3). The benzimidazolium bromide was obtained in a yield of 81% by reaction of 1-(4-fluorobenzyl)benzimidazole **22** with bromoacetonitrile in acetone under reflux for 10 h. The formation of benzimidazolium bromide **23** was confirmed by NMR spectroscopy. In the ^{1}H-NMR spectrum recorded in DMSO-d_6 the H-2 proton is strongly deshielded due to the vicinity of the two nitrogen atoms and appears as a singlet at 10.00 ppm. The protons of the two methylenic groups appear as two singlets at 5.83 and 5.98 ppm, respectively. The ^{13}C-NMR spectrum shows all the expected signals. The carbon C-2 appears strongly deshielded at 143.7 ppm and the C-4' substituted

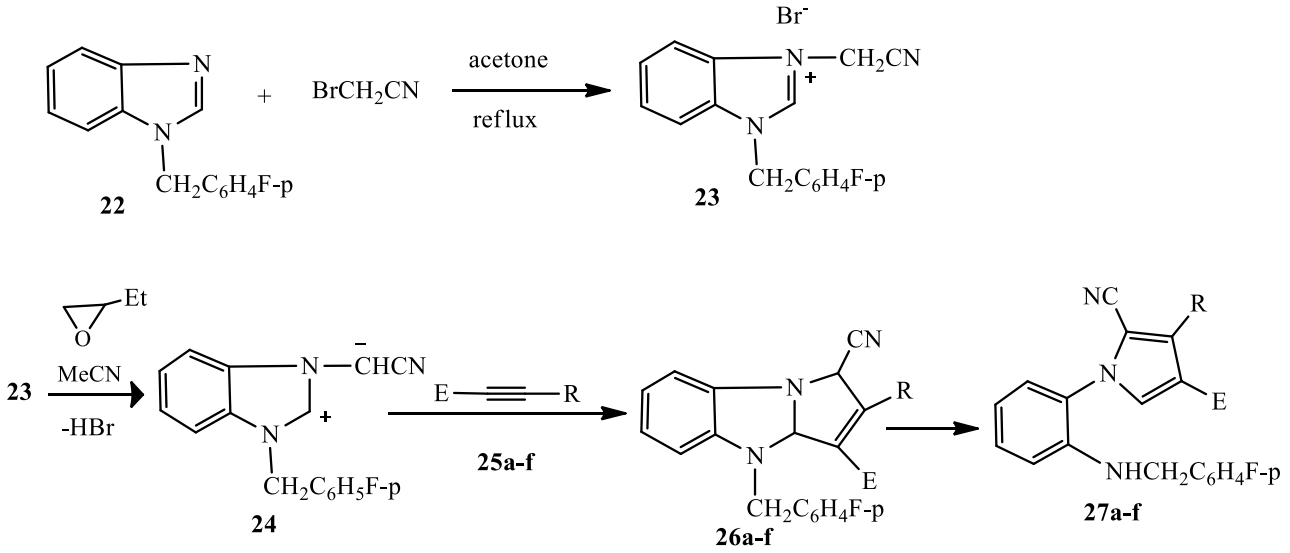
with the fluorine atom appears as a doublet at 162.3 ppm (J = 255.3 Hz) due to the heteronuclear coupling with the fluorine atom. Other relevant chemical shifts are those for the CN group (114.3 ppm) and the two methylene groups (35.2 and 49.5 ppm). It is interesting to note that the vibrational band corresponding to the cyano group has a very weak intensity in the ATR-IR spectrum.

It was reported that the transformation of 3-cyanomethylbenzimidazolium bromides into corresponding pyrroles **21** performed in 1,2-epoxybutane required a long reaction time of 3 days to complete.[40] Usually, the generation of the *N*-ylides from *N*-heterocycle salts and subsequent cycloaddition reactions of the *N*-ylides with activated alkynes proceed with high reaction rates. Probably, the long reaction time required for the formation of the pyrroles **21** is due to the low solubility of benzimidazolium salts in 1,2-epoxybutane. Taking into account this hypothesis and the solubility of benzimidazolium bromide **23** in hot acetonitrile it has been found that its transformation into corresponding pyrroles **27** could be achieved in 4-5 h using as reaction medium a mixture of 1,2-epoxybutane and acetonitrile 1:1. The reaction progress was established based on ^{1}H-NMR data which ensured that five hours are sufficient for the complete conversion of the benzimidazolium bromide.

From NMR data and X-ray analysis it was concluded that for terminal alkynes HC≡CCOR (R=Ph, OAlk) the reaction is completely regioselective because only the regioisomer having a COR group at the 4-position of the pyrrole ring was detected. The substituent electronic effects are sufficiently strong to give only a regioisomer.

The reaction pathway for the formation of pyrroles **27** implies the *in situ* generation of the benzimidazolium cyanomethylide **24** from the corresponding benzimidazolium bromide **23** under the action of 1,2-epoxybutane. By the [3+2] dipolar cycloaddition reaction between the alkyne dipolarophiles **25** such as benzoylacetylene **25a**, methyl propiolate **25b**, ethyl propiolate **25c**, isopropyl propiolate **25d**, dimethyl acetylenedicarboxylate **25d**, and diethyl acetylenedicarboxylate **25f** with the cyanomethylide **24**, the key intermediates, dihydropyrrolo[1,2-*a*]benzimidazoles **26a-f**, are produced; these intermediates, *via* spontaneous ring opening followed by deprotonation, give stable pyrrole derivatives **27a-f**.

The structural assignments of new pyrroles **27a-f** were made by elemental analysis, IR and NMR spectroscopy and X-ray diffraction. The IR bands in the range 3356-3408 cm^{-1} were attributed to the amino group NH displaying the secondary amine pattern. The frequency range 2219-2235 cm^{-1} was attributed to the C≡N groups. Other IR spectral features for the pyrroles **27b-f** are the bands in the region 1700-1745 cm^{-1} attributed to ester C=O groups.



a: R=H, E=COPh; b: R=H, E=CO_2Me; c: R=H, E=CO_2Et; d: R=H, E=CO_2*i*Pr; e: R=E=CO_2Me; f: R=E=CO_2Et

Scheme 3 – Synthesis of the pyrroles **27a-f** starting from the corresponding benzimidazolium *N*-ylide **23.**

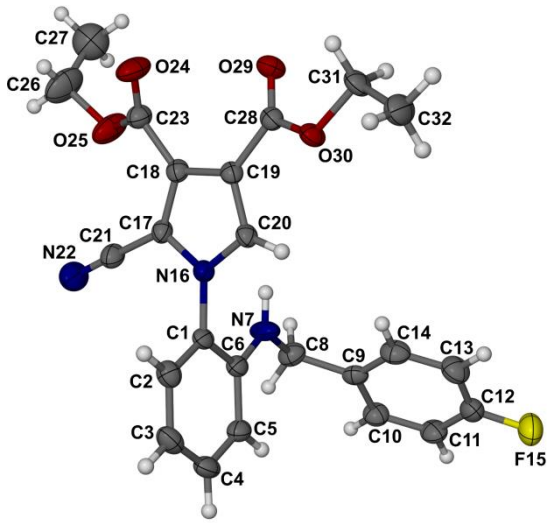


Fig. 2 – A perspective view of representative molecule A of compound **27f** showing the atomic numbering scheme and thermal ellipsoids drawn at the 50% probability level. Only the major disorder component of the ethyl group involving C26A and C27A is shown for clarity.

The NMR data for compounds **27** are in good agreement with their pyrrolic structure. In the case of pyrroles resulting from terminal alkynes (HC≡CCOR), the protons H-3 and H-5 of the pyrrole ring appear as two doublets with a coupling constant of 1.6 Hz. For pyrroles obtained from acetylenedicarboxylate esters, the proton on the pyrrole ring appears in the ^{1}H-NMR spectra as a singlet in the range δ = 7.38-7.41 ppm. A characteristic feature in the ^{1}H-NMR spectra that confirmed their pyrrole structure is emphasized by the presence of the signals due to the amino group (NH) which appears as a triplet due to the coupling with benzylic protons. The signal of the benzylic protons lies in the range 4.21-4.33 ppm, appearing as a doublet with a coupling constant of ca. 5.2 Hz. The proton signals of the two benzene rings appear in the expected aromatic regions.

The representative chemical shifts in the ^{13}C-NMR spectra are those for benzylic, OAlk and carbonyl groups. The chemical shifts for benzylic carbons are in the range δ = 46.9-47.1 ppm. The chemical shifts of the carbonyl groups appear at 188.9 ppm for ketone **27a** and in the range 161.3-163.2 ppm for esters. The chemical shifts of the fluorine-bearing C atoms of the benzene rings were easily deduced from the value of the coupling constant C-F. For example, the carbon atom attached to the fluorine atom appears as a doublet with $^{1}J_{C\text{-}F}$ = 245.6 Hz.

The stereochemistry of cycloadducts **27** were confirmed by X-ray analysis of a crystal of the representative compound **27f**, for which the crystal data and refinement parameters are provided.[42] With four molecules in the triclinic unit cell and the space group P(-1) the crystal asymmetric unit consists of two independent molecules of **27f** designated A and B, with somewhat different conformations. Figure 2 shows the common atomic numbering scheme with molecule A as representative, the full atom numbers for the two independent molecules being suffixed with 'A' and 'B' respectively in the deposited CIF file.[42]

In molecule A, the pyrrole ring and attached phenyl moiety are nearly orthogonal (interplanar angle 88.8(1)°), whereas in molecule B the corresponding parameter is 71.5(1)°. Another significant conformational difference is reflected in the dihedral angle of the chain linking the two phenyl rings, namely C6-N7-C8-C9, whose value is -86.0(2)° in A and 62.3(2)° in B. A minor irregularity in molecule A was detected, namely twofold disorder of one of the ethyl groups. This was duly modelled, the site-occupancy factors of the major and minor components refining to 0.64(1) and 0.36(1) respectively.

The presence of four molecules in the unit cell leads to interesting supramolecular features in the crystal. Thus, each of the two independent molecules (A, B) is engaged in head-to-tail hydrogen bonded dimer formation with its centrosymmetric counterpart (A′, B′ respectively). For clarity, the representative centrosymmetric dimer AA′ is shown in simplified form in Figure 3, the unique H-bond being that between the amino group of molecule A and the carbonyl oxygen of one of the -CO_2Et groups of molecule A′ [N7A-H···O29A^{i} (i = 1-x, 1-y, 1-z) with N7A··O29A^{i} 2.886(2) Å and angle N-H···O 151°].

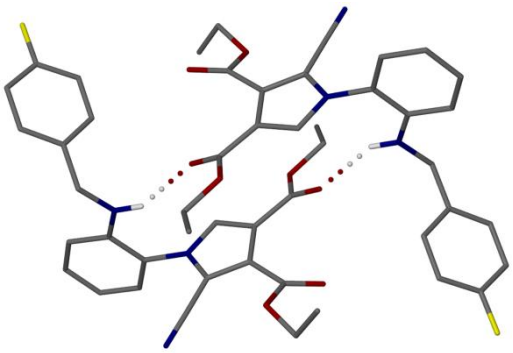


Fig. 3 – Head-to-tail N-H···O hydrogen bonding between molecule A and its centrosymmetric counterpart A′.

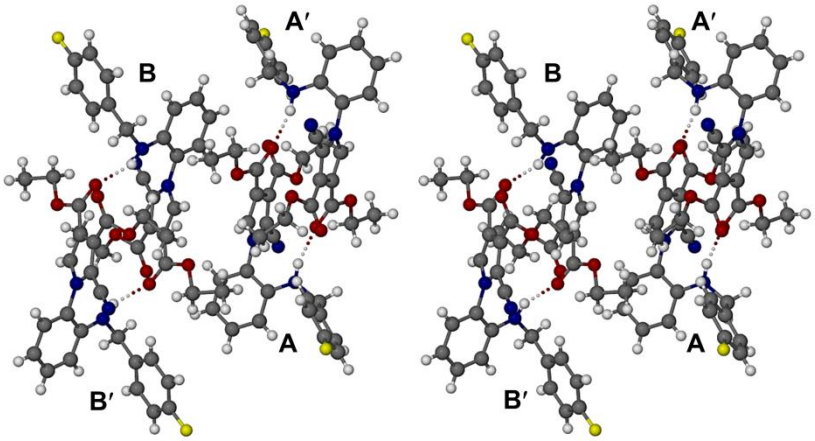


Fig. 4 – Stereoview of analogous head-to-tail N-H···O hydrogen bonding occurring in the two dimeric structures AA′ and BB′.

The corresponding parameters for the H-bonded dimer BB′ are 3.143(2) Å and 153°. It is important to mention that the carbonyl oxygen acceptor atom in molecule B′ is O29B^{ii} (ii = 1-x, 1-y, 2-z), which is chemically equivalent to O29A^{i} (see atomic numbering in Figure 2). That is, the two crystallographically distinct dimers AA′ and BB′ have the same chemical bonding connectivity but they adopt somewhat different conformational features. This is also evident from Figure 4, a stereoscopic view highlighting the hydrogen bonding geometries as well as the spatial relationship between the two dimers. One pronounced asymmetry between the dimeric structures that contributes to their different conformations is that in dimer AA′ the N···O(carbonyl) distances are quite distinct (N···O29 = 2.886(2) Å, N···O24 = 4.796(2) Å, the former distance corresponding to a fairly strong H-bond) whereas in dimer BB′ they are very similar (N···O29 = 3.142(2) Å, N···O24 = 3.161(2) Å, the former representing a weaker H-bond and the latter, a still weaker interaction, and one with inferior geometry). There are no other significant hydrogen bonds or π-interactions in the crystal.

EXPERIMENTAL

1-(4-Fluorobenzyl)-3-cyanomethyl-benzimidazolium bromide (**23**). To 20 mmol 1-(4-fluorobenzyl)-benzimidazole **22** dissolved in 100 mL acetone was added 3.4 g (30 mmol, 1 mL) of bromoacetonitrile and the mixture was refluxed for 10 h. After cooling of the reaction mixture, the precipitate was filtered and washed with acetone on the filter. The benzimidazolium bromide was used in the next step without purification. The compound was purified by crystallization from ethanol or acetonitrile as colorless crystals with mp 232-4°C. Yield 81%. Anal. Calcd. $C_{16}H_{13}BrFN_3$: C, 55.51; H, 3.78; N, 12.14. Found C, 55.80; H, 4.11; N, 12.42. ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 5.83, 5.98 (2s, 4H, 2CH$_2$); 7.25-7.31 (m, 2H, H-3', H-5"); 7.63-7.80 (m, 4H, H-5, H-6, H-2', H-6'); 8.01-8.04, 8.11-8.15 (2m, 2H, H-4, H-7); 10.00 (s, 1H, H-2). ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 35.2 (CH$_2$CN); 49.5 (CH$_2$N); 113.5, 114.4 (C-5, C-8); 114.3 (C≡N); 115.9 (d, *J*=21.5 Hz, C-3', C-5'); 127.2, 127.4 (C-6, C-7); 131.1 (d, *J*=14.5 Hz, C-2', C-6'); 129.6, 130.6, 130.7 (C-3a, C-8a, C-1'); 143.7 (C-2); 162.3 (d, *J*=255.3 Hz, C-4').

General procedure for synthesis of pyrroles 27

To a solution mixture obtained from 10 mL 1,2-epoxybutane and 10 mL acetonitrile were added 1.05 g (3 mmol) of benzimidazolium bromide **23** and 3.5 mmol of acetylenic dipolarophile. The reaction mixture was heated under reflux with stirring for 6 h and then the solvent was evaporated under vacuum and the residue was purified by column chromatography on Merck alumina (70-230 mesh) and using as eluent dichloromethane.

4-Benzoyl-2-cyano-1-[2-(4-fluorobenzylamino)phenyl)]pyrrole (**27a**). The compound was obtained from 0.45 g (3.5 mmol, 0.41 mL) benzoylacetylene (**25a**) and purified by crystallization from ethanol as colorless crystals with mp 142-4°C; Yield 51%. Anal. Calcd. $C_{25}H_{18}FN_3O$: C, 75.93; H, 4.59; N, 10.63. Found: C, 76.14; H, 4.72; N, 10.86. IR (ATR-solid): 1632 cm^{-1} ($\nu_{C=O}$); 2219 cm^{-1} ($\nu_{C\equiv N}$); 3356 cm^{-1} (ν_{NH}) 3126 cm^{-1} (ν_{CH}). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.86 (bs, 1H, *J*=5.2 Hz, NH), 4.33 (s, 2H, CH_2N), 6.71-6.75 (m, 1H, Ar), 6.79-6.84 (m, 1H, Ar), 7.01 (t, 2H, *J*=8.6 Hz, C_6H_4F), 7.17-7.21 (m, 1H, Ar); 7.27-7.34 (m, 3H, Ar, C_6H_4F), 7.45 (d, 1H, *J*=1.6 Hz, H-3); 7.46-7.52 (m, 2H, COPh), 7.52 (d, 1H, *J*=1.6 Hz, H-5), 7.56-7.61 (m, 1H, COPh), 7.81-7.85 (m, 2H, COPh).^{13}C-NMR (75 MHz, $CDCl_3$) δ: 47.1 (CH_2N); 107.6, 112.0, 122.8 (3C, quaternary); 112.7 (C-3'); 115.7 (d, *J*=21.3 Hz, C_6H_4F); 117.6 (C-5'); 122.6 (C-3); 125.8 (C-4); 127.8 (C-6'); 128.7 (d, *J*=8.0 Hz, *meta*-C_6H_4F); 128.7, 129.0, 131.6, 138.4 (6C, phenyl); 132.5 (C-4'); 132.8(C-5); 133.8 (d, *J*=3.1 Hz, C_6H_4F); 143.4 (C-1'); 162.2 (d, *J*=245.6 Hz, C-F); 188.9 (CO).

Methyl 2-cyano-1-[2-(4-fluorobenzylamino)phenyl]pyrrole-4-carboxylate (**27b**). The compound was obtained from 0.29 g (3.5 mmol, 0.31 mL) methyl propiolate (**25b**) and purified by crystallization from ethanol as colorless crystals with mp 132-4°C. Yield 61%. Anal. Calcd. $C_{20}H_{16}FN_3O_2$: C, 68.76; H, 4.62; N, 12.03. Found C, 72.77; H, 5.34; N, 12.91. IR (ATR): 1702 cm^{-1} ($\nu_{C=O}$); 2230 cm^{-1} ($\nu_{C\equiv N}$); 3125 cm^{-1} (ν_{CH}); 3384 cm^{-1} (ν_{NH}). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.76 (t, 1H, *J*=5.2 Hz, NH); 3.79 (s, 3H, MeO); 4.30 (d, 2H, *J*=5.2 Hz, CH_2N); 6.64-6.68 (m, 1H, Ar); 6.72-6.77 (m, 1H, Ar); 6.96 (t, 2H, *J*=8.6 Hz, C_6H_4F); 7.07-7.10 (m, 1H, Ar); 7.21-7.28 (m, 3H, Ar, C_6H_4F); 7.32 (d, 1H, *J*=1.6 Hz, H-3); 7.47 (d, 1H, *J*=1.6 Hz, H-5).^{13}C-NMR (75 MHz, $CDCl_3$) δ: 47.1 (CH_2N); 51.9 (MeO); 107.2, 112.1, 118.4, 122.8, 143.4 (5C, quaternary); 112.7, 117.6, 121.9, 128.0, 131.6, 131.8 (6C, tertiary); 115.7 (d, *J*=21.5 Hz, *ortho*-C_6H_4F); 128.7 (d, *J*=8.0 Hz, *meta*-C_6H_4F); 133.9 (d, *J*=3.1 Hz, *para*-C_6H_4F); 163.2 (COOMe); 162.2 (d, *J*=245.6 Hz, C-F).

Ethyl 2-cyano-1-[2-(4-fluorobenzylamino)phenyl]pyrrole-4-carboxylate (**27c**). The compound was obtained from 0.34 g (3.5 mmol, 0.35 mL) ethyl propiolate (**25c**) and purified by crystallization from ethanol as colorless crystals with mp 132-4°C. Yield 61%. Anal. Calcd. $C_{21}H_{18}FN_3O_2$: C, 69.41; H, 4.99; N, 11.56. Found C, 72.77; H, 5.34; N, 12.91. IR (ATR): 1700 cm^{-1} ($\nu_{C=O}$); 2227 cm^{-1} ($\nu_{C\equiv N}$); 3124 cm^{-1} (ν_{CH}); 3389 cm^{-1} (ν_{NH}). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (t, 3H, *J*=7.1 Hz, Me); 3.76 (t, 1H, *J*=5.4 Hz, NH); 4.21-4.30 (m, 4H, CH_2O, CH_2N); 6.64-6.68 (dd, 1H, *J*=7.4, 1.6 Hz, Ar); 6.72-6.77 (m, 1H, Ar); 6.96 (t, 2H, *J*=8.6 Hz, C_6H_4F); 7.08 (dd, 1H, *J*=7.9, 1.6 Hz, Ar); 7.21-7.28 (m, 3H, Ar, C_6H_4F); 7.32 (d, 1H, *J*=1.6 Hz, H-3); 7.47 (d, 1H, *J*=1.6 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 47.0 (CH_2N); 60.7 (CH_2O); 107.1, 112.1, 118.7, 122.9, 143.4 (5C, quaternary); 112.6, 117.6, 121.9, 128.0, 131.5, 131.7 (6C, tertiary); 115.7 (d, *J*=21.5 Hz, *ortho*-C_6H_4F); 128.7 (d, *J*=8.0 Hz, *meta*-C_6H_4F); 133.9 (d, *J*=3.1 Hz, *para*-C_6H_4F); 162.8 (COO); 162.2 (d, *J*=245.6 Hz, C-F).

Isopropyl 2-cyano-1-[2-(4-fluorobenzylamino)phenyl]pyrrole-4-carboxylate (**27d**). The compound was obtained from 0.39 g (3.5 mmol, 0.39 mL) isopropyl propiolate (**25d**) and purified by crystallization from ethanol as colorless crystals with mp 102-3°C; yield 47%. Anal. Calcd. $C_{22}H_{20}FN_3O_2$: C, 70.01; H, 5.34; N, 11.13. Found C, 70.32; H, 5.57; N, 11.38. IR (ATR): 1705 cm^{-1} ($\nu_{C=O}$); 2226 cm^{-1} ($\nu_{C\equiv N}$); 3114 cm^{-1} (ν_{CH}); 3395 cm^{-1} (ν_{NH}). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.26 (d, 6H, *J*=6.3 Hz, 2Me); 3.76 (t, 1H, *J*=5.4 Hz, NH); 4.21-4.30 (m, 4H, CH_2O, CH_2N); 5.23 (spt, 1H, *J*=6.3 Hz, $CHMe_2$); 6.64-6.68 (dd, 1H, *J*=7.4, 1.6 Hz, Ar); 6.71-6.76 (m, 1H, Ar); 6.96 (t, 2H, *J*=8.6 Hz, C_6H_4F); 7.08 (dd, 1H, *J*=7.9, 1.6 Hz, Ar); 7.21-7.28 (m, 3H, Ar, C_6H_4F); 7.31 (d, 1H, *J*=1.6 Hz, H-3); 7.46 (d, 1H, *J*=1.6 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.1 (2Me); 47.1 (CH_2N); 68.2 (CH); 107.0, 112.1, 119.2, 122.9, 143.5 (5C, quaternary); 112.6, 117.6, 121.9, 128.0, 131.5, 131.7 (6C, tertiary); 115.7 (d, *J*=21.5 Hz, *ortho*-C_6H_4F); 128.7 (d, *J*=8.0 Hz, *meta*-C_6H_4F); 133.9 (d, *J*=3.1 Hz, *para*-C_6H_4F); 162.2 (COO); 162.2 (d, *J*=245.6 Hz, C-F).

Dimethyl 2-cyano-1-[2-(4-fluorobenzylamino)phenyl]pyrrole-3,4-dicarboxylate (**27e**). The compound was obtained from 0.49 g (3.5 mmol, 0.43 mL) dimethyl acetylenedicarboxylate (**25e**) and purified by crystallization from 2-propanol as colorless crystals with mp 124-6°C; Yield 46%. Anal. Calcd. $C_{22}H_{18}FN_3O_4$: C, 64.86; H, 4.45; N, 10.31. Found C, 65.11; H, 4.77; N, 10.60. IR (ATR): 1718 cm^{-1}, 1745 cm^{-1}($\nu_{C=O}$); 2235 cm^{-1} ($\nu_{C\equiv N}$); 3127 cm^{-1} (ν_{CH}); 3408 cm^{-1} (ν_{NH}).^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.79, 3.88 (2s, 6H, MeO); 4.01 (t, 1H, *J*=5.5, NH); 4.31 (d, 2H, *J*=5.5, CH_2N); 6.62-6.66 (m, 1H, Ar); 6.71-6.77 (m, 1H, Ar); 6.96 (t, 2H, *J*=5.5, 8.5 Hz, *ortho*-C_6H_4F); 7.06-7.28 (m, 1H, Ar); 7.23-7.29 (m, 3H, Ar, *ortho*-C_6H_4F); 7.41 (s, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 46.9 (CH_2N); 52.3, 52.8, (2MeO); 110.1, 110.6, 117.8, 122.0, 125.8, 143.3 (6C, quaternary); 112.9, 117.6, 128.0, 131.9, 132.2 (5C, tertiary); 115.8 (d, *J*=21.5 Hz, *ortho*-C_6H_4F); 128.7 (d, *J*=8.0 Hz, *meta*-C_6H_4F); 133.3 (d, *J*=3.2 Hz, *para*-C_6H_4F); 161.6, 162.2 (2COO); 162.2 (d, *J*=245.6 Hz, C-F).

Diethyl 2-cyano-1-[2-(4-fluorobenzylamino)phenyl]pyrrole-3,4-dicarboxylate (**27f**). The compound was obtained from 0.59 g (3.5 mmol, 0.56 mL) diethyl acetylenedicarboxylate (**25f**) and purified by crystallization from 2-propanol as colorless crystals with mp 124-6°C; Yield 46%. Anal. Calcd. $C_{24}H_{22}FN_3O_4$: C, 66.20; H, 5.09; N, 9.65. Found C, 66.36; H, 5.27; N, 9.81. IR (ATR): 1715 cm^{-1}, 1739 cm^{-1} ($\nu_{C=O}$); 2232 cm^{-1} ($\nu_{C\equiv N}$); 3141 cm^{-1} (ν_{CH}); 3384 cm^{-1} (ν_{NH}). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.27, 1.34 (2t, 6H, *J*=7.1, 2Me); 3.88 (t, 1H, *J*=5.5, NH); 4.21-4.29 (m, 6H, CH_2N, $2CH_2O$); 6.62-6.66 (m, 1H, Ar); 6.70-6.76 (m, 1H, Ar); 6.95 (t, 2H, *J=5.5*, 8.5 Hz, *ortho*-C_6H_4F); 7.05-7.27 (m, 1H, Ar); 7.21-7.27 (m, 3H, Ar, *ortho*-C_6H_4F); 7.38 (s, 1H, H-5).^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.2, 14.3, (2Me); 46.9 (CH_2N); 61.3, 62.0 ($2CH_2O$); 109.6, 110.6, 118.3, 122.1, 126.3, 143.3 (6C, quaternary); 112.9, 117.7, 128.0, 131.89, 131.92 (5C, tertiary); 115.8 (d, *J*=21.5 Hz, *ortho*-C_6H_4F); 128.7 (d, *J*=8.0 Hz, *meta*-C_6H_4F); 133.8 (d, *J*=3.2 Hz, *para*-C_6H_4F); 161.3, 161.9 (2COO); 162.2 (d, *J*=245.6 Hz, C-F).

CONCLUSIONS

The transformation of 1-(4-fluorobenzyl)benzimidazole into highly substituted fluorinated pyrroles was achieved by a modified two-stage procedure involving alkylation of benzimidazole compounds at N3 to form the corresponding benzimidazolium salt and its reaction with electron deficient alkynes as dipolarophiles. The resulting

pyrroles **27** are under investigation regarding their possible biological activities.

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42. Crystal data for **27f**: $C_{24}H_{22}FN_3O_4$, M = 435.44, colourless plate, 0.350 × 0.130 × 0.060 mm^3, space group P(-1) (No. 2), a = 11.337(1), b = 12.540(1), c = 16.165(2) Å, α = 105.472(2), β = 91.555(2), γ = 92.361(2)°, V = 2211.2(4) $Å^3$, Z = 4, D_c = 1.308 g/cm^3, F_{000} = 912, Bruker Apex Duo diffractometer, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, $2\theta_{max}$ = 55.9º, 41849 reflections collected, 10600 unique (R_{int} = 0.0494). Final GooF = 1.016, R_1 = 0.0457, wR_2 = 0.1022, R indices based on 7237 reflections with I > 2σ(I) (refinement on F^2), 599 parameters, 14 restraints. Lp and absorption corrections applied, μ = 0.096 mm^{-1}. CCDC Number: ***2103548***.