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Pyrrolopyridazine derivatives as blue organic luminophores: synthesis and properties. Part 2☆

Gheorghita Zbancioc, Ionel I. Mangalagiu *

Al. I. Cuza University, Faculty of Chemistry, Organic Chemistry Department, Bd. Carol I no. 11, Iasi 700506, Romania

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ABSTRACT

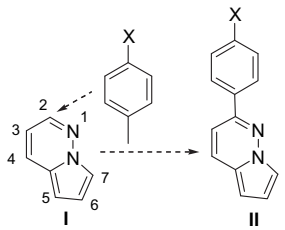
Two environmentally friendly methods, one in liquid and other in solid phase, for preparation of highly fluorescent pyrrolopyridazine (**PP**) derivatives under microwave (MW) irradiation is presented. The first synthesis in solid phase of fluorescent **PP** derivatives using activated alkynes under MW and conventional heating is also reported. Under MW irradiation the yields are higher, the amount of used solvent in liquid phase is at least five-fold less while solid phase does not use solvents, so these reactions may be considered as environmentally friendly. Eight new blue fluorescent 2-aryl-pyrrolopyridazine derivatives were synthesised. A certain influence of the **PP** substituents concerning absorption and fluorescent properties was observed. Introduction of a π-conjugated system in the second position of **PP** moiety increase the fluorescent properties. In the absorption spectra were observed a gradual decrease of wavelengths simultaneously with an increasing of molar extinction coefficient, due to increased number of ester groups from pyrrolic ring.

1. Introduction

Synthesis of highly fluorescent derivatives with extended π-conjugation has opened new research horizons because of their applications as sensors and biosensors, electroluminescent materials, lasers and other optoelectronic devices.[1–4a–d] Recent studies show that pyrrolopyridazine (**PP**) derivatives represent such a class, being a 'pure' blue-emitting moiety.[4c,d,11] During the last years MW irradiation has became an increasingly valuable tool in organic chemistry, since it offers a versatile and facile pathway in a large variety of syntheses.[5–14] Solid phase reactions have the great advantage of using no organic solvents ('solvent-free'), such reactions being more environmentally friendly and generate less side products. The application of MW irradiation under solvent-free conditions enables organic reactions to occur expeditiously at ambient pressure, providing unique chemical processes with special attributes such as higher yields, shorter reaction time, milder conditions and the associated ease of manipulation.[5–7,12–14] In a preliminary communication,[11] we synthesized a series of pyrrolopyridazine derivatives with fluorescent properties. The aim of this work was to synthesise new fluorescent **PPs**, to study the relationship between optical properties and structure (the effect of substituents and conjugation), and to develop a new environmentally friendly method for preparation of these derivatives using MW technologies (in liquid and solid phase).

2. Results and discussion

The pyrrolopyridazine moiety **I** was proved to be responsible for blue fluorescent properties.[4c,d,11] A rational design shows us that a suitable and accessible modification could be made in order to increase the fluorescent properties, would be introduction of a phenyl ring in the 2- position, which would allow expansion of the π system conjugation, as we have shown in structure **II**. In equal measure we were interested to study the influence of this modification and of the substituents at the 5-, 6- and 7- positions concerning the synthesis, absorption and emission spectra.



☆ See Ref. 11.

* Corresponding author. Tel.: +40 232 201343; fax: +40 232 201313.
E-mail address: ionelm@uaic.ro (I.I. Mangalagiu).

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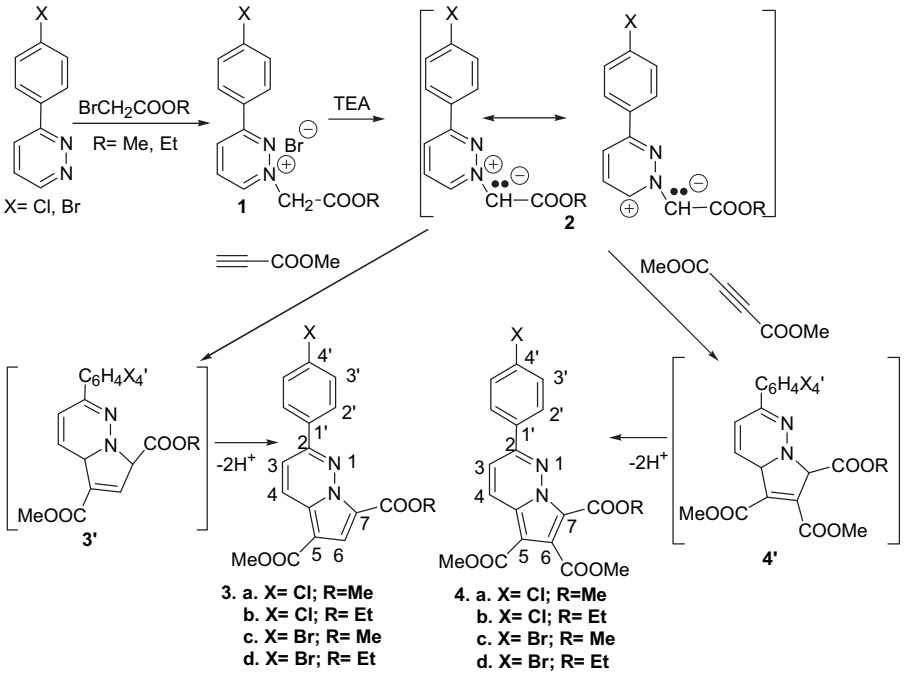
The strategies adopted for construction of fluorescent **PP** derivatives **II** are depicted in Scheme 1. The reaction pathway involves two steps: initially *N*-alkylations of the pyridazines followed by a [3+2] dipolar cycloaddition of pyridazinium ylides **2** to the corresponding dipolarophiles. Pyridazinium ylides **2** were generated in situ from the corresponding cycloimmonium salts **1**, using the Kröhnke salt method[15] (alkaline medium, Et_3N in liquid phase and KF–Al_2O_3 in solid phase). As dipolarophiles we used activated alkynes, methyl propiolate and dimethyl acetylenedicarboxylate. Fully aromatised **PP** cycloadducts **3a–d** and **4a–d** were obtained, via a spontaneously oxidative (by air) dehydrogenation of intermediates **3′** and **4′**.

As indicated in Table 1, under MW heating the reaction times decreased dramatically from hours to minutes (5 min. in liquid phase, 15 min. in solid phase) and the yields are higher. In solid phase, on solid support KF–Al_2O_3, the results are even more spectacular: while under MW heating the cycloadducts were obtained in good yields (around 50%), under conventional heating (oil bath) we obtained decomposition products only. We also observed that under MW irradiation the consumed energy decreased considerably, the amount of used solvent in liquid phase is at least five-fold less (see Experimental) while solid phase does not use solvents, so these reactions may be considered as environmentally friendly.



Scheme 1. Synthesis of fluorescent PP, under microwaves and conventional heating.

Under conventional heating this strategy has some major disadvantages: long reaction time (around 2 h), high energy consumption, low yields and the need for large amounts of solvents. This is why we decided to synthesise the desired fluorescent adducts by microwave irradiation, both in liquid and solid phase. The MW-assisted reactions were carried out using a monomode reactor, using a constant irradiation power and varying the temperature (the so-called 'power control'). The best results were obtained when 25% of the full power of the magnetron (800 W) was used. Table 1 lists the optimized conditions we employed, under MW irradiation as well as under conventional heating.

The structure of the synthesized compounds was proved by elemental (C, H, N) and spectroscopic analysis (IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). Thus, in the ^{1}H NMR spectra of **PP** adducts, the most important signals are those of the H-4, H-3 and H-6 atoms (for **3**) and H-4, H-3 (for **4**). The lack of signals between ≈4 and 7 ppm, is solid evidence for the aromatized structure. The H-4 protons appear at high chemical shifts (≈8.5 ppm), as a doublet, H-3 protons appear at ≈7.5 ppm and in compound **3**, the H-6 protons appear also at high chemical shifts (≈7.75 ppm) because of the neighbouring of the two carbonyl-ester groups (from 5 and 7 position). ^{13}C NMR spectroscopy also confirmed the proposed

Table 1
Synthesis of **PP** cycloadducts **3a–d** and **4a–d** under MW and conventional heating conditions, in liquid and solid phase

Compd.	Microwaves				Conventional heating			
	Liquid phase		Solid phase		Liquid phase		Solid phase	
	Reaction time (min)	Yield, %	Reaction time (min)	Yield, %	Reaction time (min)	Yield, %	Reaction time (min)	Yield, %
3a	5	50	15	51	120	41	15–240	—
3b	5	52	15	49	120	44	15–240	—
3c	5	53	15	52	120	43	15–240	—
3d	5	50	15	50	120	35	15–240	—
4a	5	49	15	45	120	40	15–240	—
4b	5	52	15	49	120	46	15–240	—
4c	5	51	15	48	120	41	15–240	—
4d	5	53	15	49	120	43	15–240	—

structure, the corresponding carbons appearing at chemical shifts in accordance with the proposed structure.

In the next stage of our work, we studied the absorption and emission spectra of the obtained **PP** cycloadducts. The absorption of compounds **3** and **4** (acetonitrile, recorded in the spectral range 190–600 nm), exhibit clear differences in their experimental UV–VIS spectra as can be seen in Figures 1 and 2.

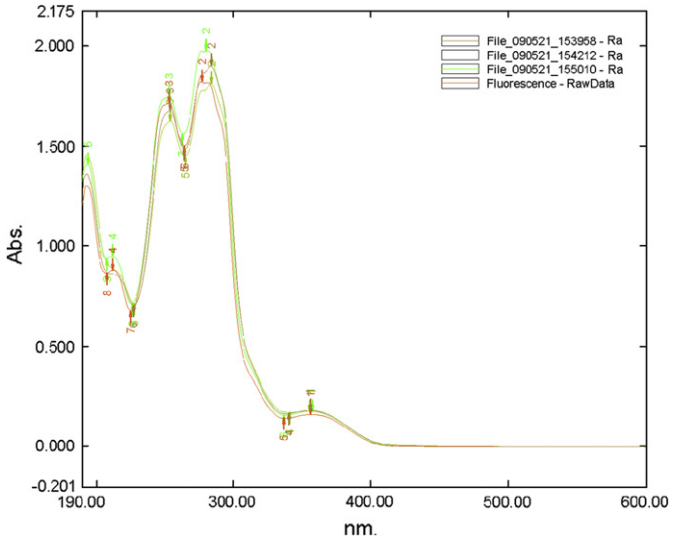


Figure 1. The absorption spectra of the compound **3a–d** (c= 5×10^{-5}) in acetonitrile.

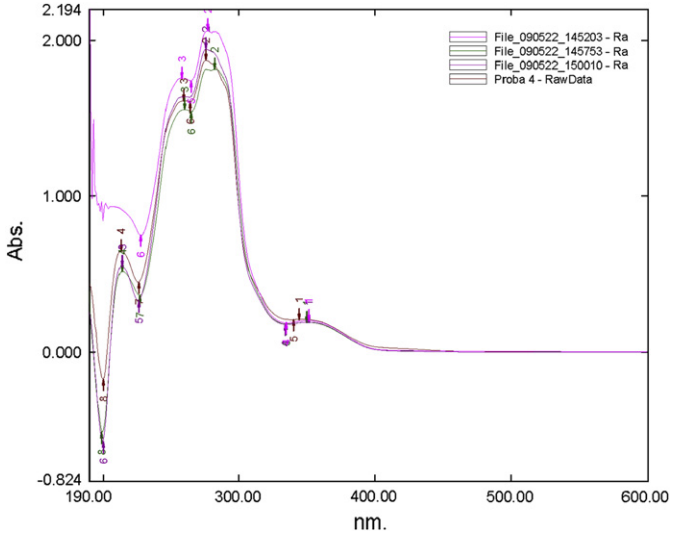


Figure 2. The absorption spectra of the compound **4a–d** (c= 5×10^{-5} M) in acetonitrile.

The absorption maxima and the corresponding molar extinction coefficients for compounds **3a–d** and **4a–d** are listed in Table 2.

As Table 2 and Figures 1 and 2 show, the position of the absorption bands and the values of the molar extinction coefficients, evidence the influence of the substituents at the pyrrolic ring. Apparently, the absorption spectral profile of compounds **3** and **4** are essentially the same: the absorption peak maxima occur around 360, 340, 280, 265 and 225 nm. However, the absorption spectra change significantly from adducts **3** (with two ester groups) to **4** (with three ester groups), a hypsochromic shift and molar extinction coefficient increase being observed. Thus, while the fourth (IV) and the fifth (V) absorption band remain roughly the same, the absorption bands I to III are significantly blue shifted in **4**. The gradual decrease in absorption wavelengths and molar extinction coefficient increasing, due to increased number of ester groups, is also reported by some other authors in related cases.[4a–d]

The fluorescence spectra were recorded with a Turner BioSystems fluorimeter using FluoOpticalKitID PN:9300-043 SN:F20 00000BB5A4C2D SIG:UV with λ_{ex}=365 nm and λ_{em}=410–460 nm. Intensity of fluorescence for compounds **3** and **4** are listed in Table 3. As can be noticed from Table 3, **PP** are very intense blue emitters [intensity of fluorescence for these compounds are much higher compared with the solvent (with about 120–190 fold higher)], which proved that introduction of a benzene ring in the 2- position from **PP** moiety **I**, has a beneficial effect concerning fluorescent properties.

It could be also noticed from Table 3 that compounds with a *para*-chlorophenyl- substituent in the 2- position of **PP** moiety and those, which possess a carbethoxy group, in it 7- position have a much higher fluorescence.

3. Conclusions

Two environmentally friendly methods, one in liquid and other in solid phase, for the preparation of highly fluorescent **PP** derivatives under microwave irradiation are presented. The first synthesis in solid phase of fluorescent **PP** derivatives using activated alkynes under microwave and conventional heating is also reported. Under MW irradiation the yields are higher, the amount of used solvent in liquid phase is at least five-fold less while solid phase do not use solvents, so these reactions may be considered as environmentally friendly. Eight new blue fluorescent 2-aryl-**PP** derivatives were synthesised. A certain influence of the **PP** substituents concerning absorption and fluorescent properties were observed. Compounds with a *para*-chlorophenyl- substituent in the 2- position of **PP** moiety and those one, which possess a carboethoxy groups, in the 7- position have a much higher fluorescence. In the absorption spectra were observed a gradual decrease of wavelengths simultaneously with an increasing of molar extinction coefficient, due to increased number of ester groups from the pyrrolic ring.

Table 2
Absorption (λ_{max}) and molar extinction coefficients (ε), for **PP** derivatives in acetonitrile

Compound/number of absorption maxima	λ_{max} (nm) [ε (L mol^{-1} cm^{-1})×10^3]				
	I	II	III	IV	V
3a	356.00 [2.65]	347.00 [2.33]	277.00 [30.33]	264.00 [25.02]	225.00 [11.30]
3b	357.00 [2.93]	337.00 [2.58]	280.00 [32.95]	263.00 [26.00]	226.00 [11.90]
3c	355.00 [2.93]	341.00 [2.80]	284.00 [30.23]	265.00 [24.15]	228.00 [11.91]
3d	356.00 [3.00]	340.00 [2.73]	284.00 [31.68]	264.00 [24.73]	227.00 [11.75]
4a	344.00 [3.50]	340.00 [3.46]	276.00 [31.15]	264.00 [26.75]	226.00 [7.45]
4b	350.00 [3.18]	335.00 [2.95]	276.00 [32.38]	264.00 [26.75]	226.00 [11.51]
4c	350.00 [3.18]	335.00 [3.01]	282.00 [30.21]	265.00 [25.68]	227.00 [6.00]
4d	350.00 [3.31]	334.00 [3.06]	276.00 [34.46]	264.00 [29.01]	228.00 [12.33]

Table 3
Intensity of fluorescence for **3** and **4 PP** derivatives in acetonitrile

Compd.	3a	3b	3c	3d	4a	4b	4c	4d	Solvent
Intensity of fluorescence	6276.11	6554.21	7510.05	8264.76	5016.82	5269.64	6018.34	6304.55	40.86

4. Experimental section

4.1. General procedures

All the reagents and solvents used were of the best grade available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 DRX spectrometer, downfield from an internal standard, $SiMe_4$ in $CDCl_3$. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hertz. IR spectra were recorded with a Shimadzu Prestige 8400s FTIR spectrophotometer in KBr. UV–VIS spectra were recorded with a Schimadzu UV-1800 spectrometer in acetonitrile. The fluorescence values were recorded with a Turner BioSystems fluorimeter. For the microwave (MW) irradiation a monomode reactor (STAR-2, CHEM corporation, USA, (800 W) was used. Melting points were determined using an electrothermal apparatus and are uncorrected. Flash chromatography was performed with Aldrich 230–400 mesh silica gel (eluent: CH_2Cl_2:CH_3OH=99:1). TLC was carried out with Merck silica gel 60-F-254 plates.

4.2. General procedure for [3+2] dipolar cycloaddition in the liquid phase

3-(4-Halophenyl)-pyridazinium bromide (5 mmol) and dipolarophile (5.5 mmol) were suspended in 50 mL of anhydrous toluene (under conventional heating) and 10 mL of anhydrous toluene (under microwave heating). Then, triethylamine (5.5 mmol) was added. Under conventional conditions, the solution was refluxed (oil bath) for 2 h. Under microwave heating, the solution was exposed to microwaves for 5 min. Using MW irradiation, the best results were obtained using a constant irradiation power (25% from the full power of the magnetron, 800 W) and varying the temperature (the so-called 'power control'). The resulting mixture was filtered hot to remove triethylamine hydrobromide and the clear solution was evaporated. The crude product was purified by chromatography on silica gel with dichloromethane/methanol (99/1) as eluent.

4.3. General procedure for [3+2] dipolar cycloaddition in the solid phase

3-(4-Halophenyl)-pyridazinium bromide (2 mmol), dipolarophile (2.1 mmol) and 15 g of mineral support (KF–Al_2O_3) were ground in an agate mortar until a fine homogeneous mixture was obtained. The mixture was heated under conventional conditions (oil bath) or exposed to microwaves. The mixture was exposed to microwaves for 15 min. using 20% power of the magnetron. The activated solid was cooled, then washed four times: three times with 10 mL of dichloromethane and once with 10 mL of acetone. The acetone and dichloromethane were then evaporated and the product was purified by chromatography on silica gel with dichloromethane/methanol (99/1) as eluent.

*4.3.1. Dimethyl 2-(4-chlorophenyl)pyrrolo[1,2-b]pyridazine-5,7-dicarboxylate (**3a**).* White solid, mp 225–226 °C. **IR** (KBr, cm^{-1}): 3112 (C–H arom.), 2950 (C–H aliph.), 1728, 1697 (C=O est.), 1552, 1465, 1406 (C=C, C=N), 1245, 1199 (C–O–C), 810 (C–Cl). ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 3.93 (s, 3H: CH_3 from 5 position), 3.97 (s, 3H: CH_3 from 7 position), 7.52–7.47 (m, overlapped peaks, 3H: $2H_{3'}$, $1H_3$), 7.99 (s, 1H: H_6), 8.04 (dd, J=8.8, J=2.0, 2H: $H_{2'}$), 8.64 (d, J=9.2, 1H: H_4); ^{13}C NMR (TMS, $CDCl_3$, δ, ppm): 51.51 (CH_3 from 5, COOMe), 51.69 (CH_3 from 7, COOMe), 105.02 (C_5), 114.87 (C_3), 119.71 (C_7), 122.79 (C_6), 128.12 (C_4), 128.30 ($C_{2'}$), 129.34 ($C_{3'}$), 131.84 (C_{4a}), 133.63 ($C_{1'}$), 136.65 ($C_{4'}$), 151.09 (C_2), 159.53 (7-CO), 163.90 (5-CO). Anal. calcd for $C_{17}H_{13}ClN_2O_4$ (344.75): C 59.23, H 3.80, N 8.13; found: C 59.20, H 3.73, N 8.05.

*4.3.2. 7-Ethyl, 5-methyl 2-(4-chlorophenyl)pyrrolo[1,2-b] pyridazine-5,7-dicarboxylate (**3b**).* White solid, mp 167–168 °C. IR (KBr, cm^{-1}): 3122 (C–H arom.), 2952 (C–H aliph.), 1708, 1672 (C=O est.), 1550, 1521, 1479, 1469 (C=C, C=N), 1242, 1209 (C–O–C), 825 (C–Cl). ^{1}H NMR (TMS, $CDCl_3$, δ, ppm): 1.45(t, J=7.2, 3H: CH_3–CH_2), 3.93 (s, 3H: CH_3 from 5 position), 4.45 (q, J=7.2, 2H: CH_2–CH_3), 7.51–7.47 (m, overlapped peaks, 3H: $2H_{3'}$, $1H_3$), 8.00 (s, 1H: H_6), 8.04 (dd, J=8.8, J=2.0, 2H: $H_{2'}$), 8.64 (d, J=9.6, 1H: H_4); ^{13}C NMR ($CDCl_3$, δ, ppm, J, Hz): 14.43 (CH_3–CH_2), 51.48 (CH_3 from 5, COOMe), 60.60 (CH_2), 104.92 (C_5), 114.72 (C_3), 120.06 (C_7), 122.74 (C_6), 128.08 (C_4), 128.27 ($C_{2'}$), 129.30 ($C_{3'}$), 131.77 (C_{4a}), 133.67 ($C_{1'}$), 136.60 ($C_{4'}$), 150.98 (C_2), 159.16 (7-CO), 163.93 (5-CO). Anal. calcd for $C_{18}H_{15}ClN_2O_4$ (358.78): C 60.26, H 4.21, N 7.81; found: C 60.23, H 4.12, N 7.71.

*4.3.3. Dimethyl 2-(4-bromophenyl)pyrrolo[1,2-b]pyridazine-5,7-dicarboxylate (**3c**).* Yellow solid, mp 220–221 °C. IR (KBr, cm^{-1}): 3124 (C–H arom.), 2947 (C–H aliph.), 1726, 1695 (C=O est.), 1560, 1463, 1434, 1404 (C=C, C=N), 1245, 1193 (C–O–C), 810 (C–Br). ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 3.94 (s, 3H: CH_3 from 5 position), 3.97 (s, 3H: CH_3 from 7 position), 7.52 (d, J=9.6, 1H: H_3), 7.65 (dd, J=8.4, J=2.0, 2H: $H_{3'}$), 7.98 (dd, J=8.4, J=2.0, 2H: $H_{2'}$), 8.00 (s, 1H: H_6), 8.65 (d, J=9.6, 1H: H_4); ^{13}C NMR (TMS, $CDCl_3$, δ, ppm): 51.54 (CH_3 from 5, COOMe), 51.72 (CH_3 from 7, COOMe), 105.06 (C_5), 114.83 (C_3), 119.73 (C_7), 122.82 (C_6), 125.05 ($C_{4'}$), 128.16 (C_4), 128.55 ($C_{2'}$), 131.87 (C_{4a}), 132.33 ($C_{3'}$), 134.12 ($C_{1'}$), 151.18 (C_2), 159.55 (7-CO), 163.92 (5-CO). Anal. calcd for $C_{17}H_{13}BrN_2O_4$ (389.20): C 52.46, H 3.37, N 7.20; found: C 52.37, H 3.29, N 7.10.

*4.3.4. 7-Ethyl, 5-methyl 2-(4-bromophenyl)pyrrolo[1,2-b] pyridazine-5,7-dicarboxylate (**3d**).* Yellow solid, mp 163–164 °C. IR (KBr, cm^{-1}): 3070 (C–H arom.), 2948 (C–H aliph.), 1706, 1674 (C=O est.), 1552, 1517, 1473 (C=C, C=N), 1242, 1203 (C–O–C), 821 (C–Br). ^{1}H NMR (DMSO, δ, ppm, J, Hz): 1.40(t, J=6.8, 3H: CH_3–CH_2), 3.88 (s, 3H: CH_3 from 5 position), 4.38 (q, J=6.8, 2H: CH_2–CH_3), 7.77 (dd, J=8.4, J=2.0, 2H: $H_{3'}$), 7.81 (s, 1H: H_6), 7.91 (d, J=9.6, 1H: H_3), 8.09 (dd, J=8.4, J=2.0, 2H: $H_{2'}$), 8.58 (d, J=9.6, 1H: H_4); ^{13}C NMR (TMS, DMSO, δ, ppm): 13.90 (CH_3–CH_2), 51.05 (CH_3 from 5, COOMe), 59.93 (CH_2), 104.00 (C_5), 115.42 (C_3), 119.29 (C_7), 121.48 (C_6), 123.96 ($C_{4'}$), 127.51 (C_4), 128.50 ($C_{2'}$), 130.98 (C_{4a}), 131.74 ($C_{3'}$), 133.56 ($C_{1'}$), 150.27 (C_2), 157.85 (7-CO), 162.65 (5-CO). Anal. calcd for $C_{18}H_{15}BrN_2O_4$ (403.23): C 53.62, H 3.75, N 6.95; found: C 53.57, H 3.69, N 6.83.

*4.3.5. Trimethyl 2-(4-chlorophenyl)pyrrolo[1,2-b]pyridazine-5,6,7-tricarboxylate (**4a**).* White solid, mp 185–186 °C. IR (KBr, cm^{-1}): 3109 (C–H arom.), 2954 (C–H aliph.), 1743, 1716, 1685 (C=O est.), 1550, 1523, 1488, 1442 (C=C, C=N), 1255, 1209, 1178 (C–O–C), 817 (C–Cl). ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 3.92 (s, 3H: CH_3 from 5 position), 3.96 (s, 3H: CH_3 from 7 position), 4.02 (s, 3H: CH_3 from 6 position), 7.49 (dd, J=8.4, J=2.0, 2H: $H_{3'}$), 7.57 (d, J=9.6, 1H: H_3), 8.02 (dd, J=8.4, J=2.0, 2H: $H_{2'}$), 8.64 (d, J=9.6, 1H: H_4); ^{13}C NMR (TMS, $CDCl_3$, δ, ppm): 51.97 (CH_3 from 5, COOMe), 52.21 (CH_3 from 7, COOMe), 53.05 (CH_3 from 6, COOMe), 102.85 (C_5), 115.99 (C_3), 117.45 (C_6), 128.39 ($C_{2'}$), 128.53 (C_4), 128.93 (C_7), 129.44 ($C_{3'}$), 130.63 (C_{4a}),

133.25 ($C_{1'}$), 137.00 ($C_{4'}$), 151.99 (C_2), 158.64 (7-CO), 162.72 (5-CO), 165.59 (6-CO). Anal. calcd for $C_{19}H_{15}ClN_2O_6$ (402.79): C 56.66, H 3.75, N 6.95; found: C 56.62, H 3.69, N 6.89.

*4.3.6. 7-Ethyl, 5,6-dimethyl 2-(4-chlorophenyl)pyrrolo[1,2-b] pyridazine-5,6,7-tricarboxylate (**4b**).* White solid, mp 142–143 °C. IR (KBr, cm^{-1}): 3066 (C–H arom.), 2954 (C–H aliph.), 1739, 1699 (C=O est.), 1552, 1483, 1442 (C=C, C=N), 1232, 1188, 1133 (C–O–C), 819 (C–Cl). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.42(t, *J*=7.2, 3H: CH_3–CH_2), 3.92 (s, 3H: CH_3 from 5 position), 4.01 (s, 3H: CH_3 from 6 position), 4.43 (q, *J*=7.2, 2H: CH_2–CH_3), 7.49 (dd, *J*=8.4, *J*=2.0, 2H: $H_{3'}$), 7.56 (d, *J*=9.6, 1H: H_3), 8.02 (dd, *J*=8.4, *J*=2.0, 2H: $H_{2'}$), 8.63 (d, *J*=9.6, 1H: H_4); ^{13}C NMR (TMS, $CDCl_3$, δ, ppm): 14.15 (CH_3–CH_2), 51.92 (CH_3 from 5, COOMe), 52.90 (CH_3 from 6, COOMe), 61.14 (CH_2), 102.74 (C_5), 115.83 (C_3), 117.61 (C_6), 128.34 ($C_{2'}$), 128.48 (C_4), 128.84 (C_7), 129.38 ($C_{3'}$), 130.55 (C_{4a}), 133.27 ($C_{1'}$), 136.93 ($C_{4'}$), 151.87 (C_2), 158.14 (7-CO), 162.73 (5-CO), 165.57 (6-CO). Anal. calcd for $C_{20}H_{17}ClN_2O_6$ (416.81): C 57.63, H 4.11, N 6.72; found: C 57.60, H 4.03, N 6.67.

*4.3.7. Trimethyl 2-(4-bromophenyl)pyrrolo[1,2-b]pyridazine-5,6,7-tricarboxylate (**4c**).* White solid, mp 177–178 °C. IR (KBr, cm^{-1}): 3087 (C–H arom.), 2954 (C–H aliph.), 1743, 1716, 1685 (C=O est.), 1591, 1548, 1488, 1442 (C=C, C=N), 1253, 1209, 1178 (C–O–C), 815 (C–Br). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 3.92 (s, 3H: CH_3 from 5 position), 3.97 (s, 3H: CH_3 from 7 position), 4.02 (s, 3H: CH_3 from 6 position), 7.54 (d, *J*=9.6, 1H: H_3), 7.66 (dd, *J*=8.4, *J*=2.0, 2H: $H_{3'}$), 7.95 (dd, *J*=8.4, *J*=2.0, 2H: $H_{2'}$), 8.65 (d, *J*=9.6, 1H: H_4); ^{13}C NMR (TMS, $CDCl_3$, δ, ppm): 51.98 (CH_3 from 5, COOMe), 52.22 (CH_3 from 7, COOMe), 53.05 (CH_3 from 6, COOMe), 102.88 (C_5), 115.93 (C_3), 125.40 (C_6), 128.58 (C_4), 128.62 ($C_{2'}$), 128.95 (C_7), 130.66 (C_{4a}), 132.42 ($C_{3'}$), 133.74 ($C_{1'}$), 152.09 (C_2), 158.65 (7-CO), 162.73 (5-CO), 165.58 (6-CO). Anal. calcd for $C_{19}H_{15}BrN_2O_6$ (447.24): C 51.03, H 3.38, N 6.26; found: C 50.98, H 3.32, N 6.17.

*4.3.8. 7-Ethyl, 5,6-dimethyl 2-(4-bromophenyl)pyrrolo[1,2-b] pyridazine-5,6,7-tricarboxylate (**4d**).* White solid, mp 151–152 °C. IR (KBr, cm^{-1}): 3103 (C–H arom.), 2952 (C–H aliph.), 1737, 1697 (C=O est.), 1552, 1519, 1479, 1440 (C=C, C=N), 1230, 1180, 1141 (C–O–C), 817 (C–Br). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.42(t, *J*=7.2, 3H: CH_3–CH_2), 3.92 (s, 3H: CH_3 from 5 position), 4.01 (s, 3H: CH_3 from 6 position), 4.43 (q, *J*=7.2, 2H: CH_2–CH_3), 7.55 (d, *J*=9.6, 1H: H_3), 7.64 (dd, *J*=8.4, *J*=2.0, 2H: $H_{3'}$), 7.95 (dd, *J*=8.4, *J*=2.0, 2H: $H_{2'}$), 8.63 (d, *J*=9.6, 1H: H_4); ^{13}C NMR (TMS, $CDCl_3$, δ, ppm): 14.18 (CH_3–CH_2), 51.95 (CH_3 from 5, COOMe), 52.92 (CH_3 from 6, COOMe), 61.17 (CH_2), 102.81 (C_5), 115.79 (C_3), 125.35 ($C_{4'}$), 126.78 (C_6), 128.53 (C_4), 128.60 ($C_{2'}$), 128.89 (C_7), 130.59 (C_{4a}), 132.38 ($C_{3'}$), 133.77 ($C_{1'}$), 151.97 (C_2), 158.17 (7-CO), 162.75 (5-CO), 165.58 (6-CO). Anal. calcd for $C_{20}H_{17}BrN_2O_6$ (461.26): C 52.08, H 3.71, N 6.07; found: C 52.04, H 3.64, N 5.99.

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