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Efficient regioselective heterocyclisation leading to fluorescent fused pyrazine derivatives

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ABSTRACT

The regioselective syntheses of substituted pyrrolo[2,3-*b*]quinoxaline, pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazine, pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazine and pyrido[3,4-*b*]pyrrolo[3,2-*e*]pyrazine are reported. Differential reactivity between two amino groups in *ortho*-diaminopyridine can be exploited to obtain new regio-defined unsymmetrical pyridopyrrolopyrazine derivatives. Weak electron-donating methyl or moderately electron-withdrawing carboxylic groups attached to the aromatic *ortho*-diamines reduce the regioselectivity of obtaining unsymmetrical substituted pyrrolo[2,3-*b*]quinoxaline. The fluorescence properties of the resultant 1-alkyl pyridopyrrolopyrazine and substituted pyrrolo[2,3-*b*]quinoxaline derivatives are presented.

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1. Introduction

Synthesising analogues of bioactive natural products containing unsymmetrical units very often requires applying regio-defined procedures or efforts in the separation of regioisomers. Aromatic and heteroaromatic *ortho*-diamines and α-dicarbonyl compounds are usually used as the building blocks in the synthesis of various substituted quinoxalines, regioisomeric pyridopyrazine derivatives, potential DNA intercalators[1] and fluorophores.

The different nucleophilicity of amino groups in substituted aromatic *ortho*-diamines, including 2,3-diaminopyridine, 3,4-diaminopyridine, 3,4-diaminotoluene and 3,4-diaminobenzoic acid, should influence the distribution of products. The presence of the deactivating group or a nitrogen atom in the aromatic ring differentiates the reactivity and influences the regioselectivity of the reactions. According to the chemoselectivity, the most basic amino group should react with the most reactive carbonyl carbon atom, and the reaction should lead to the formation of the predominant regioisomer.[2–12] However, the protection of this amino group with complete control of the regiochemistry should lead to the other regioisomer. Our previous study[13,14] confirmed that condensation of polycarbonyl *N*-arylpyrrole **1** (p*K*=2.63) derivatives with 2,3-diaminopyridine in the presence of TsOH (p*K*=0.7) in the ratio 1:1.3:0.6 proceeded with the deactivation of the more basic C-3 amino group via formation of a salt. We obtained only one regioisomer, 1-arylpyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazine-2-one, as the product of the reaction of the more reactive carbonyl group at C-3 of **1** and the weakest nucleophilic C-2 amino group of 2,3-diaminopyridine.

In this paper, we report the methods to prepare 1-alkyl,1-aryl-pyrroloquinoxaline **2**–**6** and regio-defined 1-alkyl,1-aryl-pyridopyrrolopyrazine **7**–**9** derivatives and their fluorescent properties (Fig. 1). Regioselective heterocyclisation was achieved by applying two procedures. The first procedure was based on the direct condensation of *N*-alkyl, *N*-arylpyrrolidinetrione **1** with 3,4-diaminotoluene, 3,4-diaminobenzoic acid and 2,3- or 3,4-diaminopyridine. The second procedure was a multistep method exploiting the *exo*-*enol* tautomerism of **1** in CH_2Cl_2 during the first step, which leads to 3-chloropyrrolinedione.[15] Then, the latter was easily substituted with complete control of the regiochemistry by the more reactive amino group of *ortho*-diaminoarene. In the last step, the monosubstituted 3-amino-4-benzoylopyrroline-2,5-dione derivatives were cyclised to form fused heterocyclic systems.[16–18]

2. Results and discussion

The inductive effect of the methyl group in 3,4-diaminotoluene activates the C-4 position in the benzene ring, whereas the same

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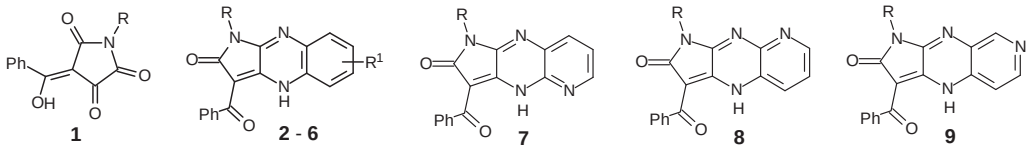


Fig. 1. General structure of heterocycles studied in this paper.

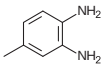
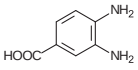
effect of the carboxylic acid group deactivates the C-3 position in 3,4-diaminobenzenecarboxylic acid. Therefore, the more basic amino group in direct condensation conditions preferentially forms the acid **1** salts with OH, which enables the nucleophilic attack of the C-3 amino group in 3,4-diaminotoluene or the C-4 group in 3,4-diaminobenzoic acid on the nonamide carbonyl carbon atom first. In both cases, we obtain a mixture of two pairs of regioisomers, **3**,**4** and **5**,**6**, respectively, with a slight excess of one form, i.e., **4** and **5** (Table 1). We could not manage to separate regioisomers **3**, **4** and **5**,**6** via TLC, but we isolated **3a** and **5a** during fractional recrystallisation from DMSO and DMF, respectively (Scheme 1).

formation of one product, 2*H*-pyrido[3,4-*b*]pyrrolo[3,2-*e*]pyrazin-2-one, as a salt for **9ad** and non-bonded for **9b** (Scheme 2).

The application of the second concept to the synthesis without separation of intermediate products in the case of the reaction with 3,4-diaminotoluene and 3,4-diaminobenzoic acid did not improve the regioselectivity (Scheme 3, Table 1). The presence of a methyl or carboxylic group in the aromatic *ortho*-diamine did not establish differential reactivity between these two amino groups.

On the contrary, 2,3-diaminopyridine selectively reacted with 3-chloropyrroline 2,5-dione derivatives to provide the mono-

Table 1
Cyclocondensation of *o*-diamines with **1**

		Product yield [%]				RS [%]
		A	B	C	D	
	**1a** R=Bn **1b** R=CH_2CH_2Ph **1c** R=C_6H_3(2,5-OMe)[14]	**2a** 90 **2b** 89 **2c** 89[14]				
	**1a** **1b** **1c**	**3a**/**4a** 70 **3b**/**4b** 75 **3c**/**4c** 66	68		34	(A) 41:59; (D) 49:51 (A) 42:58; (B) 41:59 (A) 45:55
	**1a** **1b** **1c**	**5a**/**6a** 94 **5b**/**6b** 96 **5c**/**6c** 80		56	36	(A) 55:45; (C) 63:36; (D) 70/30 (A) 71:29 (A) 74:26
	**1a** **1b** **1c**[14]		**7a**/**8a** 52 **7b**/**8b** 62 **7c** 60[14]	32	32 34	(B) 90:10; (D) 28:72 (B) 85:15; (C) 75:25; (D) 0:100 (B) 100
	**1a** **1b** **1d** R=C_6H_4(4-Me)		**9a** 43 **9b** 38 **9d** 43			100 100 100

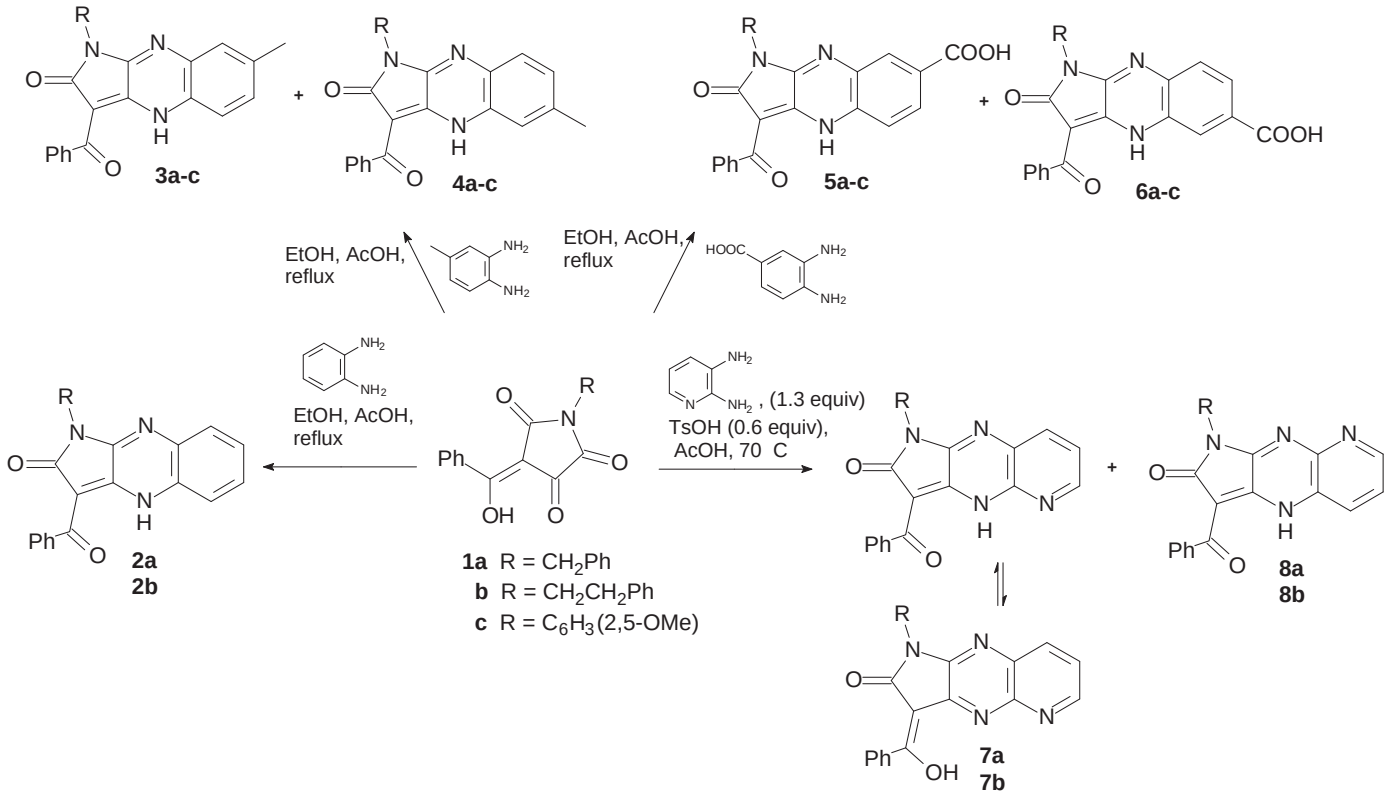
A: EtOH, AcOH, refluxed; B: AcOH, TsOH (1:1.3:0.6), 70 °C; C: AcOH, refluxed; D: (i) $SOCl_2$; (ii) H_2NAr; (iii) EtOH, AcOH, 70 °C; RS: reaction selectivity (±2%).

Contrary to our previous results, in the reaction of 2,3-diaminopyridine with *N*-alkylpyrrolidinetrione **1a**,**1b** with the addition of TsOH in a ratio of 1.3:1:0.6, we obtained the mixture of two regioisomers **7a**, **8a** and **7b**, **8b** (Table 1), respectively. The electron-donating influence of the *N*-alkyl group in **1** probably activates the amide carbon atom at C-2 to the nucleophilic attack. Repeating this reaction with **1b** without TsOH and in an equimolar ratio shows that TsOH displaces the weakest acid **1** and favours the formation of pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazine **7b** (Table 1, Scheme 1).

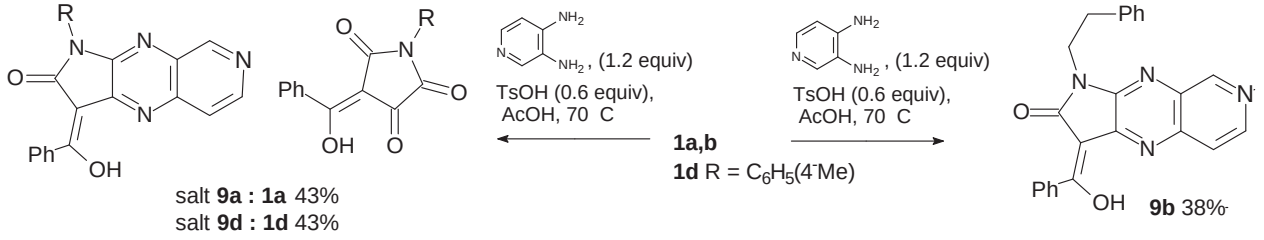
3,4-Diaminopyridine is less prone to nucleophilic attack; therefore, the condensation without TsOH gives very poor yields for **9ab**. The addition of 0.6 equiv of the condensing agent and extending the reaction time to 50 h leads to the regioselective substituted intermediate **12ab** with complete control of the regiochemistry (Scheme 4). Cyclisation of the 3-amino-4-benzoylpyrroline-2,5-dione derivative **12ab** in EtOH with the addition of acetic acid allowed us to obtain the regioisomer **8a** in excess and the pure compound **8b**.

The formation of two regioisomers in the last step of this procedure is likely due to the hydrolysis of the enamine bond of C3–N caused by the water evolved during cyclisation.

The structure of the regioisomers was confirmed by NMR spectroscopy. We reported that the ^{1}H NMR data of **2** revealed the solvent effect of DMSO-d_6 and $CDCl_3$ on H-5, H-2″/6″ chemical shifts.[14] The proton H-5 was deshielded in DMSO-d_6 for **2a** at 0.67 ppm and **2b** at 0.63 ppm; whereas, the protons H-2″/6″ were upfield shifted for **2a** at 0.21 ppm and **2b** at 0.25 ppm. The



Scheme 1. Direct condensation of **1** with substituted aromatic *ortho*-diamines.



Scheme 2. Direct condensation of **1** with 3,4-diaminopyridine.

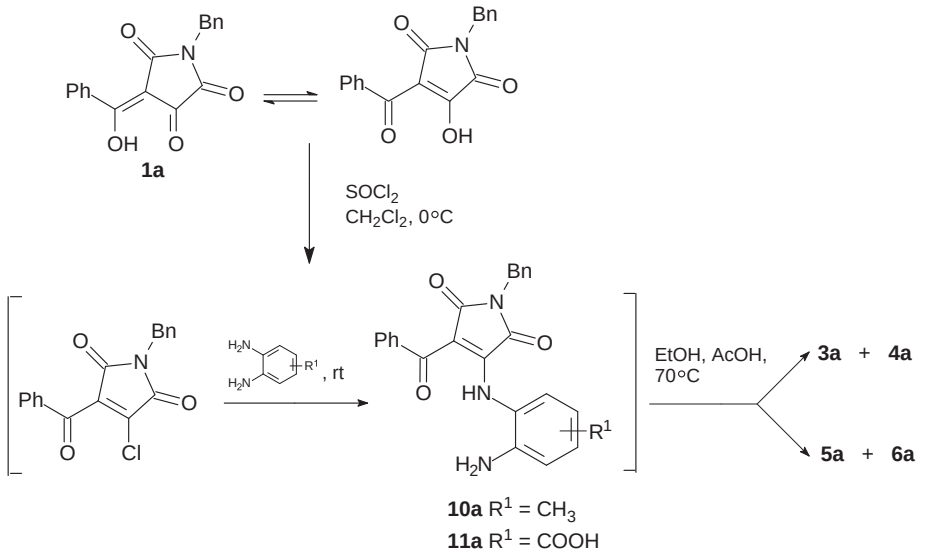
resolution of the pair of regioisomers, **3** and **4**, was based on the same effect. The signals for H-2″/6″ were observed at lower field (for **3b** and **4b** at 0.27 ppm). Additionally, a different population for both sets showed the domination of one regioisomer. The presence of the nuclear Overhauser effect (NOE) for **3a** between distinguishable H-2″/6″ and H-5 protons definitively assigned the structure of **3**. The ^{1}H NMR data for **5** and **6** gave two sets of signals with the doublet at 8.82 ppm for benzyl and 2,5-dimethoxyphenyl derivatives and 8.85 ppm for 2-phenylethyl, all with a long range constant of ^4J 1.8 Hz. According to the electronic effect of the carboxylic group and the solvent effect of DMSO-d_6, we attributed these signals to the H-5 proton of regioisomer **6**. The structure of compounds **8** and **9** was confirmed by 1D and 2D NMR experiments involving HSQC, HMBC and NOESY (Table 2).

The ^{1}H NMR data of **12a** and **12b** revealed one set of signals, which we attributed to the substitution product of the more nucleophilic amino group at C-3 in 2,3-diaminopyridine in accordance with the structure of the fused compounds **8ab**.

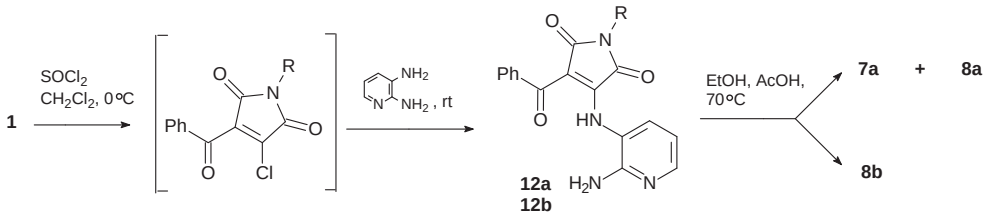
Fluorescence detection can be used in a wide range of studies related to life science. Fluorophores based on nitrogen heterocycles can be applied for labelling amino acids, peptides, proteins, DNA and other biomolecules; however, we found several papers concerning the photophysical studies of quinoxaline,[19,20] pyridopyrazine,[20] pyrrolopyrazine[21,22] and pyrrolo[2,3-*b*]quinoxaline[22] systems. Here, we present the preliminary study of the fluorescent properties of the 1-alkyl pyrrolo[2,3-*b*]quinoxaline **2a**–**c**, **3a**, **5b**, pyrido[2,3-*b*]pyrrolo [2,3-*e*]pyrazine **7b**, pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazine **8b**, and pyrido[3,4-*b*]pyrrolo[3,2-*e*]pyrazine **9b** derivatives.

Typical absorption and emission spectra in acetonitrile for the compounds under study are presented in Fig. 2. The absorption spectra of compounds **2a**–**c** exhibited peaks centred at 392 nm with a shoulder at 414 nm. The differences in absorption spectra of the compounds **2a**, **3a** and **5a**, as presented in Table 3, are probably due to substituents with different electron-donor abilities. For regioisomers **7b** and **8b**, no significant differences were observed in the absorption maxima, with the exception of the blue shift in the absorption spectrum of compound **9b**.

The fluorescence emission spectra exhibited features similar to those of the corresponding absorption spectra. The quantum yields (Φ_n) and lifetimes (τ_n) for all of the analysed compounds were determined in acetonitrile at 25 °C upon excitation at selected



Scheme 3. Three-step method of synthesis of 6- or 7-substituted pyrrolo[2,3-*b*]quinoxaline derivatives.



Scheme 4. Three-step method of synthesis of regioisomer **8a** in excess and **8b**.

Table 2
NMR spectral data for **8b** and **9b** [300.18 MHz, DMSO-d_6, δ (ppm)]

Atom	**8b**				**9b**			
	HSQC		HMBC	NOESY	HSQC		HMBC	NOESY
	^{13}C	^{1}H			^{13}C	^{1}H		
2	166.0	—			166.0	—	H–CH_2N	
3	94.9	—			98.15	—		
3a	139.3	—			139.68	—		
4	N	13.76		H-5	N	—		
4a	124.0	—	H-6		138.66	—	H-5, H-6	
5	128.2	8.65		H-4, H-6	114.29	8.30	H-6	H-6, H-8
6	122.2	7.62		H-7	138.32	8.68	H-8	H-5, H-8
7	145.5	8.69		H-6	N			
8	N	—			142.86	9.34	H-6	H-5, H-6, H-3′/5′, H–CH_2N, H–CH_2Ph
8a	145.8	—	H-5, H-7		132.04	—	H-8	
9a	151.3	—	H–CH_2N		151.09	—	H–CH_2N	
10	188.7	—	H-2″/6″		189.13	—	H-2″/6″	
1′	138.4	—	H-3′/5′, H–CH_2Ph		138.21	—	H-2′/6′, H–CH_2N	
2′/6′	128.7	7.24	H–CH_2Ph		128.76	7.26	H–CH_2Ph	
3′/5′	128.4	7.28			126.38	7.24	H-2′/6′	
4′	126.3	7.20			128.37	7.29	H-2′/6′	
CH_2N	39.5	4.11		H-3′/5′, H-2′/6′	40.35	4.09	H–CH_2Ph	H-8
CH_2Ph	33.5	3.04		H-2′/6′	34.61	3.04	H-3′/5′	H-8, H-3″/5″
1″	138.5	—	H-3″/5″		137.76	—	H-3″/5″	
2″/6″	128.7	7.76		H-3″/5″, H-4″	128.90	7.75	H-4″, H-3″/5″	
3″/5″	127.6	7.47			127.08	7.49		H-8
4″	131.6	7.57	H-2″/6″	H-2″/6″	132.37	7.62	H-2″/6″	

wavelengths, and the results are presented in Table 3. Incorporation of the C_6H_3(2,5-OMe) moiety (compound **2c**) in place of $(CH_2)_n$Ph (compounds **2a** and **2b**) resulted in a loss of fluorescence properties. The fluorescence decay for all the samples was reasonably fitted to a monoexponential equation, suggesting the emission originated from the singlet-excited state in each case. The fluorescence quantum yields and lifetimes of compounds **7b** and **9b** were significantly lower in comparison to the other analysed compounds, possibly as a consequence of the nonradiative deactivation of the singlet state.

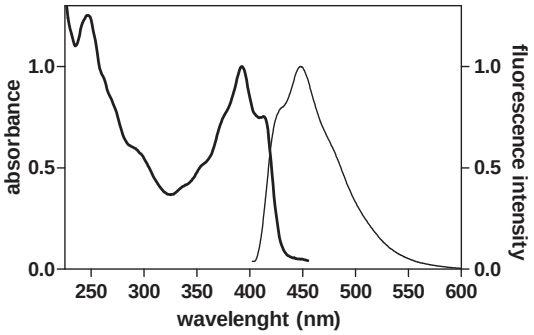


Fig. 2. Normalised absorption (bold line) and emission (fine line) spectra of compound **2a** in acetonitrile.

Table 3
Photophysical properties of the analysed compounds dissolved in acetonitrile

Compound	λ_{abs} (nm)	ε ($M^{-1}\,cm^{-1}$)	λ_{em} (nm)	Φ_n[a,b]	τ_n[b] (ns)
2a	392	22,350	447	0.132±0.021	0.585±0.003
2b	392	24,900	447	0.128±0.020	0.569±0.002
2c	392	25,500	—	—	—
3a	398	21,450	455	0.189±0.027	0.675±0.002
5a	394	19,500	452	0.153±0.028	0.621±0.005
7b	392	20,800	447	0.092±0.016	0.393±0.003
8b	392	21,800	452	0.202±0.028	0.770±0.002
9b	381	19,900	441	0.046±0.015	0.280±0.005

[a] The fluorescence quantum yields (Φ_n) were estimated from the corrected fluorescence spectra using 9,10-diphenylanthracene in cyclohexane (Φ_s=0.90) as a standard.
[b] Average of five measurements.

The changes in the fluorescence properties of compound **2b** in different solvents are summarised in Table 4. Compound **2b**, dissolved in protic solvents, showed a bathochromic shift in the fluorescence emission maximum of the fluorescence spectra. The shift was accompanied by a lowering of the fluorescence quantum yield and lifetime due to the polar interactions participating in nonradiative deactivation.

Table 4
Solvent effect on the spectral properties of compound **2b**

Solvent	λ_{abs} (nm)	λ_{em} (nm)	Φ_n	τ_n (ns)
$CHCl_3$	395	450	0.113±0.022	0.484±0.005
THF	394	449	0.119±0.020	0.539±0.003
Acetone	389	449	0.101±0.020	0.566±0.003
EtOH	392	455	0.038±0.005	0.397±0.003
MeOH	392	455	0.028±0.007	0.252±0.002
MeCN	392	447	0.128±0.023	0.569±0.005

3. Conclusions

In conclusion, we have shown that the differential reactivity between two amino groups in *ortho*-diaminopyridine can be exploited to obtain regio-defined unsymmetrical pyridopyrrolopyrazine derivatives. When the most nucleophilic amino group is involved in the formation of a salt in direct condensation with the presence of TsOH (method B), pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazine **7** and pyrido[3,4-*b*]pyrrolo[3,2-*e*]pyrazine **9** are obtained with control of the regiochemistry. When the most nucleophilic amino group of 2,3-diaminopyridine substitutes a chlorine atom in the three-step procedure (method D), the reaction predominantly leads to the formation of pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazine **8**. A weak electron-donating methyl group attached to the *ortho*-diaminobenzene reduced the ability to construct compounds in a regioselective manner, whereas a moderately electron-withdrawing carboxylic acid group favours the formation of the 7-carboxylic acid of pyrrolo[2,3-*b*]quinoxaline independent of the method used. The presence of a nitrogen atom in 2,3-diaminopyridine and 3,4-diaminopyridine diverts more of the nucleophilicity of the *ortho*-diamino groups than the carboxylic group. We also showed that 1-alkyl pyrrolo[2,3-*b*]quinoxaline, pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazine, pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazine and pyrido[3,4-*b*]pyrrolo[3,2-*e*]pyrazine had weak fluorescence properties. The presence of the aryl group at the N-1 position for pyrrolo[2,3-*b*]quinoxaline resulted in a loss of fluorescence emission. The position of the nitrogen atom in the pyridine of the fused heterocyclic system affects the fluorescence intensity, which is higher for pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazine **8b.**

4. Experimental section

4.1. General

Phenylenediamine, 3,4-diaminotoluene, 3,4-diaminobenzoic acid, 2,3- and 3,4-diaminepyridine were commercial products (Aldrich). The melting points were determined on a *Boetius* PHMK 05 melting point apparatus. The IR spectra were measured on a Bruker IFS 48 in KBr pellets or Nujol. The ^{1}H NMR, ^{13}C NMR, COSY, NOESY, HSQC and HMBC spectra were recorded with a Bruker Avance II 300 spectrometer at 300 K. The chemical shifts (δ) were reported in parts per million (ppm) on a δ scale downfield from TMS. The ^{1}H NMR spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm) or DMSO-d_6 (δ 2.50 ppm). The ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm) or DMSO-d_6 (δ 39.5 ppm). The coupling constants (J) were reported in Hertz (Hz). The mass spectra were measured on a Finnigan Mat 95 (EI, 70 eV) and ESI. The microanalyses were performed with a Euro EA 3000 Elemental Analyser; the results agreed satisfactorily with calculated values. The ^{13}C NMR spectra were not taken for **3a**, **3c**, **4a** and **4c** because of their extremely low solubility.

All the solvents for the UV and fluorescence spectra were obtained from Sigma–Aldrich or Merck and were of spectroscopic purity. The analysed compounds were dissolved in acetonitrile to prepare 20 μM stock solutions for determination of their photophysical properties. The effect of solvent polarity was examined by measuring the absorbance and fluorescence of the compounds diluted in selected solvents using 1 mM stock solution prepared in *N*,*N*-dimethylformamide (DMF).

The absorption spectra were recorded with a Power WaveX-Select spectrophotometer (Bio-Tek Instruments) in 1-cm cells. The fluorescence measurements were performed using a HITACHI F-4500 spectrofluorometer. All the spectra were recorded at 25 °C with an excitation slit width of 5 nm, an emission slit of 10 nm and 700 V of PMT voltage.

The fluorescence quantum yields of the analysed compounds were determined using 9,10-diphenylanthracene (Φs=0.90 in cyclohexane) as a standard. The fluorescence lifetimes were determined using a time-correlated single photon counting system based on the Horiba Jobin Yvon IBH lifetime spectrofluorometer system components, which consisted of a picosecond single-photon detection TBX-04 module, integrated with a fast photomultiplier, high-voltage power supply, GHz preamplifier and picosecond-timing discriminator. A picosecond pulsed laser diode (NanoLED-11, Horiba Jobin, Yvon) was used as a light source. The specimens were excited at 372 nm with 1 MHz repetition. The fluorescence decays were observed through a cut-off filter of 475 nm (Andover Corporation Optical Filter). To avoid pulse pile-up, the power of the diode was adjusted to the appropriate low level by a neutral gradient filter. The excitation pulse diode laser

profile, required for the deconvolution analysis, was measured on a diluted glycogen suspension without using a filter. For the data acquisition and decay analysis, the Jobin Yvon IBH data station and DAS6 software were used. All the measurements were performed at 25 °C, and each recorded lifetime was averaged from five independent decay measurements.

4.2. General procedure for preparing *N*-aryl-, *N*alkylpyrrolidine-2,3,5-trione 1

A solution of amine (0.2 mol) in xylene (100 mL) with pyridine (1 mL) was added gradually to a solution of 3-oxo-3-phenylpropionic acid ethyl ester (40 g, 0.2 mol) in boiling xylene (200 mL). The rate of addition of the amine was the same as the rate of distillation of xylene with pyridine. The distillate (120 mL) was again added gradually to the reaction mixture. This procedure was repeated three times. The distillation ended when the boiling flask contained one-thirtieth of the original reaction mixture. The crude product precipitated from the reaction mixture was collected and crystallised.[23]

3-Oxo-3-phenyl-N-(benzyl)propanamide.[24] Light yellow needles (EtOH), yield: 23.83 g (45%); mp: 89 °C (lit.[24] mp: 91–92 °C).

3-Oxo-3-phenyl-N-(2-phenylethyl)propanamide.[25] This compound was obtained as light yellow needles (EtOAc), yield: 24.5 g (44%); mp: 87 °C (lit.[25] mp: 83–85 °C); IR (KBr): ν=3303 (NH), 1694, 1663 (CO) cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.83 (t, 2H, 2-H′, J=7), 3.56 (q, 2H, 1-H′, J=7), 3.90 (s, 2H, 2-H, J=7), 7.02 (s, 1H, NH), 7.18 (d, 2H, 2-H–Ar″, J=7), 7.22 (t, 1H, 4-H–Ar″, J=7), 7.27 (t, 2H, 3-H–Ar″, J=7), 7.48 (t, 2H, 3-H–Ar′, J=8), 7.61 (t, 1H, 4-H–Ar′, J=8), 7.98 (d, 2H, 2-H–Ar′, J=8); ^{13}C NMR ($CDCl_3$): δ 35.86 2-C′, 41.17 1-C′, 45.86 2-C, 126.73–138.98 C–Ar, 165.83 1-C, 196.18 3-C; MS-EI: m/z 267 (M^+), 176 (M^+-PhCH_2), 147 ($M^+-PhCH_2CH_2NH$), 104 (PhCNH), 91 ($PhCH_2$), 77. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.46; H, 6.63; N, 5.32.

3-Oxo-3-phenyl-N-(2,5-dimethoxyphyl)propanamide.[26] Light yellow needles (MeOH), yield: 31.09 (50%); mp: 77 °C (lit.[26] mp: 76–78 °C).

Oxalyl chloride (3 mL, 34 mmol) was added dropwise at rt to a stirred solution of 3-oxo-3-phenyl-*N*-(2-phenylethyl)propanamide (8.01 g, 30 mmol) in dry toluene (150 mL). The solution was stirred at 60 °C for 20 h. The crude product precipitated from the reaction mixture was collected and crystallised from acetic acid.

1-Benzyl-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione (***1a***).[15] Light yellow plates (AcOH), yield: 8.50 g (96%); mp: 125–6 °C (lit.[15] mp: 96 °C).

1-(2-Phenylethyl)-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione (***1b***). Light yellow plates, yield: 5.95 g (62%); mp: 134–5 °C; IR (KBr): ν=3439 (OH), 3082, 3060, 3028 (=CH, Ar), 2987, 2950 (CH_2), 1776, 1739, 1656 (C=O) cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ 3.02 (m, 2H, CH_2Ph), 3.97 (m, 2H, CH_2N), 7.24–7.68 (m, 8H, H–Ar), 8.20 (d, 2H, H–Ar); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 33.70 (CH_2Ph), 39.43 (CH_2N), 126.69, 128.45, 128.52, 129.75, 130.07, 130.48, 134.74, 136.98 (Ar–C), 160.97 (C-2), 174.49 (C-3), 184.57 (C-6); MS-EI: 321 (M^+), 105 (PhCO), 91 ($PhCH_2$). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.70; N, 4.35. Found: C, 71.08; H, 4.66; N, 4.38.

1-(2,5-Dimethoxyphenyl)-4-(phenylhydroxylmethylidene)pyrrolidine-2,3,5-trione (***1c***).[14]

4.3. Procedure for the reaction with *o*-phenylenediamine

Method A. Aromatic *ortho*-diamine (3.4 mmol) was added to a solution of **1** (3.1 mmol) in EtOH (50 mL) with the addition of glacial acetic acid (2 mL). The solution was refluxed for 3 h and left overnight. The precipitate was filtered off and crystallised from chlorobenzene.

3-Benzoyl-1-benzyl-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (***2a***). Yellow needles, yield: 1.06 g (90%); mp: 275–277 °C; IR (KBr): ν=3490 (OH), 3264 (NH), 3060, 3026 (CH, Ar), 2916 (CH, CH_2), 1708 (C=O), 1653 (C=N), 1616 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 5.08 (s, 2H, CH_2), 7.24 (dd, 1H, ^3J=7.4, ^4J=1.1, H-4′), 7.31 (dddd, 2H, ^3J=7.9, ^3J=7.4, ^4J=1.4, ^5J=0.7, H-3′/5′), 7.34 (dddd, 2H, ^3J=7.9, ^4J=2.0, ^4J=1.1, ^5J=0.7, H-2′/6′), 7.48 (dddd, 2H, ^3J=7.7, ^3J=7.5, ^4J=1.4, ^5J=0.6, H-3″/5″), 7.50 (dd, 1H, ^3J=8.1, ^3J=7.2, ^4J=1.4, H-7), 7.54 (dd, 1H, ^3J=8.3, ^3J=7.2, ^4J=1.4, H-6), 7.56 (dd, 1H, ^3J=7.5, ^4J=1.2, H-4″), 7.83 (m, ^3J=8.1, ^4J=1.4, ^5J=0.2, 1H, H-8), 7.86 (dddd, 2H, ^3J=7.7, ^4J=1.7, ^4J=1.2, ^5J=0.6, H-2″/6″), 8.25 (m, ^3J=8.3, ^4J=1.4, ^5J=0.2, 1H, H-5), 13.77 (br, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 41.4 (CH_2), 94.6 (C-3), 118.9 (C-5), 125.9 (C-7), 127.1 (C-6), 127.1 (C-4′), 127.2 (C-3″/5″), 127.4 (C-8), 127.5 (C-3′/5′), 127.7 (C-4a), 128.4 (C-2′/6′), 128.7 (C-2″/6″), 131.4 (C-4″), 135.6 (C-8a), 137.2 (C-1′), 138.9 (C-1″), 139.2 (C-3a), 148.2 (C-9a), 166.1 (C-2), 188.8 (C-10); MS-EI: 379 (M^+), 105 (PhCO), 91 ($PhCH_2$). Anal. Calcd for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.07. Found: C, 76.11; H, 4.44; N, 11.04.

3-Benzoyl-1-(2-phenylethyl)-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (***2b***). Yellow needles, yield: 1.08 g (89%); mp: 245 °C; IR (KBr): ν=3486 (OH), 3182 (NH), 3061, 3026 (CH, Ar), 2936 (CH, CH_2), 1703 (C=O), 1653 (C=N), 1620 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.02 (m, 2H, CH_2Ph), 4.09 (m, 2H, CH_2N), 7.18 (dd, 1H, ^3J=7.5, ^4J=1.2, H-4′), 7.21 (dddd, 2H, ^3J=7.7, ^4J=1.8, ^4J=1.2, ^5J=0.5, H-2′/6′), 7.26 (dddd, 2H, ^3J=7.7, ^3J=7.5, ^4J=1.4, ^5J=0.5, H-3′/5′), 7.45 (dddd, 2H, ^3J=7.7, ^3J=7.5, ^4J=1.4, ^5J=0.6, H-3″/5″), 7.50 (dd, 1H, ^3J=8.2, ^3J=7.3, ^4J=1.4, H-6), 7.52 (dd, 1H, ^3J=8.2, ^3J=7.3, ^4J=1.3, H-7), 7.55 (dd, 1H, ^3J=7.5, ^4J=1.2, H-4″), 7.77 (dddd, 2H, ^3J=7.7, ^4J=1.7, ^4J=1.2, ^5J=0.6, H-2″/6″), 7.84 (m, ^3J=8.2, ^4J=1.4, ^5J=−0.4, 1H, H-8), 8.21 (m, ^3J=8.2, ^4J=1.3, ^5J=−0.4, 1H, H-5), 13.66 (br, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 33.6 (CH_2Ph), 39.4 (CH_2N), 94.5 (C-3), 118.7 (C-5), 125.8 (C-6), 126.3 (C-4′), 126.9 (C-7), 127.3 (C-8), 127.4 (C-4a), 127.5 (C-3″/5″), 128.3 (C-3′/5′), 128.7 (C-2′/6′), 128.7 (C-2″/6″), 131.4 (C-4″), 135.5 (C-8a), 138.5 (C-1′), 138.7 (C-1″), 138.8 (C-3a), 148.1 (C-9a), 166.0 (C-2), 188.8 (C-10); MS-EI: 393 (M^+), 302 (M^+-PhCH_2), 289 ($M^+-PhCH_2CH_2$), 105 (PhCO). Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.86; N, 10.68. Found: C, 76.33; H, 4.87; N, 10.72.

4.4. Procedure for the reaction with 3,4-diaminotoluene, 3,4-diaminobenzoic acid

Method A. Aromatic *ortho*-diamine (3.4 mmol) was added to a solution of **1** (3.1 mmol) in EtOH (50 mL) with addition of glacial acetic acid (2 mL). The solution was refluxed for 3 h and left overnight. The precipitate was filtered off and crystallised from chlorobenzene.

Method B. Compound **1** (3.1 mmol) was added to a solution of aromatic *o*-diamine (4.03 mmol) and TsOH (0.32 g, 1.86 mmol) in AcOH (25 mL). The solution was refluxed for 3 h and left overnight. The precipitate was filtered off and crystallised from chlorobenzene.

Method C. Aromatic *ortho*-diamine (3.4 mmol) was added to a solution of **1** (3.1 mmol) in AcOH (50 mL). The solution was refluxed for 3 h and left overnight. The precipitate was filtered off and crystallised from chlorobenzene.

Method D. $SOCl_2$ (212 mg, 0.13 mL, 1.78 mmol) was added to an ice-cooled stirred solution of **1** (1.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 1 h, the mixture was warmed to rt and stirred for 24 h; then H_2O (100 mL) was added to the stirred mixture. The CH_2Cl_2 phase was separated and dried ($MgSO_4$). Aromatic *o*-diamine (1.7 mmol) was added to the CH_2Cl_2 phase. The mixture was stirred for 5 days. The solvent was removed, and the residue was dissolved in EtOH (50 mL) with AcOH (0.5 mL) and stirred at 70 °C for 5 days. The precipitate was filtered off and crystallised.

3-Benzoyl-1-benzyl-7-methyl-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (***3a***), *3-benzoyl-1-benzyl-6-methyl-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one* (***4a***). Yellow needles, yield: (A) 853 mg

(70%), (D) 227 mg (34%); mp: 263 °C; IR (KBr): ν=3455 (OH), 3180 (NH), 3085, 3062, 3029 (CH, Ar), 2920 (CH, CH_2), 1700 (C=O), 1652 (C=N), 1624, 1611, 1587 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 2.43 (s, 3H, 7-CH_3 for **3a**), 2.45 (s, 3H, 6-CH_3 for **4a**), 5.05 (s, 4H, CH_2Ph for **3a** and **4a**), 7.24–7.55 (m, 18H, H–Ar, **3a** and **4a**), 7.63 (s, 1H, H-8, **3a**), 7.64 (d, 1H, ^3J=8.3, H-8, **4a**), 7.78 (m, 4H, ^3J=7.3, H-2″/6″, **3a** and **4a**), 8.03 (s, 1H, H-5, **4a**), 8.13 (d, ^3J=8.4, 1H, H-5, **3a**), 13.7 (s, 2H, NH, **3a** and **4a**); MS-ESI: 394 (M^++1). Anal. Calcd for $C_{25}H_{18}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.31; H, 4.81; N, 10.71.

*3-Benzoyl-1-benzyl-7-methyl-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (**3a**).* Yellow needles, yield: (A): 28 mg (2%); mp: 265 °C; IR (KBr): ν=3476 (OH), 3185 (NH), 3085, 3062, 3029 (CH, Ar), 2954, 2920 (CH, CH_2), 1700 (C=O), 1653 (C=N), 1625, 1609, 1584 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 2.37 (s, 3H, 7-CH_3), 5.05 (s, 4H, CH_2Ph), 7.24–7.55 (m, 9H, H–Ar), 7.63 (s, 1H, H-8), 7.78 (m, 2H, ^3J=6.8, H-2″/6″), 8.13 (d, ^3J=8.4, 1H, H-5), 13.67 (s, 1H, NH); MS-ESI: 394 (M^++1).

*3-Benzoyl-7-methyl-1-(2-phenylethyl)-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (**3b**), 3-benzoyl-6-methyl-1-(2-phenylethyl)-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (**4b**).* Yellow needles, yield: (A): 0.95 g (75%), (B): 0.86 g (68%); mp: 243 °C; IR (KBr): ν=3447 (OH), 3184 (NH), 3087, 3061, 3027 (CH, Ar), 2978, 2940 (CH, CH_2), 1700, 1697 (C=O), 1651 (C=N), 1622, 1603 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 2.44 (s, 6H, 6-CH_3 (**4b**), 7-CH_3, (**3b**)), 2.99 (t, 4H, CH_2Ph), 4.06 (t, 4H, CH_2N), 7.17–7.55 (m, 18H, H–Ar, **3b** and **4b**), 7.65 (s, 1H, H-8, **3b**), 7.72 (d, 1H, ^3J=8.3, H-8, **4b**), 7.76 (m, 4H, ^3J=6.9, H-2″/6″, **3b** and **4b**), 7.99 (s, 1H, H-5, **4b**), 8.09 (d, 1H, H-5, **3b**), 13.6 (s, 2H, NH, **3b** and **4b**); ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.51 (s, 3H, 6-CH_3 (**4b**)), 2.55 (s, 3H, 7-CH_3, (**3b**)), 3.17 (m, 4H, CH_2Ph), 4.27 (m, 4H, CH_2N), 7.20–7.55 (m, 20H, H–Ar, **3b** and **4b**), 7.81 (s, 1H, H-5, **4b**), 7.87 (d, 1H, ^3J=8.6, H-5, **3b**), 8.01 (m, 4H, ^3J=6.9, H-2″/6″, **3b** and **4b**); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ=21.16, 21.74, 34.09, 34.12, 39.82, 94.67, 94.97, 118.74, 118.99, 125.65, 126.74, 126.76, 127.45, 127.64, 127.73, 127.95, 127.96, 127.98, 128.79, 128.82, 129.01, 129.16, 129.17, 129.19, 129.22, 129.24, 129.71, 131.78, 131.84, 134.17, 136.06, 137.34, 138.94, 138.98, 139.00, 139.02, 139.27, 139.31, 147.96, 148.51, 166.35, 166.36, 189.11, 189.20; MS-ESI: 408 (M^++1). Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.38; H, 5.10; N, 10.34.

*3-Benzoyl-7-methyl-1-(2,5-dimethoxyphenyl)-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (**3c**), 3-benzoyl-6-methyl-1-(2,5-dimethoxyphenyl)-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (**4c**).* Yellow needles, yield: (A): 892 mg (66%); mp: 212 °C; ^1H NMR (300.13 MHz, DMSO-d_6): δ 2.41 (s, 3H, 7-CH_3, (**3c**)); 2.46 (s, 3H, 6-CH_3 for **4c**), 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 7.01–7.52 (m, 14H, H–Ar, **3c** and **4c**), 7.57 (s, 1H, H-9, **3c**), 7.63 (d, 1H, ^3J=8.2, H-9, **4c**), 7.87 (m, 4H, ^3J=6.7, H-2″/6″, **3c** and **4c**), 7.97 (s, 1H, H-5, **4c**), 8.14 (d, 1H, ^3J=8.4, H-5, **3c**), 13.76 (s, 2H, NH, **3c** and **4c**); MS-ESI: 439 (M^++1). Anal. Calcd for $C_{26}H_{20}N_3O_4$: C, 71.22; H, 4.60; N, 9.58. Found: C, 71.20; H, 4.69; N, 9.65.

*3-Benzoyl-1-benzyl-2-oxo-2,4-dihydro-1H-pyrrolo[2,3-b]quinoxaline-7-carboxylic acid (**5a**), 3-benzoyl-1-benzyl-2-oxo-2,4-dihydro-1H-pyrrolo[2,3-b]quinoxaline-6-carboxylic acid (**6a**).* Yellow needles, yield: (A): 1.23 g (94%), (C): 0.74 g (56%), (D): 259 mg (36%); mp: 337–357 °C; IR (KBr): 3398, 3154, 3060, 3030, 2919, 2851, 1703, 1688, 1655, 1620, 1588 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 5.04 (s, 4H, CH_2Ph, **5a**, **6a**), 7.21–7.32 (m, 10H, Ar–H, **5a**, **6a**), 7.39–7.51 (m, 7H, Ar–H, **5a**, **6a**), 7.83 (d,d ^3J=7.3, ^4J=1.5, 4H, H-2″/6″, **5a**, **6a**), 7.94 (dd, ^3J=8.5, ^4J=1.9, 1H, H-6, **6a**), 8.23 (d, ^3J=8.5, 1H, H-5, **5a**), 8.24 (d, ^4J=1.8, 1H, H-8, **5a**), 8.82 (d, ^4J=1.8, 1H, H-5, **6a**), 13.11 (s, 2H, COOH, **5a**, **6a**), 13.83 (s, 2H, NH, **5a**, **6a**); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 42.16, 96.18, 119.59, 127, 92, 128.15, 128.29, 128.37, 129.16, 129.48, 131.55, 132.30, 135.60, 137.73, 139.32, 140.12, 149.59, 166.84, 167.24, 189.65; MS (EI, 70 eV): *m*/*z* 423 (100) [M^+], 318 (6) [M^+–PhCO], 290 (19)[M^+–PhCO–CO], 105 (20) [PhCO], 91 (27) [$PhCH_2$]. Anal. Calcd for $C_{25}H_{17}N_3O_4$: C, 70.91; H, 4.05; N, 9.92. Found: C, 70.83; H, 4.10; N, 9.87.

*3-Benzoyl-1-(2-phenylethyl)-2-oxo-2,4-dihydro-1H-pyrrolo[2,3-b]quinoxaline-7-carboxylic acid (**5b**), 3-benzoyl-(2-phenylethyl)-2-oxo-2,4-dihydro-1H-pyrrolo[2,3-b]quinoxaline-6-carboxylic acid (**6b**).* Yellow needles, yield: (A): 1.3 g (96%); mp: 305–323 °C; IR (KBr): 3505, 3303, 3028, 2922, 2852, 1699, 1653, 1618, 1584 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.03 (t, ^3J=7, 4H, CH_2Ph, **5b**, **6b**), 4.09 (t, ^3J=7, 4H, NCH_2, **5b**, **6b**), 7.19–7.31 (m, 12H, Ar–H, **5b**, **6b**), 7.47 (t, ^3J=7.5, 2H, Ar–H, **5b**), 7.59 (t, 2H, Ar–H, **6b**), 7.77 (dd, ^3J=7.5, ^4J=1.4, 4H, H-2″, 6″, **5b**, **6b**), 7.87 (d, ^3J=8.5, 1H, H-8, **6b**), 7.98 (dd, ^3J=8.5, ^4J=1.6, 1H, H-7, **6b**), 8.0 (dd, ^3J=8.5, ^4J=1.6, 1H, H-6, **5b**), 8.23 (d, ^3J=8.5, 1H, H-5, **5b**), 8.31 (d, ^4J=1.6, 1H, H-8, **5b**), 8.86 (d, ^4J=1.8, 1H, H-5, **6b**), 13.17 (s, 2H, COOH, **5b**, **6b**), 13.78 (s, 2H, NH, **5b**, **6b**); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 34.11, 41.49, 95.14, 95.86, 116.82, 119.27, 121.04, 126.80, 127.57, 128.06, 128.85, 129.06, 129.29, 131.09, 132.11, 135.35, 138.74, 138.96, 139.03, 139.12, 139.53, 139.81, 149.28, 149.98, 163.58, 166.48, 167.09, 189.21, 189.40; MS (EI, 70 eV): *m*/*z* 437 (70) [M^+], 346 (26) [M^+–$PhCH_2$], 333 (100) [M^+–$PhCH_2CH_2$], 105 (89) [PhCO]. Anal. Calcd for $C_{26}H_{19}N_3O_4$: C, 71.38; H, 4.38; N, 9.60. Found: C, 71.25; H, 4.47; N, 9.51.

*3-Benzoyl-1-(2,5-dimethoxyphenyl)-2-oxo-2,4-dihydro-1H-pyrrolo[2,3-b]quinoxaline-7-carboxylic acid (**5c**), 3-benzoyl-(2,5-dimethoxyphenyl)-2-oxo-2,4-dihydro-1H-pyrrolo[2,3-b]quinoxaline-6-carboxylic acid (**6c**).* Yellow needles, yield: (A): 1.16 g (80%); mp: 280–305 °C; IR (KBr): 3429, 3118, 3001, 2943, 2836, 1698, 1649, 1619, 1602 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.64 (s, 6H, OCH_3, **5c**, **6c**), 3.73 (s, 6H, OCH_3, **5c**, **6c**), 7.01–7.16 (m, 6H, Ar–H, **5c**, **6c**), 7.42–7.56 (m, 6H, Ar–H, **5c**, **6c**), 7.75 (d, 2H, H-8, **6c**), 7.83 (d, 4H, H-2″, 6″, **5c**, **6c**), 7.90 (d, 2H, H-7, **6c**), 7.99 (d, 1H, H-6, **5c**), 8.14 (s, 1H, H-8, **5c**), 8.20 (d, 1H, H-5, **5c**), 8.82 (s, 1H, H-5, **6c**), 12.60 (s, 2H, COOH, **5c**, **6c**), 13.99 (s, 2H, NH, **5c**, **6c**); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 56.37, 56.97, 95.34, 96.01, 114.25, 115.80, 117.27, 120.16, 122.80, 128.28, 129.52, 132.29, 135.76, 139.20, 139.44, 150.72, 152.88, 153.72, 166.54, 167.29, 172.71, 189.68; MS (EI, 70 eV): *m*/*z* 496 (100) [M^+], 438 (27), 105 (69) [PhCO], 77 (30) [C_6H_5]. Anal. Calcd for $C_{26}H_{19}N_3O_6$: C, 66.52; H, 4.08; N, 8.95. Found: C, 66.23; H, 4.26; N, 8.84.

4.5. General procedure for the preparation of 2*H*-pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazin-2-one 7 and 2*H*-pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazin-2-one 8

Method B. 2,3-Diaminopyridine (0.47 g, 4.3 mmol) was added to a solution of **1** (3.3 mmol) in AcOH (25 mL) with the addition of TsOH (0.34 g, 2 mmol). The solution was stirred at 70 °C for 10 h, allowed to cool and then poured into water. The crude product was collected and purified by column chromatography: Al_2O_3/EtOAc/*n*-heptane (2:1) for **7a**, **8a** and EtOAc/*n*-heptane (1:1) for **7b**, **8b**.

*3-Benzoyl-1-benzyl-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**7a**).* Yellow needles, yield: (B): 580 mg (46%); mp: 186 °C; R_f (Al_2O_3, 2:1 EtOAc/*n*-heptane) 0.54; IR (KBr): ν=3450 (OH), 3190 (NH), 3064, 3031 (CH, Ar), 2956, 2920 (CH, CH_2), 1700 (C=O), 1651 (C=N), 1620 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 5.08 (s, 2H, CH_2), 7.25 (dd, 1H, ^3J=7.4, ^4J=1.0, H-4′), 7.31 (dddd, 2H, ^3J=7.7, ^4J=2.0, ^4J=1.0, ^5J=0.7, H-2′/6′), 7.34 (dddd, 2H, ^3J=7.7, ^3J=7.4, ^4J=1.5, ^5J=0.7, H-3′/5′), 7.48 (dddd, 2H, ^3J=7.8, ^3J=7.5, ^4J=1.4, ^5J=0.6, H-3″/5″), 7.55 (dd, 1H, ^3J=8.1, ^4J=4.8, H-7), 7.57 (dd, 1H, ^3J=7.5, ^4J=1.3, H-4″), 7.84 (dddd, 2H, ^3J=7.8, ^4J=1.7, ^4J=1.3, ^5J=0.6, H-2″/6″), 8.31 (m, ^3J=8.1, ^4J=1.6, 1H, H-8), 8.57 (m, ^3J=4.8, ^4J=1.6, 1H, H-6), 13.24 (br, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 41.4 (CH_2), 95.6 (C-3), 121.1 (C-7), 127.2 (C-4′), 127.2 (C-2′/6′), 127.6 (C-3″/5″), 128.4 (C-3′/5′), 128.9 (C-2″/6″), 131.1 (C-8a), 131.7 (C-4″), 136.5 (C-8), 137.0 (C-1′), 138.7 (C-1″), 140.6 (C-3a, C-4a), 145.4 (C-6), 148.7 (C-9a), 166.6 (C-2), 188.7 (C-10); MS-ESI: *m*/*z* 381

(M^++1). Anal. Calcd for $C_{23}H_{16}N_4O_2$: C, 72.62; H, 4.24; N, 14.73. Found: C, 72.62; H, 4.17; N, 14.60.

*3-Benzoyl-1-benzyl-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[3,2-e] pyrazin-2-one (**8a**).* Light orange needles, yield: (B): 65 mg (5%); mp: 225 °C; R_f (Al_2O_3, 2:1 EtOAc/*n*-heptane) 0.18; IR (KBr): ν=3454 (OH), 3110 (NH), 3053 (CH, Ar), 2927 (CH_2), 1702 (C=O), 1652 (C=N), 1615, 1590 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 5.10 (s, 2H, CH_2), 7.25 (dd, 1H, ^3J=7.5, ^4J=1.2, H-4′), 7.32 (dddd, 2H, ^3J=7.7, ^3J=7.5, ^4J=1.3, ^5J=0.6, H-3′/5′), 7.36 (dddd, 2H, ^3J=7.7, ^4J=1.7, ^4J=1.2, ^5J=0.6, H-2′/6′), 7.49 (dddd, 2H, ^3J=7.7, ^3J=7.5, ^4J=1.4, ^5J=0.7, H-3″/5″), 7.57 (dd, 1H, ^3J=8.2, ^3J=4.6, H-6), 7.57 (dd, 1H, ^3J=7.5, ^4J=1.2, H-4″), 7.85 (dddd, 2H, ^3J=7.7, ^4J=1.2, ^4J=1.0, ^5J=0.7, H-2″/6″), 8.61 (dd, 1H, ^3J=8.2, ^4J=1.6, H-5), 8.65 (m, ^3J=4.6, ^4J=1.6, 1H, H-7), 13.88 (br, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 41.5 (CH_2), 94.9 (C-3), 122.3 (C-6), 123.9 (C-4a), 127.2 (C-4′), 127.3 (C-2′/6′), 127.6 (C-3″/5″), 127.7 (C-5), 128.4 (C-3′/5′), 128.7 (C-2″/6″), 131.5 (C-4″), 137.0 (C-1′), 138.7 (C-1″), 139.4 (C-3a), 146.1 (C-8a), 147.0 (C-7), 151.0 (C-9a), 166.2 (C-2), 188.8 (C-10); MS-ESI: *m*/*z* 381 (M^++1). Anal. Calcd for $C_{23}H_{16}N_4O_2$: C, 72.62; H, 4.24; N, 14.73. Found: C, 72.34; H, 4.17; N, 14.60.

*3-Benzoyl-1-(2-phenylethyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**7b**).* Yellow needles, yield: (B): 643 mg (49%); mp: 179 °C; R_f (Al_2O_3, 1:1, EtOAc/*n*-heptane) 0.38; IR (KBr): ν=3405 (OH), 3185 (NH), 3055, 3023 (CH, Ar), 2936 (CH, CH_2), 1707 (C=O), 1651 (C=N), 1624 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.03 (m, 2H, CH_2Ph), 4.10 (m, 2H, CH_2N), 7.19 (dd, 1H, ^3J=7.4, ^4J=1.0, H-4′), 7.22 (dddd, 2H, ^3J=7.7, ^4J=2.0, ^4J=1.0, ^5J=0.7, H-2′/6′), 7.27 (dddd, 2H, ^3J=7.7, ^3J=7.4, ^4J=1.5, ^5J=0.7, H-3′/5′), 7.46 (dddd, 2H, ^3J=7.8, ^3J=7.5, ^4J=1.4, ^5J=0.6, H-3″/5″), 7.57 (dd, 1H, ^3J=4.8, ^3J=1.6, H-7), 7.57 (dd, 1H, ^3J=7.5, ^4J=1.3, H-4″), 7.74 (dddd, 2H, ^3J=7.8, ^4J=1.7, ^4J=1.3, ^5J=0.6, H-2″/6″), 8.32 (m, ^3J=8.1, ^4J=1.6, 1H, H-8), 8.56 (m, ^3J=4.8, ^4J=1.6, 1H, H-6), 13.44 (br, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 33.6 (CH_2Ph), 39.6 (CH_2N), 95.5 (C-3), 121.1 (C-7), 126.3 (C-4′), 127.6 (C-3″/5″), 128.3 (C-3′/5′), 128.7 (C-2′/6′), 128.9 (C-2″/6″), 131.0 (C-8a), 131.7 (C-4″), 136.4 (C-8), 138.4 (C-1′), 138.4 (C-1″), 140.7 (C-4a), 142.2 (C-3a), 145.4 (C-6), 148.6 (C-9a), 166.5 (C-2), 188.7 (C-10); MS-ESI: *m*/*z* 395 (M^++1). Anal. Calcd for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found: C, 72.72; H, 4.40; N, 14.20.

*3-Benzoyl-1-(2-phenylethyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[3,2-e]pyrazin-2-one (**8b**).* Light orange needles, yield: (B): 160 mg (12%); mp: 242 °C; R_f (Al_2O_3, 1:1, EtOAc/*n*-heptane) 0.08; IR (KBr): ν=3471 (OH), 3225 (NH), 3079, 3053, 3023 (CH, Ar), 2945 (CH, CH_2), 1716 (C=O), 1653 (C=N), 1618 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.04 (m, 2H, CH_2Ph), 4.11 (m, 2H, CH_2N), 7.20 (dd, 1H, ^3J=7.4, ^4J=1.0, H-4′), 7.24 (dddd, 2H, ^3J=7.7, ^4J=2.0, ^4J=1.0, ^5J=0.7, H-2′/6′), 7.28 (dddd, 2H, ^3J=7.7, ^3J=7.4, ^4J=1.5, ^5J=0.7, H-3′/5′), 7.47 (dddd, 2H, ^3J=7.8, ^3J=7.5, ^4J=1.4, ^5J=0.6, H-3″/5″), 7.57 (dd, 1H, ^3J=7.5, ^4J=1.3, H-4″), 7.62 (dd, 1H, ^3J=8.1, ^3J=4.8, H-6), 7.76 (dddd, 2H, ^3J=7.8, ^4J=1.7, ^4J=1.3, ^5J=0.6, H-2″/6″), 8.65 (m, ^3J=8.1, ^4J=1.6, 1H, H-5), 8.69 (m, ^3J=4.8, ^4J=1.6, 1H, H-7), 13.76 (br, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 33.5 (CH_2Ph), 39.5 (CH_2N), 94.9 (C-3), 122.2 (C-6), 124.0 (C-4a), 126.3 (C-4′), 127.6 (C-3″/5″), 128.2 (C-5), 128.4 (C-3′/5′), 128.7 (C-2′/6′), 128.7 (C-2″/6″), 131.6 (C-4″), 138.4 (C-1′), 138.5 (C-1″), 139.3 (C-3a), 145.5 (C-7), 145.8 (C-8a), 151.3 (C-9a), 166.0 (C-2), 188.7 (C-10); MS-ESI: *m*/*z* 395 (M^++1). Anal. Calcd for $C_{24}H_{18}N_4O_2$+EtOAc: C, 69.70; H, 5.43; N, 11.61. Found: C, 71.10; H, 5.88; N, 11.14.

Method D. $SOCl_2$ (212 mg, 0.13 mL, 1.78 mmol) was added to an ice-cooled stirred solution of **1** (1.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 1 h, the mixture was warmed to rt and stirred for 24 h; then H_2O (100 mL) was added to the stirred mixture. The CH_2Cl_2 phase was separated and dried ($MgSO_4$). Aromatic *o*-diamine (1.7 mmol) was added to the CH_2Cl_2 phase. The mixture was stirred for 5 days at rt. The precipitate **12ab** was filtered and, without purification, was dissolved in EtOH (50 mL) with AcOH (0.5 mL) and stirred at 70 °C for 5 days. The precipitate was filtered off and crystallised.

*4-Benzoyl-1-benzyl-3-amino-N-(2-amino-3-pyridyl)-pyrrolino-2,5-dione (**12a**).* Light grey needles, yield: (D): 0.270 g (40%); mp: tt. 153 °C; IR (KBr): ν=3385, 3272, 3197.11 (NH), 3063 (C–H, Ar), 2952 (C–H, CH_2), 1701 (O=C), 1640 (O=C–N), 1605 (C=C, Ar) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.49 (s, 2H, H-CH_2Ph), 6.68 (dd, 1H, ^3J=6.8, ^3J=7.7, H-5‴), 7.00 (dd, 1H, ^4J=1.4, ^3J=7.7, H-4‴), 7.14–7.32 (m, 8H, H–Ar), 7.37 (s, 2H, NH_2), 7.43 (m, 2H, H–Ar, H-2′/6′), 13.01 (s, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 40.74 (C–CH_2), 99.25 (C-4), 114.69, 120.86, 123.36, 127.98, 128.10, 128.34, 128.35, 129.43, 129.49, 130.72, 134.50, 139.17, 142.67 (C–Ar), 166.55 (C-3), 172.10 (C-2), 176.15 (C-5), 187.50 (O=C–Ph); MS-ESI: 352 (M^+-H_2O-CO). Anal. Calcd for $C_{23}H_{18}N_4O_3$+H_2O: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.75; H, 4.45; N, 13.16.

*3-Benzoyl-1-benzyl-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e] pyrazin-2-one (**7a**), 3-benzoyl-1-benzyl-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[3,2-e]pyrazin-2-one (**8a**).* Yield: (D): 205 mg (32%).

*4-Benzoyl-1-(2-phenylethyl)-3-amino-N-(2-amino-3-pyridyl)-pyrrolino-2,5-dione (**12b**).* Light grey needles, yield: 0.552 g (79%); mp: 158 °C; IR (KBr): ν=3381.95, 3279.64, 3195.79 (NH), 3061.07 (C–H, Ar), 2946.82 (C–H, CH_2), 1698.22 (C=O), 1637.98 (O=C–N), 1605.59 (C=C, Ar) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 2.74 (t, 2H, H–CH_2Ph), 3.55 (t, 2H, 1CH–CH_2N), 6.67 (dd, 1H, ^3J=6.3, ^3J=7.7, H-5‴), 7.01 (dd, 1H, ^4J=1.4, ^3J=7.7, H-4‴), 7.10–7.35 (m, 9H, H–Ar), 7.39–7.44 (m, 4H, H–Ar, H-2′, H-6′, NH_2), 13.1 (s, 1H, NH); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 35.04 (2C–CH_2), 38.5 (1C–CH_2), 99.33 (C-4), 114.64, 120.84, 123.41, 127.28, 128.12, 129.42, 129.52, 129.71, 130.82, 134.52, 139.90, 142.51, 145.79 (C–Ar), 166.44 (C-3), 172.35 (C-2), 176.51 (C-5), 187.68 (O=CPh); MS-ESI: 366 (M^+-H_2O-CO). Anal. Calcd for $C_{24}H_{20}N_4O_3$+H_2O: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.45; H, 5.05; N, 12.71.

*3-Benzoyl-1-(2-phenylethyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[3,2-e]pyrazin-2-one (**8b**).* Yield: (D): 226 mg (34%); mp: 242 °C.

4.6. General procedure for the reaction with 3,4-diaminopyridine

Method B. 3,4-Diaminopyridine (0.47 g, 4.3 mmol) was added to a solution of **1** (3.3 mmol) in AcOH (25 mL) with the addition of TsOH (0.34 g, 2 mmol). The solution was stirred at 70 °C for 50 h. The crude products (salt **9a**·**1a**, **9b**, salt **9d**·**1d**) precipitated from the reaction mixture were collected and crystallised from acetic acid.

*Salt of 3-benzoyl-1-benzyl-1,4-dihydro-2H-pyrido[3,4-b]pyrrolo [3,2-e]pyrazin-2-one **9a** and 4-[hydroxy(phenyl)methylene]-1-benzylpyrrolidine-2,3,5-trione **1a**.* Yellow needles, yield: (B): 487 mg (43%); mp: 275 °C; IR (KBr): ν=3436 (OH), 3153 (NH), 3059, 3032 (CH, Ar), 2968, 2931 (CH, CH_2), 1740, 1720, 1707 (C=O), 1644 (C=N), 1625, 1600 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.49 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 7.15–33 (m, 13H, H–Ar), 7.45 (m, 4H, H–Ar), 7.56 (m, 1H, H–Ar), 7.80 (d, ^3J=7.0, 2H, H-2″/6″), 8.24 (d, ^3J=6.5, 1H, H-5), 8.60 (d, ^3J=6.5, 1H, H-6), 9.25 (s, 1H, H-8); MS: *m*/*z* 381 (M^++1 for **7a**). Anal. Calcd for $C_{41}H_{29}N_5O_6$: C, 71.61; H, 4.25; N, 10.18. Found: C, 71.28; H, 4.20; N, 10.30.

*3-Benzoyl-1-(2-phenylethyl)-1,4-dihydro-2H-pyrido[3,4-b]pyrrolo[3,2-e]pyrazin-2-one **9b**.* Yellow needles, yield: (B): 493 mg (38%); mp: 298 °C; IR (KBr): ν=3455 (OH), 3057, 3015 (CH, Ar), 2903 (CH_2), 1671 (C=O), 1643 (C=N), 1618, 1592 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ Table 2; ^{13}C NMR (75.47 MHz, DMSO-d_6): δ Table 2; MS-ESI: *m*/*z* 395 (M^++1). Anal. Calcd for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found: C, 72.54; H, 4.44; N, 14.20.

*Salt of 3-benzoyl-(4-methylphenyl)-1,4-dihydro-2H-pyrido[3,4-b] pyrrolo[3,2-e]pyrazin-2-one **9d** and 4-[hydroxy(phenyl)methylene]-1-(4-methylphenyl)pyrrolidine-2,3,5-trione **1d**.* Yellow needles, yield: (B): 486 mg (43%); mp: 278–9 °C; IR (KBr): ν=3574 (OH), 3106 (NH), 3073 (CH, Ar), 2920, 2858 (CH_3), 1740, 1727, 1707 (C=O),

1668 (C=N), 1631, 1590 (C=C) cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.12–7.56 (m, 16H, H–Ar), 7.83 (d, ^3J=7.0, 2H, H-2″/6″), 8.23 (d, ^3J=6.5, 1H, H-5), 8.59 (d, ^3J=6.5, 1H, H-6), 9.18 (s, 1H, H-8); MS-ESI: 403 $(M+Na)^+$. Anal. Calcd for $C_{41}H_{29}N_5O_6$: C, 71.61; H, 4.25; N, 10.18. Found: C, 71.24; H, 4.06; N, 10.09.

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