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THE REGIOSELECTIVE SYNTHESIS OF 2*H*-PYRIDO[2,3-*b*]PYRROLO[2,3-*e*]PYRAZIN-2-ONE

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Abstract – The regioselective reaction of 1-aryl-4-(phenylhydroxymethylidene)-pyrrolidine-2,3,5-triones **1** with 2,3-diaminopyridine in boiling glacial AcOH in the presence of TsOH led to the formation of new 2*H*-pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazin-2-ones. The structure of this fused heterocyclic system was confirmed by IR, 1D and 2D NMR experiments.

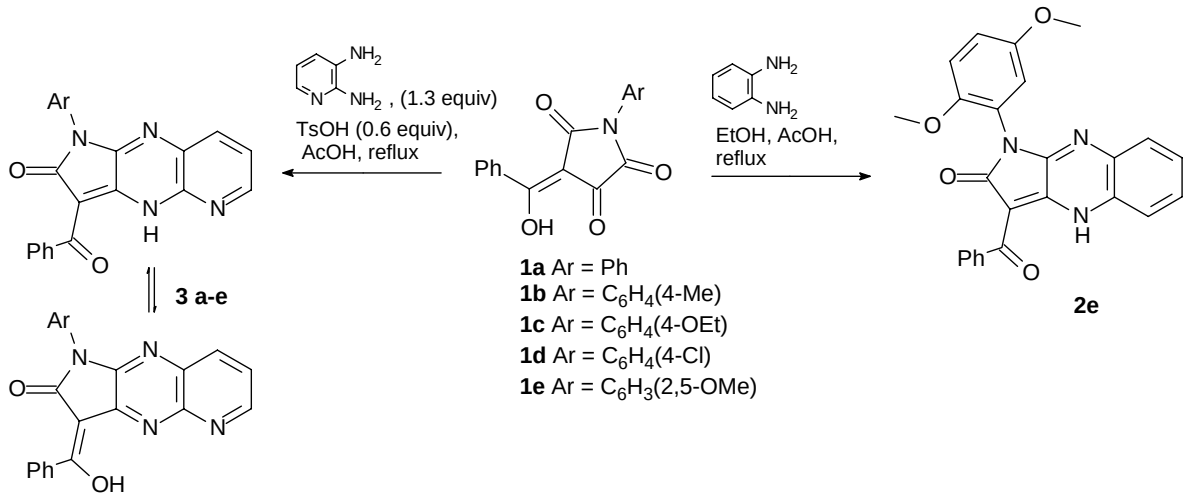
INTRODUCTION

Antitumor properties of the indol alkaloid ellipticine[1] initiated research of their bioactive structural analogues such as 6*H*-indolo[2,3-*b*]quinoxaline[2] possessing significant anti-HSVI activity. The syntheses[3-6] of these heterocyclic systems are usually based on the reaction of indole-2,3-dione derivatives with *o*-phenylenediamine or *o*-diaminopyridine. These two-step syntheses proceed *via* opening fused pyrrole-2,3-dione ring along amide bond to give intermediates, that undergo cyclization subsequently. With *o*-diaminopyridine, used as reactant, cyclization occurred to form two regioisomers. Introduction of the good leaving triflate[2] group at nonamide carbonyl carbon atom of indole-2,3-dione or bromine atom at C-2 position of 3-indolinone[6] led also to the formation of two regioisomers whereas, application of 3,4-dichloropyrrol-2,5-dione[7] as reactant gave only one product. Moreover, 4-aroylpyrrole-2,3,5-trione **1**, activated by thionyl chloride at nonamide carbonyl carbon atom, in the reaction with *o*-phenylenediamine and aliphatic diamines gave always bispyrrole[8] system. We have recently reported[9] that **1** underwent condensation with *o*-phenylenediamine in AcOH exclusively at C-2 and C-3 yielding pyrrolo[2,3-*b*]quinoxaline **2**.

RESULTS AND DISCUSSION

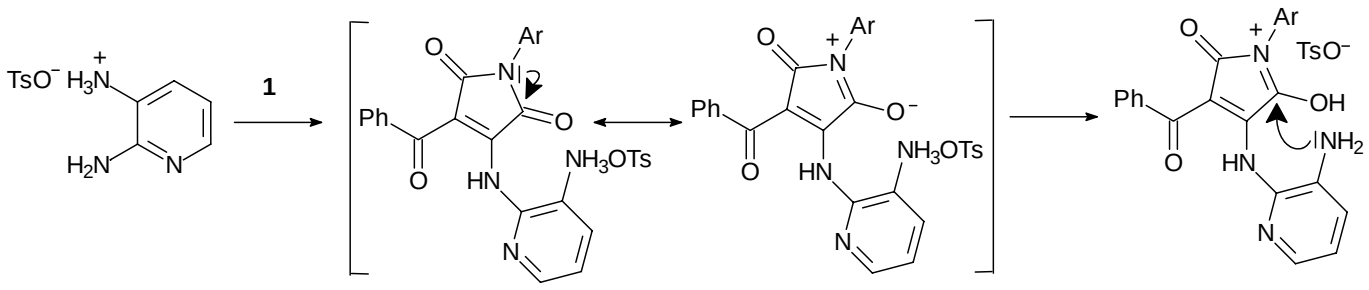
As a continuation of our study on the condensation of polycarbonyl pyrrole derivatives with aromatic *o*-diamines we report the regioselective synthesis of the new potentially bioactive

2*H*-pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazin-2-ones **3**. This fused heterocyclic system was formed in boiling glacial AcOH in the reaction of 1-aryl-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione **1** (pK = 2.63)[10] with 2,3-diaminopyridine in the presence of TsOH (pK = 0.7) in the ratio 1 : 1.3 : 0.6 (Scheme 1).



Scheme 1

Reaction carried out without TsOH at ambient temperature gave salt of OH acid **1** and 2,3-diaminopyridine, what was in accordance with our previous study.[10] Isolated salt refluxed in AcOH for several hours remains unreactive and does not give **3**, whereas refluxing the reaction mixture without TsOH for twenty hours showed that reaction was not completed. The ^{1}H NMR data of crude product revealed signals of one regioisomer **3**, open chain intermediate and salt. It has been shown[11] that boric acid was an effective condensing agent in reaction of alloxan and 2,3-diaminopyridine, which is less prone to undergo cyclocondensation than *o*-phenylenediamine. What is more, TsOH[12] used as catalyst in nucleophilic substitution of oxalamic acid ethyl ester by the same diamine led to the formation of only one regioisomer at C-2 amine group. So, application of TsOH as a condensing agent and strong OH acid **1** as reactant could also explain the regioselectivity by the deactivation of the more basic C-3 amine group of the starting 2,3-diaminopyridine *via* the formation of salt with TsOH or **1**. Thus, in the synthesis of **3** the non-bonded C-2 amine group could react, at first at more reactive nonamide carbon atom of **1** to form open chain intermediate (Scheme 2).



Scheme 2

Elemental analyses, IR, and MS for **3** confirmed that condensation took place at C-2 and C-3 carbonyl carbon atom. IR spectra taken in KBr, showed enaminone and imino-*exo*-enol tautomeric forms of **3** in solid by the presence of OH and NH stretching bands. ^{1}H NMR data gave the set of signals for only one enaminone tautomeric form of **3** in solution. Compounds **3a-d** are only slightly soluble in deuteriated solvents, so the structure was confirmed for **3e** by IR, 1D and 2D NMR experiment involving ^{1}H-^{1}H COSY, HSQC, HMBC and NOESY taken in DMSO-d_6 and $CDCl_3$ (Table 1, 2).

Table 1. NMR spectral data for **2e** and **3e** [300.18 MHz, DMSO-d_6, $CDCl_3$, δ (ppm)]

Atom	**2e** (DMSO-d_6)		**2e** ($CDCl_3$)		**3e** (DMSO-d_6)		**3e** ($CDCl_3$)	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
2	165.6	-	166.0	-	166.1	-	166.0	-
3	94.6	-	95.4	-	95.7	-	96.5	-
3a	139.1	-	140.8	-	142.2br	-	142.0	-
4	-	13.80br	-	12.35br	-	13.45br	-	9.56br
4a	127.5	-	126.3	-	140.6br	-	138.9	-
5	118.8	8.25	117.2	7.59	-	-	-	-
6	127.4	7.54	127.6	7.50	145.4br	8.56	147.4	8.55
7	126.0	7.47	126.3	7.47	121.0	7.53	121.9	7.44
8	127.3	7.75	128.7	7.87	136.7	8.25	136.4	8.16
8a	135.6	-	136.6	-	131.2	-	131.6	-
9a	148.5	-	148.6	-	148.9	-	149.2	-
10	189.0	-	191.6	-	188.8	-	191.4	-
1’	122.3	-	121.7	-	122.1	-	121.4	-
2’	150.1	-	150.2	-	150.0	-	150.1	-
3’	113.5	7.16	113.4	7.02	113.5	7.16	113.4	7.02
4’	115.0	7.07	115.9	7.00	115.1	7.07	116.1	7.02
5’	153.0	-	153.6	-	153.0	-	153.7	-
6’	116.7	7.04	116.0	6.98	116.6	7.02	116.0	6.95
2’-OCH_3	56.3	3.67	56.5	3.73	56.3	3.67	56.4	3.73
5’-OCH_3	55.7	3.75	55.8	3.79	55.7	3.75	55.8	3.80
1”	138.7	-	137.9	-	138.6	-	137.8	-
2”, 6”	128.8	7.87	129.3	8.10	129.0	7.84	129.3	8.09
3”, 5”	127.6	7.47	127.7	7.44	127.7	7.48	127.7	7.46
4”	131.5	7.56	132.1	7.51	131.8	7.57	132.3	7.54

Table 2. NMR spectral data for **2e** and **3e** [300.18 MHz, DMSO-d_6, $CDCl_3$, δ (ppm)]

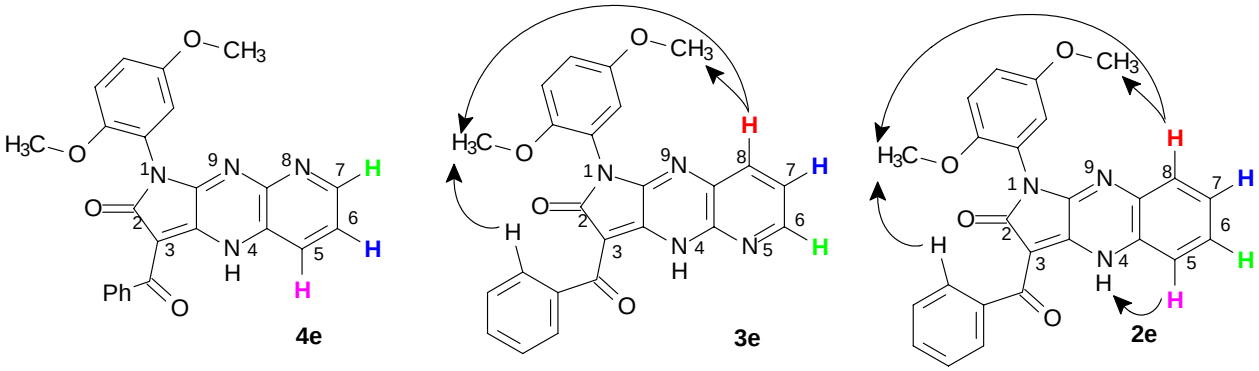
	3e /DMSO-d_6			**2e** /$CDCl_3$		
Atom	HSQC	HMBC	COSY	HSQC	HMBC	COSY
C-4a	-	H-6, H-7, H-8	-	-	H-5, H-6	-
C-5	-	-	-	H-5	H-7, H-8	H-6, H-7
C-6	H-6	H-7, H-8	H-7	H-6	H-5, H-7, H-8	H-8, H-5, H-7
C-7	H-7	H-6	H-6, H-8	H-7	H-8	H-8, H-5, H-6
C-8	H-8	H-6	H-7	H-8	H-5, H-6	H-7, H-6
C-8a	-	H-6, H-7, H-8	-	-	H-5, H-7, H-8	-
C-9a	-	H-7	-	-	-	-
C-10	-	H-2”/6”; H-3”/5”	-	-	H-2”/6”; H-3”/5”	-
C-1’	-	H-3’, H-4’, H-6’	-	-	H-3’, H-4’, H-6’	-
C-2’	-	H-3’, H-4’, H-6’; C2’-OC**H**$_3$	-	-	H-3’, C2’-OC**H**$_3$	-
C2’-O**C**H_3	C2’-OC**H**$_3$	-	-	C2’-OC**H**$_3$	-	-
C-3’	H-3’	C2’-OC**H**$_3$	H-4’	H-3’	H-6’; C2’-OC**H**$_3$	H-4'
C-4’	H-4’	H-3’, H-6’	H-3’	H-4’	H-6’, H-3’	H-6', H-3'
C-5’	-	H-3’, H-4’, H-6’, C5’-OC**H**$_3$	-	-	H-4’, H-6’; C5’-OC**H**$_3$	-
C5’-O**C**H_3	C5’-OC**H**$_3$	-	-	C5’-OC**H**$_3$	-	-
C-6’	H-6’	H-3’, H-4’	-	H-6’	H-3’, H-4’	H-4'
C-1”	-	H-3”/5”; H-4”	-	-	H-3”/5”	-
C-2”/6”	H-2”/6”	H-3”/5”, H-4”	H-3”/5”	H-2”/6”	H-2”/6”, H-3”/5”, H-4”	H-3”/5”
C-3”/5”	H-3”/5”	H-2”/6”	H-2”/6”, H-4”	H-3”/5”	H-2”/6”, H-3”/5”, H-4”	H-2”/6”, H-4”
C-4”	H-4”	H-2”/6”	H-3”/5”	H-4”	H-2”/6”, H-3”/5”	H-3”/5”, H-2”/6”

The vicinal coupling constants for pyridopyrazine system **3**: $^{3}J_{6,7}$ = 4.8 Hz and $^{3}J_{7,8}$ = 8.4, Hz have typical values for pyridine so they are diagnostic for protons H-6 and H-8. The structure of this compound **3e** was assigned by NOESY experiment featuring a diagnostic NOE between OCH_3 at C-2' and C-5' position and the aromatic proton H-8 which should be absent for regioisomer 2*H*-pyrido[2,3-*b*]pyrrolo[3,2-*e*]pyrazin-2-one **4e** (Scheme 3).

Additionally, the NOESY spectrum of **2e** showed correlation between methoxyl groups at C-2' and C-5'/H-8 and N-H/H-5. The latter in principle is absent for **3e**.

^{1}H NMR data of **2** revealed the solvent effect of DMSO-d_6 and $CDCl_3$ on H-5, H-8 and H-2"/6" chemical shifts. The proton H-5 was deshielded in DMSO-d_6 (for: **2a**,[9] 0.37 ppm; **2c**,[9] 0.34 ppm; **2e**, 0.66 ppm), whereas, signals of H-8 (for: **2a** and **2c**[9] signals are in aromatic region; **2e**, 0.12 ppm), and H-2"/6" (for: **2a**,[9] 0.22 ppm; **2c**,[9] 0.21 ppm; **2e**, 0.23 ppm) were upfield shifted. The same effect was only observed for H-2"/6" of **3** (for: **3a**, 0.20 ppm; **3c**, 0.23 ppm; **3e**, 0.25 ppm). It means that H-5 proton of **2** was deshielded by DMSO-HN hydrogen bonding and probably the presence or absence of this effect may allow to distinguish, in easy way, between regioisomers **3** and **4**.

In conclusion, we have shown that synthesis of 2*H*-pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazin-2-ones **3** proceeds smoothly in the presence of TsOH as a condensing agent and the efficient regioselective catalyst.



Scheme 3

EXPERIMENTAL

Melting points were determined on a *Boetius* PHMK 05 melting point apparatus. IR spectra: Bruker IFS 48 in KBr pellets or Nujol. ^{1}H and ^{13}C NMR, COSY, NOESY, HSQC and HMBC spectra were recorded with Bruker Avance II 300 spectrometer at 300 K. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{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). ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm) or DMSO-d_6 (δ 39.5 ppm). Coupling constants (J) were reported in Hertz (Hz). Mass spectra: Finningan Mat 95 (EI, 70 eV). Microanalyses were performed with an Euro EA 3000 Elemental Analyzer;

their results agreed satisfactorily with the calculated values. ^{13}C NMR spectra were not taken for **3a-3d** because of theirs extremely low solubility.

General procedure for acylation with oxalyl chloride

To a stirred solution of 3-oxo-3-phenyl-*N*-2,5-dimethoxyphenylpropaneamide (11.96 g, 40 mmol) in 150 mL of dry toluene, oxalyl chloride (4 mL, 46 mmol) was added dropwise at rt. After the reaction was completed the mixture was heated up to the boiling point to remove the remainder of hydrogen chloride. From the cooled mixture the precipitate was filtered off and recrystallized from acetic acid.

1-(2,5-Dimethoxyphenyl)-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione (**1e**): mp 206-207 ºC: Yield 9.63 g (68%): $\tilde{\nu}_{max}$/cm^{-1} (KBr): 3429 (OH); 3062 (C-H, Ar); 2984 (C-H, OCH_3); 1784, 1737, 1665 (C=O); 1589 (C=C, Ar); ^{1}H NMR (300.18 MHz, DMSO-d_6); δ 3.69 (s, 3H, 2'-OCH_3), 3.72 (s, 3H, 5'-OCH_3), 5.58 (br, 1H, OH), 6.83 (dd, ^4J = 3.1, ^5J = -0.1, 1H, H-6'), 6.97 (dd, ^3J = 9.1, ^4J = 3.1, 1H, H-4'), 7.06 (dd, ^3J = 9.1, ^5J = -0.1, 1H, H-3'), 7.40 (dddd, 2H, ^3J = 7.6, ^3J = 7.4, ^4J = 1.3, ^5J = 0.7, H-3"/5"), 7.49 (dd, 1H, ^3J = 7.4, ^4J = 1.3, H-4"), 7.63 (dddd, 2H, ^3J = 7.6, ^4J = 1.7, ^4J = 1.3, ^5J = 0.7, H-2"/6"); ^{13}C NMR (75.48 MHz, DMSO-d_6); δ 55.6 (5'-OCH_3), 56.2 (2'-OCH_3), 100.2 (C-4), 113.1 (C-3'), 114.5 (C-4'), 116.1 (C-6'), 121.9 (C-1'), 127.5 (C-3"/5"), 128.8 (C-2"/6"), 131.0 (C-4"), 139.2 (C-1"), 149.7 (C-2'), 152.9 (C-5'), 164.2 (C-2 or C-5), 169.4 (C-5 or C-2), 172.2 (C-3), 185.7 (C-6). ^{1}H NMR (300.18 MHz, $CDCl_3$); δ 3.79 (s, 6H, OCH_3), 6.80 (d, 1H), 6.99 (d, 1H), 6.99 (s, 1H), 7.57 (m, J = 7.5, 2H), 7.70 (t, 1H), 8.27 (d, J = 7.5, 2H); ^{13}C NMR (75.48 MHz, $CDCl_3$); δ 55.7 (OCH_3), 56.2 (OCH_3), 98.0 (C-4), 112.9, 113.1, 114.5, 116.3, 118.8, 128.3, 129.8, 130.2, 134.8, 148.8, 153.4, 160.1 (C-2), 175.5 (C-3), 180.7 (C-6); MS-EI: *m/z* (%) = 353 (73, M^+), 325 (38, M^+–CO), 179 (100, $(CH_3O)_2C_6H_3NCO$); 105 (48, PhCO); *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.55; H, 4.45; N, 3.92.

Procedure for the reaction with *o*-phenylenediamine

To a solution of **1e** (1 g, 2.8 mmol), in 50 mL EtOH with addition of 2 mL of glacial acetic acid, *o*-phenylenediamine (0.37 g, 3.4 mmol) was added. The solution was refluxed for 3 h and left overnight. The precipitate was filtered off and crystallized from chlorobenzene.

3-Benzoyl-1-(2,5-dimethoxyphenyl)-1,4-dihydropyrrolo[2,3-b]quinoxalin-2(4H)-one (**2e**): mp 267-268 ºC, Yield 1.11g (92%); $\tilde{\nu}_{max}$/cm^{-1} (KBr): 3491 (OH), 3189 (NH), 3064 (C-H, Ar), 2996, 2938, 2836 (C-H, CH_3), 1702 (C=O), 1642 (C=N), 1610 (C=C, Ar); ^{1}H-NMR (300.18 MHz, DMSO-d_6): δ 3.67 (s,

3H, C2'-OCH_3), 3.75 (s, 3H, C5'-OCH_3), 7.04 (dd, ^4J = 2.8, ^5J = -0.3, 1H, H-6'), 7.07 (dd, ^3J = 9.2, ^4J = 2.8, 1H, H-4'), 7.16 (dd, ^3J = 9.2, ^5J = -0.3, 1H, H-3'), 7.47 (dddd, ^3J = 7.8, ^3J = 7.4, ^4J = 1.3, ^5J = 0.6, 2H, H-3"/5"), 7.47 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.4, 1H, H-7), 7.54 (ddd, ^3J = 8.5, ^3J = 7.1, ^4J = 1.6, 1H, H-6), 7.56 (dd, ^3J = 7.4, ^4J = 1.2, 1H, H-4"), 7.75 (ddd, ^3J = 8.2, ^4J = 1.6, ^5J = 0.0, 1H, H-8), 7.87 (dddd, ^3J = 7.8, ^4J = 1.5, ^4J = 1.2, ^5J = 0.6, 2H, H-2"/6"), 8.25 (ddd, ^3J = 8.5, ^4J = 1.4, ^5J = 0.0, 1H, H-5), 13.80 (br, 1H, H-4); ^{13}C-NMR (75.48 MHz, DMSO-d_6): δ 55.7 (C5'-OCH_3), 56.3 (C2'-OCH_3), 94.6 (C-3), 113.5 (C-3'), 115.0 (C-4'), 116.7 (C-6'), 118.8 (C-5), 122.3 (C-1'), 126.0 (C-7), 127.3 (C-8), 127.4 (C-6), 127.5 (C-4a), 127.6 (C-3"/5"), 128.8 (C-2"/6"), 132.5 (C-4"), 135.6 (C-8a), 138.7 (C-1"), 139.1 (C-3a), 148.5 (C-9a), 150.1 (C-2'), 153.0 (C-5'), 165.6 (C-2), 189.0 (C-10). ^{1}H-NMR (300.18 MHz, $CDCl_3$): δ 3.73 (s, 3H, C2'-OCH_3), 3.79 (s, 3H, C5'-OCH_3), 6.98 (dd, ^4J = 3.0, ^5J = 0.7, 1H, H-6'), 7.00 (dd, ^3J = 9.1, ^4J = 3.0, 1H, H-4'), 7.02 (dd, ^3J = 9.1, ^5J = 0.7, 1H, H-3'), 7.44 (dddd, ^3J = 7.7, ^3J = 7.5, ^4J = 1.3, ^5J = 0.6, 2H, H-3"/5"), 7.47 (ddd, ^3J = 8.4, ^3J = 7.6, ^4J = 1.1, 1H, H-7), 7.50 (ddd, ^3J = 8.3, ^3J = 7.6, ^4J = 1.2, 1H, H-6), 7.51 (dd, ^3J = 7.5, ^4J = 1.2, 1H, H-4"), 7.59 (ddd, ^3J = 8.3, ^4J = 1.1, ^5J = 0.4, 1H, H-5), 7.87 (ddd, ^3J = 8.4, ^4J = 1.2, ^5J = 0.4, 1H, H-8), 8.10 (dddd, ^3J = 7.7, ^4J = 1.6, ^4J = 1.2, ^5J = 0.6, 2H, H-2"/6"), 12.35 (br, 1H, H-4); ^{13}C-NMR (75.48 MHz, $CDCl_3$): δ 55.8 (C5'-OCH_3), 56.5 (C2'-OCH_3), 95.4 (C-3), 113.4 (C-3'), 115.9 (C-4'), 116.0 (C-6'), 117.2 (C-5), 121.7 (C-1'), 126.3 (C-7), 126.3 (C-4a), 127.6 (C-6), 127.7 (C-3"/5"), 128.7 (C-8), 129.3 (C-2"/6"), 132.1 (C-4"), 136.6 (C-8a), 137.9 (C-1"), 140.8 (C-3a), 148.6 (C-9a), 150.2 (C-2'), 153.6 (C-5'), 166.0 (C-2), 191.6 (C-10); MS-EI: m/z (%) = 425 (100, M^+), 394 (28, M^+–OCH_3), 105 (86, PhCO), 77 (41, Ph); *Anal*. Calcd for $C_{25}H_{19}N_3O_4$: C, 70.57; H, 4.50; N, 9.87. Found: C, 70.49; H, 4.68; N, 9.78.

General procedure for preparation of 2*H*-pyrido[2,3-*b*]pyrrolo[2,3-*e*]pyrazin-2-one

To a solution of **1** (10 mmol), in 100 mL of AcOH with addition of TsOH (1.0 g, 6 mmol), 2,3-diaminopyridine (1.5 g, 13 mmol) was added. The solution was refluxed for 10 h, allowed to cool and then poured into water. The crude product was collected and purified by column chromatography (silica gel/$CHCl_3$/*n*-heptane (1:1) for **3a-3d**; AcOEt/*n*-heptane (3:1) for **3e**).

3-Benzoyl-1-phenyl-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**3a**): mp 275 ºC; Yield 1.95 g (53%): $\tilde{\nu}_{max}$/cm^{-1} (KBr): 3409 (OH), 3272 (NH), 3055 (C-H, Ar), 1713 (C=O), 1647 (C=N), 1617 (C=C, Ar); ^{1}H NMR (300.18 MHz, DMSO-d_6): δ 7.45 – 7.57 (m, 9H, Ar-H), 7.86 (d, ^3J = 6.9, 2H, H-2"/6"), 8.24 (d, $^3J_{8,7}$ = 8.2, 1H, H-8), 8.58 (d, $^3J_{6,7}$ = 4.9, 1H, H-6); ^{1}H NMR (300.18 MHz, $CDCl_3$): δ 7.40 – 7.63 (m, 9H, Ar-H), 8.06 (d, ^3J = 6.9, 2H, H-2"/6"), 8.18 (d, $^3J_{8,7}$ = 8.2, 1H, H-8), 8.57 (d, $^3J_{6,7}$ =

4.9, 1H, H-6), 12.40 (s, 1H, NH); MS-EI: *m/z* (%) = 366 (100, M^+), 365 (99, M^+–H), 105 (32, PhCO); *Anal*. Calcd for $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found: C, 71.47; H, 3.80; N, 15.17.

3-Benzoyl-1-(4-methylphenyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**3b**): mp 265 ºC; Yield 2.65 g (69%): $\tilde{\nu}_{max}/cm^{-1}$ (KBr): 3410 (OH), 3276 (NH), 3057, 3033 (C-H, Ar), 2989 (C-H, CH_3), 1712 (C=O), 1647 (C=N), 1616 (C=C, Ar); ^{1}H NMR (300.18 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 7.31 – 7.58 (m, 8H, Ar-H), 7.84 (d, ^3J = 6.9, 2H, H-2"/6"), 8.22 (d, $^3J_{8,7}$ = 8.2, 1H, H-8), 8.54 (d, $^3J_{6,7}$ = 4.7, 1H, H-6); MS-EI: *m/z* (%) = 380 (67, M^+), 379 (65, M^+–H), 105 (100, PhCO), 77 (79, Ph); *Anal*. Calcd for $C_{23}H_{16}N_4O_2$: C, 72.62; H, 4.24; N, 14.73. Found: C, 72.57; H, 4.28; N, 14.72.

3-Benzoyl-1-(4-ethoxyphenyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**3c**): mp 274 ºC; Yield 2.75 g (67%): $\tilde{\nu}_{max}/cm^{-1}$ (KBr): 3411 (OH), 3272 (NH), 3076 (C-H, Ar), 1715 (C=O), 1644 (C=N), 1611 (C=C, Ar); ^{1}H NMR (300.18 MHz, DMSO-d_6): δ 1.47 (t, 3H, CH_3), 4.08 (q, 2H, OCH_2), 7.06 (d, 2H, H-2'), 7.38 – 7.58 (m, 6H, Ar-H), 7.83 (d, ^3J = 6.9, 2H, H-2"/6"), 8.21 (d, $^3J_{8,7}$ = 8.0, 1H, H-8), 8.45 (d, $^3J_{6,7}$ = 5.0, 1H, H-6); ^{1}H NMR (300.18 MHz, $CDCl_3$) δ 1.42 (t, 3H, CH_3), 4.08 (q, 2H, OCH_2), 7.03 (d, 2H, H-2'), 7.25 – 7.58 (m, 6H, Ar-H), 8.06 (d, 2H, H-2"/6"), 8.26 (d, 1H, H-8), 8.57 (d, 1H, H-6); MS-EI: *m/z* (%) = 410 (100, M^+), 409 (31, M^+–H), 105 (55, PhCO); *Anal*. Calcd for $C_{24}H_{18}N_4O_3$: C, 70.23; H, 4.42; N, 13.65. Found: C, 69.85; H, 4.35; N, 13.49.

3-Benzoyl-1-(4-chlorophenyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**3d**): mp 278 ºC; Yield 2.15 g (53%): $\tilde{\nu}_{max}/cm^{-1}$ (KBr): 3419 (OH), 3235 (NH), 3035, 3030 (C-H, Ar), 1719 (C=O), 1649 (C=N), 1610 (C=C, Ar); ^{1}H NMR (300.18 MHz, DMSO-d_6): δ 7.44 – 7.61 (m, 8H, Ar-H), 7.84 (d, ^3J = 6.8, 2H, H-2"/6"), 8.23 (d, $^3J_{8,7}$ = 7.9, 1H, H-8), 8.58 (d, $^3J_{6,7}$ = 4.8, 1H, H-6); MS-EI, *m/z* (%) = 402 (35, M^++2), 400 (100, M^+), 399 (45, M^+–H), 105 (39, PhCO), 77 (22, Ph); *Anal*. Calcd for $C_{22}H_{13}ClN_4O_2$: C, 65.92; H, 3.27; N, 13.98. Found: C, 65.90; H, 3.27; N, 13.98.

3-Benzoyl-1-(2,5-dimethoxyphenyl)-1,4-dihydro-2H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-2-one (**3e**): mp 205 ºC; Yield 2.52 g (60%): $\tilde{\nu}_{max}/cm^{-1}$ (KBr): 3435 (OH), 3191 (NH), 3072, 3002 (C-H, Ar), 2962, 2937 (C-H, CH_3), 1723 (C=O), 1657 (C=N), 1618 (C=C, Ar); ^{1}H-NMR (300.18 MHz, DMSO-d_6): δ 3.67 (s, 3H, C2'-OCH_3), 3.75 (s, 3H, C5'-OCH_3), 7.02 (dd, ^4J = 3.1, ^5J = -0.2, 1H, H-6'), 7.07 (dd, ^3J = 9.2, ^4J = 3.1, 1H, H-4'), 7.16 (dd, ^3J = 9.2, ^5J = -0.2, 1H, H-3'), 7.48 (dddd, ^3J = 7.7, ^3J = 7.5, ^4J = 1.11, ^5J = 0.7, 2H, H-3"/5"), 7.53 (dd, ^3J = 8.1, ^3J = 4.8, 1H, H-7), 7.57 (dd, ^3J = 7.5, ^4J = 1.3, 1H, H-4"), 7.84 (dddd, ^3J

= 7.7, ^4J = 1.7, ^4J = 1.3, ^5J = 0.7, 2H, H-2”/6”), 8.25 (dd, ^3J = 8.1, ^4J = 1.6, 1H, H-8), 8.56 (dd, ^3J = 4.8, ^4J = 1.6, 1H, H-6), 13.45 (br, 1H, H-4); ^{13}C-NMR (75.48 MHz, DMSO-d_6): δ 55.7 (C5’-OCH_3), 56.3 (C2’-OCH_3), 95.7 (C-3), 113.5 (C-3’), 115.1 (C-4’), 116.6 (C-6’), 121.0 (C-7), 122.1 (C-1’), 127.7 (C-3”/5”), 129.0 (C-2”/6”), 131.2 (C-8a), 131.8 (C-4”), 136.7 (C-8), 138.6 (C-1”), 140.6 (br, C-4a), 142.2 (br, C-3a), 145.4 (br, C-6), 148.9 (C-9a), 150.0 (C-2’), 153.0 (C-5’), 166.1 (C-2), 188.8 (C-10). ^{1}H-NMR (300.18 MHz, $CDCl_3$): δ 3.73 (s, 3H, C2’-OCH_3), 3.80 (s, 3H, C5’-OCH_3), 6.95 (t, J = 1.7, 1H, H-6’), 7.02 (d, J = 1.7, 2H, H-3’, H-4’), 7.44 (dd, ^3J = 8.5, ^3J = 5.1, 1H, H-7), 7.46 (dd, ^3J = 7.8, ^3J = 7.4, 2H, H-3”/5”), 7.54 (d, ^3J = 7.4, 1H, H-4”), 8.09 (d, ^3J = 7.8, 2H, H-2”/6”), 8.16 (d, ^3J = 8.5, 1H, H-8), 8.55 (d, ^3J = 5.1, 1H, H-6), 9.56 (br, 1H, H-4); ^{13}C-NMR (75.48 MHz, $CDCl_3$): δ 55.8 (C5’-OCH_3), 56.4 (C2’-OCH_3), 96.5 (C-3), 113.4 (C-3’), 116.0 (C-6’), 116.1 (C-4’), 121.4 (C-1’), 121.9 (C-7), 127.7 (C-3”/5”), 129.3 (C-2”/6”), 131.6 (C-8a), 132.3 (C-4”), 136.4 (C-8), 138.9 (C-4a), 137.8 (C-1”), 142.0 (C-3a), 147.4 (C-6), 149.2 (C-9a), 150.1 (C-2’), 153.7 (C-5’), 166.0 (C-2), 191.4 (C-10); MS-EI, *m/z* (%) = 426 (100, M^+), 395 (32, M^+–OCH_3), 105 (62, PhCO), 77 (34, Ph); *Anal*. Calcd for $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found: C, 67.88; H, 4.23; N, 13.27.

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