Synthesis and fluorescence properties of 4-aminobenzo[*f*]isoindole derivatives

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We report a new route to benzo[*f*]isoindole derivatives that possess strong fluorescence. The structure of the newly synthesised compounds was confirmed by NMR, IR and mass spectra, along with X-ray crystallographic studies. Absorption and fluorescence spectra of the new compounds were recorded. It was established that tautomerism of 4-aminobenzo[*f*]isoindoles defines the properties of these compounds. Also, the influence of substituents at the N-2 position on the luminescence properties was studied; the fluorescence intensity is dependent on the water content in organic solvents, and can be used to indicate their moisture content.

Keywords: isoindoles, maleimides, cycloadditions, rearrangements, fluorescence spectra

One of the major aspects of isoindole chemistry[1,2] is the aspect of isoindole–isoindoline tautomerism.[3] It is well-known that the isoindole tautomer easily undergoes the Diels–Alder reaction. This fact allows not only the identification of unstable isoindoles[4–6] but also, which is highly important, enables the design of unusual spatial structures that cannot be formed by other synthetic routes. Depending on the type of reaction control (kinetic or thermodynamic) it is possible to isolate either the *endo*- or the *exo*-adducts, and a variety of methods can be used to determine their structure.[7,8]

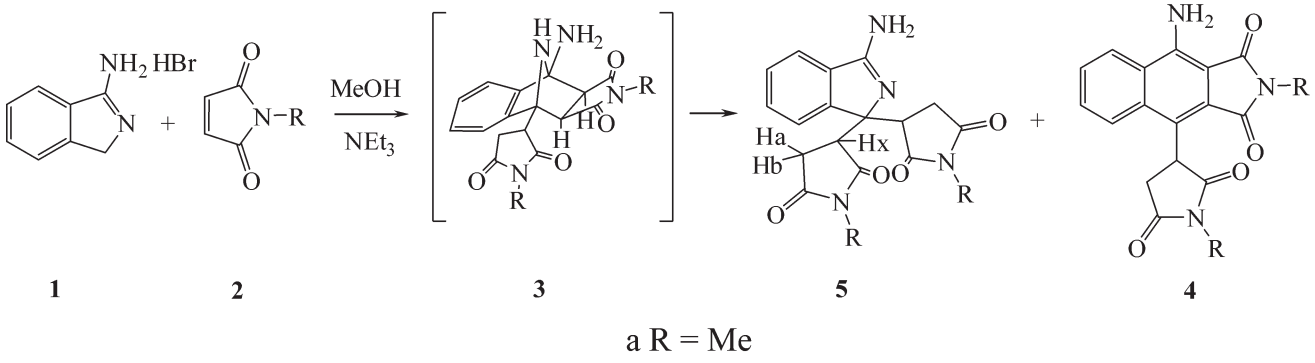
The aptitude of non-fused isoindoles, which exist primarily in the isoindoline form, to undergo cycloaddition reactions has not been investigated and therefore is of interest. Recently, we have shown that 1-aminoisoindole, with its primary form being the isoindoline tautomer, is also capable of undergoing [2+4]-cycloaddition which can be accounted for by the Curtin–Hammett principle. Diels–Alder adducts derived from fused azino- and azoloisoindoles with maleimides undergo further rearrangements and form compounds with addends in both a 1:1 and 1:2 ratio, that possess intriguing properties.[9–12]

Reaction of 2,4-dimethylpyrimido[2,1-*a*]isoindole with a variety of maleimides gives derivatives of 4-aminobenzo[*f*] isoindole which exhibit notably strong fluorescence.[12] In the current research, we developed a new synthetic route to the latter compounds, giving better yields and easier to implement than the existing one.[12] The structures of the substances synthesised were confirmed by spectral methods and X-ray crystal analysis. Absorption and fluorescence spectra were recorded and it was noted that these spectral data are highly dependent upon substituents and on the water content in organic solvents. Solvatochromic dyes have been used as indicators for the determination of micro water content in aprotic organic solvents. There are fluorescence lifetime-based sensors, and wavelength-based fluorescent and intensity-based indicators.[13–15] However, measurement of lifetime is not applicable to convenient on-line determinations. Indicators based on decreasing of fluorescence suffer greatly from external disturbance of the indicator dye and signal drift of the measuring equipment, especially in determinations of low-level water concentrations. The compounds described in the manuscript can be used as increasing intensity-based indicators for determining the water content in aprotic organic solvents. Compared with the decreasing intensity-based indicators, the new dyes could be less susceptible to these adverse effects.

Results and discussion

We have recently shown that a *bis*-Michael adduct **5** is formed when 1-aminoisoindole reacts with maleimide derivatives.[16] We noticed that a small amount of a substance having strong blue fluorescence was also obtained. Analysis of the data[12] and the newly acquired data proved the fluorescent product to be a derivative of benzo[*f*]isoindole. Formation of this compound provided evidence that the reaction involves formation of the Diels–Alder cycloaddition product which can transform into either the *bis*-Michael adduct **5** (when the C–C bond is cleaved) or the adduct **4** (when a molecule of ammonia is eliminated).

However, the new route to fluorescent benzo[*f*]isoindole derivatives is strongly dependent upon the nature of the



Scheme 1 Interaction of 1-aminoisoindole hydrobromide with *N*-methylmaleimide in the ratio 1:2.

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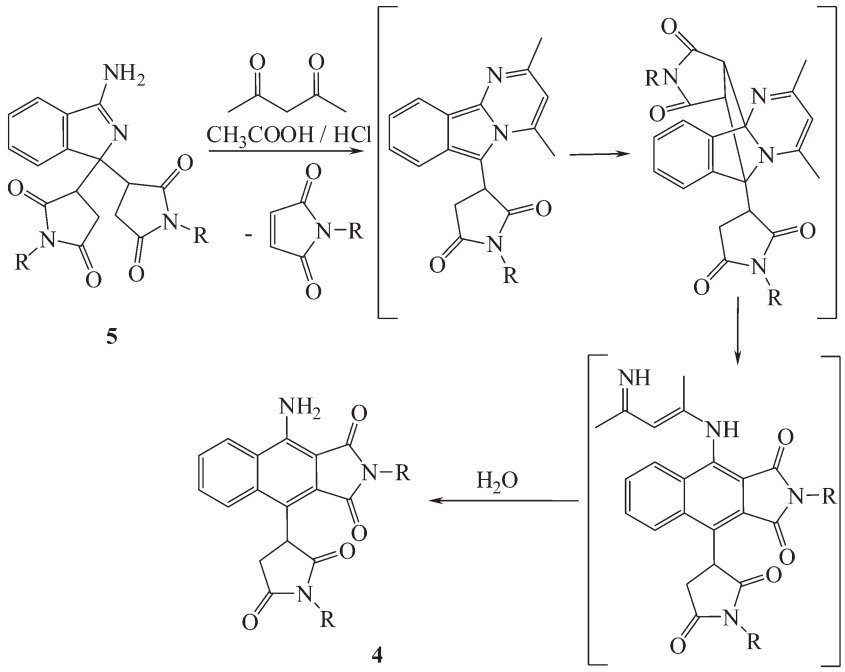


Product	R	Yield (%)
4a	Me	40
4b	4-$CH_3C_6H_4$	85
4c	C_6H_5	77

Scheme 2 Mechanism of rearrangement of the compounds **5a–c** with the formation of the fluorescent compounds **4a–c**.

substituent R and gives low yields. The major product of the transformation is the *bis*-Michael adduct **5**.

We have now succeeded in finding the optimal conditions for the rearrangement of the product **5** into **4** with higher yields (Scheme 2). Thus, refluxing **5** and 10-fold excess of acetylacetone in acetic acid saturated with hydrogen chloride leads to the formation of **4**.

The mechanism for the transformation outlined in Scheme 2 is based upon studies of the interaction of 2,4-dimethylpyrimido[2,1-*a*]isoindole with maleimide.[12] Condensation of the 1-aminoisoindole fragment and acetylacetone is accompanied by elimination of maleimide, giving the pyrimidine ring. The liberated maleimide then acts as a dienophile in a Diels–Alder reaction and the adduct so formed undergoes rearrangement including elimination of the pyrimidine ring fragment, as shown.

The X-ray diffraction study demonstrated that compound **4c** exists in the crystal phase as a solvate with DMF and water. The asymmetric part of the unit cell contains four crystallographically independent molecules of **4c** (A, B, C and D), one molecule of DMF and one water molecule. The solvate molecules are disordered over two positions in the ratio 59:41 % for the dimethylformamide and 58:42 % for the water molecule.

The tricyclic fragment of **4c** is planar within 0.02 Å in all molecules within the asymmetric part of the unit cell. The amino group has a pyramidal configuration with different degrees of pyramidality (the sum of bond angles centred on the N2 atom is 349° in the molecule **A**, 343° in **B**, 347.5° in **C** and 359° in **D**). The formation of the N2–H…O2 intramolecular hydrogen bond between amino group and the C12–O2 carbonyl group (H…O 2.28 Å N–H…O 133° **A**, 2.23 Å and 130° **B**, 2.27 Å and 135° **C**, 2.29 Å and 128° **D**) contribute to some elongation of the C12–O2 bond (1.228(2) Å **A**, 1.227(3) Å **B**, 1.224(3) Å **D** as compared to average value[17] 1.210 Å). The phenyl substituent at the N1 atom is twisted relative to the planar tricyclic fragment (the C12–N1–C13–C18 torsion angle is –77.8(4)° **A**, –126.6(3)° **B**, 126.3(3)° **C**, 129.8(3)° **D**). The pyrrolidine ring adopts an envelope conformation with

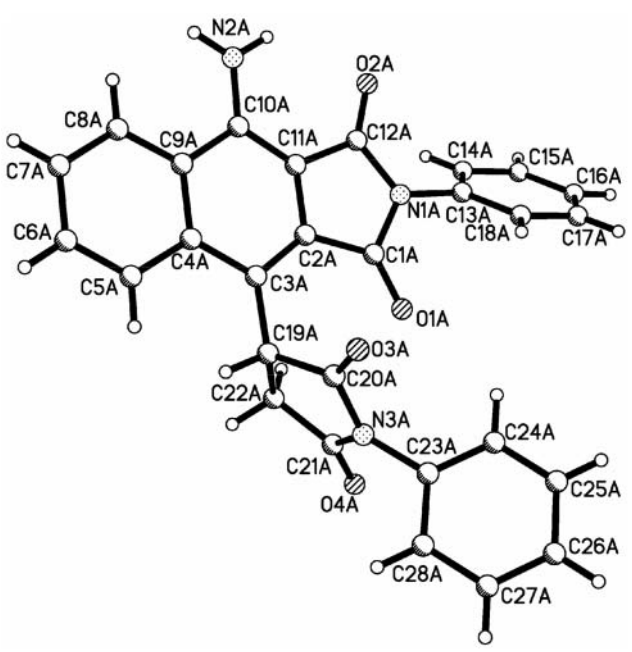


Fig. 1 The X-ray crystal structure of compound **4c.** Only one molecule located in asymmetric part of unit cell is depicted for clarity.

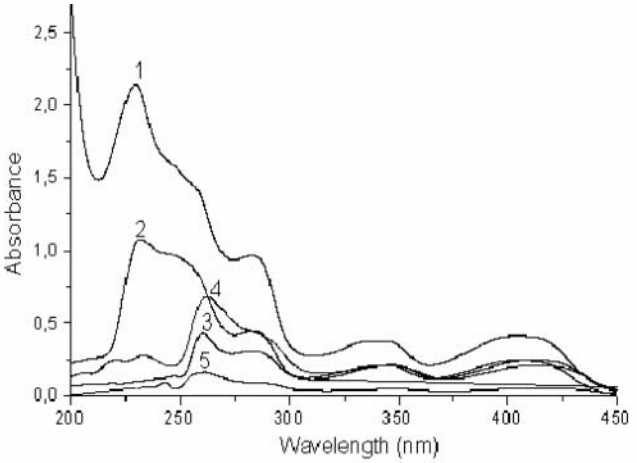


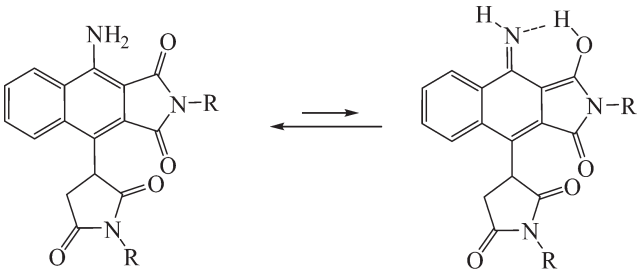
Fig. 2 Absorption spectra of 2.6·x 10^{-5} M acetonitrile solution of **4b**, **4c** (1, 2) and DMSO solution of **4a–c** (3–5). *l* = 10 mm.

different degrees of puckering. The deviation of the C19 atom from the mean plane of the remaining atoms of the ring is –0.22 Å **A**, 0.32 Å **B**, –0.25 Å **C**, 0.14 Å **D**. The substituent at the C3 atom is twisted relative to the plane of the tricyclic fragment (the C2–C3–C19–C20 torsion angle is –55.6(3)° **A**, –50.5(3)° **B**, –49.7(4)° **C**, 58.1(3)° **D**). Such an orientation of the substituent is caused by the balance of repulsion between the oxygen atoms of carbonyl groups and hydrogen atoms at the C5 and C19 atoms (shortened H…H intramolecular contacts are within 1.90–1.93 Å, the sum of van der Waals radii[18] is 2.32 Å). The phenyl group at the N3 atom is turned relative to the mean plane of the pyrrolidine ring (the C21–N3–C23–C24 torsion angle is –50.7(3)° **A**, –54.7(3)° **B**, –42.0(3)° **C**, 92.6(3)° **D**).

The absorption spectra of **4a–c** for acetonitrile and for DMSO solutions are presented in Fig. 2. All of the compounds showed five absorption bands at 232, 260, 284, 344 and 406 nm. The compounds in acetonitrile showed maxima in the spectra at shorter wavelengths (232 nm) in comparison with those in the DMSO solutions (260 nm). The absorption characteristics of **4a–c** are summarised in the Table 1.

The primary fragment responsible for fluorescence in compounds **4a–c** is the aminophthalimide core.[19] Low reactivity of the amino group (which practically does not react with metal ions, such as Cu(II), Zn(II), that form amino complexes) can be explained by conjugation of the amino group with the aromatic ring and with the electron-withdrawing amide group and also by tautomerism (Scheme 3).

The ^{1}H NMR spectral data show the presence of the minor tautomeric form, best indicated by the signal of the methine proton from the succinimide moiety, which is shifted downfield in the minor tautomer (Fig. 3). The large chemical shift difference (~1 ppm) can be explained by the presence of an *ortho*-quinonoid system that strongly influences the chemical shift of the methine proton. Other proton signals from the minor tautomer unfortunately cannot be seen because of overlapping by the signals of the major tautomer. The presence



Scheme 3 Tautomerism of 4-aminobenzo[*f*]isoindole derivatives **4**.

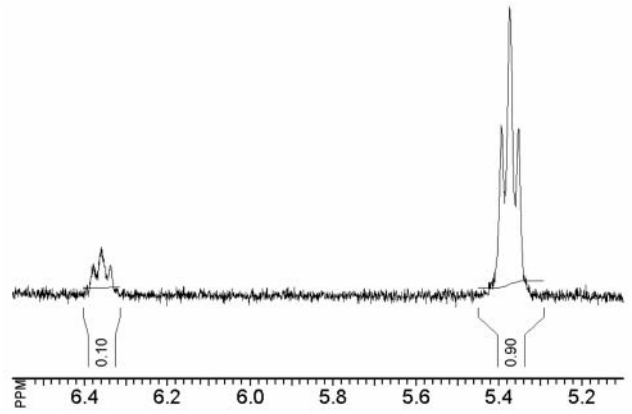


Fig. 3 Partial ^{1}H NMR spectrum of compound **4b**.

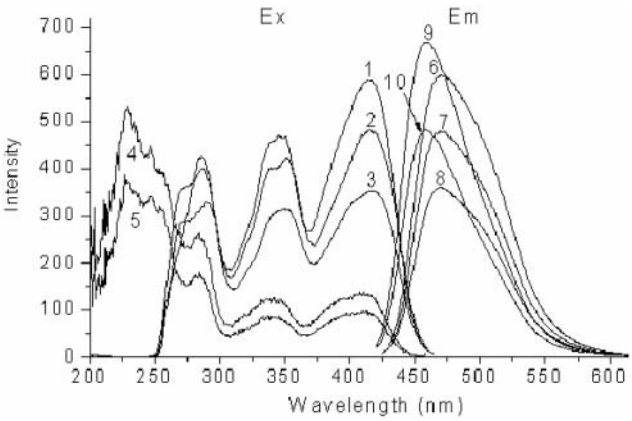


Fig. 4 Fluorescence spectra of 1·10^{-6} M DMSO solution of **4a–c** (1–3, 6–8) and acetonitrile solution of **4b**, **4c** (4, 5 and 9, 10) and λ_{ex} = 400 (9,10), 415 (6–8) nm, λ_{em} = 460 (4, 5), 470 (1–3) nm. *l* = 10 mm.

of the minor tautomer can also be confirmed by the abnormal bathochromic luminescence maximum shift in DMSO (Fig. 4), and in water–organic mixtures by increased luminescence upon addition of a proton-donor solvent (Fig .5). [20]

Table 1 Absorption data of **4a–c** solutions in organic solvents. (**4a** is not soluble in acetonitrile)

Compound (solvent)	ε_{232}, 10^4 L mol^{-1} cm^{-1}	ε_{284}, 10^4 L mol^{-1} cm^{-1}	ε_{344}, 10^4 L mol^{-1} cm^{-1}	ε_{406}, 10^4 L mol^{-1} cm^{-1}
4b (acetonitrile)	8.04	3.70	1.46	1.58
4c (acetonitrile)	4.10	1.70	0.81	0.92
4a (DMSO)	0.37	1.18	0.80	0.92
4b (DMSO)	1.12	1.69	0.79	0.79
4c (DMSO)	0.78	1.85	0.93	1.05

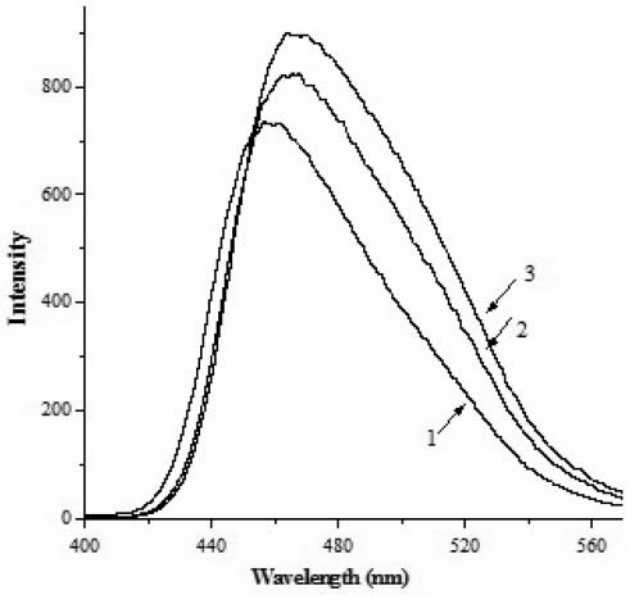


Fig. 5 Fluorescence spectra of $1.04 \cdot 10^{-6}$ M acetonitrile aqueous solution of **4c** in the presence of added H_2O in the following concentrations, %: 0 (1); 10 (2); 20 (3). λ_{ex} = 255 nm, *l* = 10 mm.

The increase of luminescent properties in the series **4c>4b>4a** (Fig. 4) can be explained by progressive weakening of the interaction of the imide nitrogen lone pair with the N-substituent.

The fluorescence of **4c** was strongly dependent on the water content in aqueous organic solvents (Fig. 5).

In 100% acetonitrile, **4c** exhibited a fluorescence emission maximum at 461 nm. As the water content increased up to around 10%, the emission of **4c** was increased with a red shift to 467.5 nm. The chemosensing behavior of **4c** was found to be efficient and is thus of potential as a sensitive indicator of the water content in acetonitrile.

Experimental

The ^{1}H NMR spectra (400.396 MHz) were recorded with a Varian Mercury 400 with TMS as internal standard. The IR-spectra were recorded on Specord M82. The chromatomass-spectra were recorded on Agilent 1100 Series with selective detector Agilent LC/MSD SL. Elemental analyses were determined using a Carlo Erba Strumenization analyser. Fluorescence measurements were performed using a Perkin Elmer Spectrometer LS 55 equipped with a xenon flash lamp and a computer. All working measurements took place in a standard 10 mm path-length quartz cell, thermostated at 25±0.5 °C, with 5 nm bandwidths for the emission and excitation monochromators. All solvents (acetonitrile, DMSO) used for spectroscopic measurements were purchased from Aldrich Chemical Co. as 'anhydrous' grade having water content less than 0.1%. l = 10 mm. Absorption spectra were recorded on UV-Vis Spectrometers Lambda-20 (Perkin Elmer) and UV-2800 (UNICO) at l = 10 mm.

*Synthesis of compounds **4a–c***

The appropriate 3-amino-1,1-bis-(1-substituted-2,5-dioxopyrrolidin-3-yl)-1*H*-isoindole **5a–c** (0.50 g)[16] was refluxed for 15 h with acetylacetone (1.5 mL) in acetic acid (5 mL) saturated with hydrogen chloride. On cooling of the reaction mixture the precipitate was collected by filtration and washed with methanol. The product was obtained with 99–100% purity as indicated by liquid chromatography.

4-Amino-9-(1-methyl-2,5-dioxopyrrolidin-3-yl)-1-methylbenzo[f]isoindole-1,3-dione (**4a**): Yield: 40%; 0.19 g; m.p. = 265 ºC; [Found: C, 64.01; H, 4.51; N, 12.43. $C_{18}H_{15}N_3O_4$ requires C, 64.09; H, 4.48; N, 12.46] IR (KBr): ν_{max} 3432, 3340, 2944, 1728, 1684, 1520, 1432, 1372, 1280, 1112, 676 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.59 (dd, *J* = 7.2, 17.6 Hz, 1H), 2.98 (s, 3H), 3.02 (s, 3H), 3.06 (dd, *J* = 9.2, 17.6 Hz, 1H), 5.07 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.30 (s, NH_2), 7.64 (t, *J* = 7.8 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 23.98, 25.05, 37.35, 38.62, 101.98, 122.48, 125.19, 125.50, 126.05, 126.23, 128.06, 130.49, 136.41, 144.98, 168.59, 169.05, 176.96, 178.80. MS: *m/z* = 338.0 [MH$^+$].

4-Amino-9-(2,5-dioxo-1-(4-methylphenyl)-pyrrolidin-3-yl)-1-(4-methylphenyl)benzo[f]isoindole-1,3-dione (**4b**): Yield: 85%; 0.41 g; m.p. = 279 ºC; [Found: C, 73.58; H, 4.78; N, 8.65. $C_{30}H_{23}N_3O_4$ requires C, 73.61; H, 4.74; N, 8.58] IR (KBr): ν_{max} 3440, 3352, 3032, 2916, 1696, 1632, 1508, 1372, 1164, 760 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.39 (s, 3H), 2.42 (s, 3H), 2.88 (dd, *J* = 7.2, 17.6 Hz, 1H), 3.30 (dd, *J* = 9.2, 17.6 Hz, 1H), 5.33 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.25–7.33 (m, 6H), 7.49 (s, NH_2), 7.71 (t, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.53 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 21.29, 37.24, 38.83, 101.55, 122.67, 125.23, 125.34, 126.13, 126.31, 127.42, 127.53, 128.29, 129.85, 129.90, 130.80, 130.98, 136.64, 137.84, 138.18, 145.75, 167.54, 168.79, 176.04, 177.81. MS: *m/z* = 490.0 [MH$^+$].

4-Amino-9-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-1-phenylbenzo[f]isoindole-1,3-dione (**4c**)*:* Yield: 77%; 0.37 g; m.p. = 273 ºC; [Found: C, 72.83; H, 4.11; N, 9.17. $C_{28}H_{19}N_3O_4$ requires C, 72.88; H, 4.15; N, 9.11] IR (KBr): ν_{max} 3428, 3334, 3066, 1698, 1638, 1494, 1370, 1164, 764 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.06 (dd, *J* = 7.2, 17.6 Hz, 1H), 3.36 (dd, *J* = 9.2, 17.6 Hz, 1H), 5.46 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.40–7.54 (m, 8H), 7.58 (s, NH_2), 7.78 (t, *J* = 7.8 Hz, 1H), 7.87 (t, *J* = 7.8 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.58 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 37.39, 39.01, 101.65, 122.81, 125.37, 125.51, 126.29, 126.47, 127.78, 127.89, 128.49, 128.53, 128.88, 129.53, 129.68, 131.01, 132.69, 133.72, 136.80, 146.00, 167.64, 168.84, 176.13, 177.89. MS: *m/z* = 462.0 [MH$^+$].

The crystals of **4c** were grown from the solvent system: acetone: *N*,*N*-dimethylformamide:water in the ratio 10:1:1). The crystals of **4c** ($4\ C_{28}H_{19}N_3O_4 \cdot C_3H_7NO \cdot H_2O$) are triclinic. At 100 K *a* = 12.4913(5), *b* = 16.9446(7), *c* = 23.068(1) Å, α = 72.296(4)°, β = 84.766(4)°, γ = 87.003(3)°, V = 4630.5(4) Å^3, M_r = 1936.96, Z = 2, space group P$\bar{1}$, d_{calc} = 1.389 g cm^{-3}, μ(MoK_α) = 0.096 mm^{-1}, F(000) = 2020. Intensities of 31367 reflections (16152 independent, R_{int} = 0.060) were measured on the Xcalibur-3 diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 50°). The structure was solved by direct methods using the SHELXTL package.[21] Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with Uiso = nUeq of the carrier atom (*n* = 1.5 for methyl groups and for water molecule and *n* = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 15943 reflections was converged to wR_2 = 0.074 (R_1 = 0.044 for 6722 reflections with $F>4\sigma(F)$, S = 0.685). The final atomic coordinates, and crystallographic data for molecule **4c** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 793608).

Conclusions

We have developed a new synthetic route to fluorescent derivatives of 4-aminobenzo[*f*]isoindoles, that is much simpler and gives better yields than the one described earlier in the literature.[18] We proved the structure of the products using NMR, IR, mass-spectroscopy and X-ray crystallography. It was shown that 4-amino-benzo[*f*]isoindoles exhibit tautomerism, and the presence of the minor tautomer defines the properties of the compounds, such as the low reactivity of the amino group, the luminescent properties and the dependence of the fluorescence spectra on the nature of the solvent. Finally, as the luminescent properties of the compounds are sensitive to the water content in organic solvents, they may be used for quantitative analysis of the moisture content in solvents.

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