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3-(2-Nitrobenzyl)quinoxalin-2-ones, and pyrido- and 1,2,5-oxadiazolo-fused 2-(2-nitrobenzyl)pyrazin-3-ones in the synthesis of bi-, bis- and condensed heterocyclic systems

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Dedicated to Prof. Julia H. Budnikova in recognition of her outstanding contributions to the fields of electrochemistry and organic synthesis

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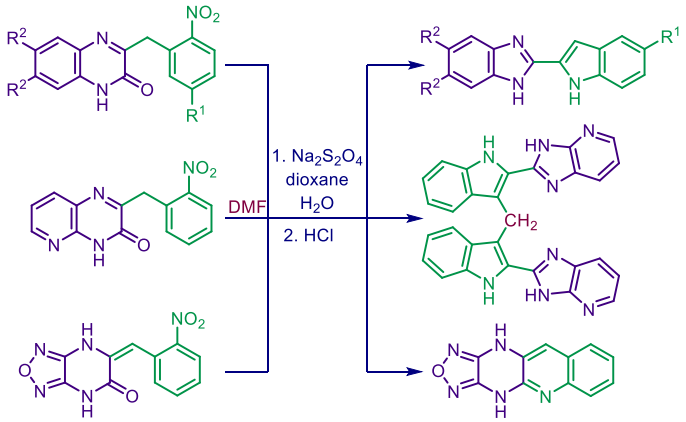
Abstract

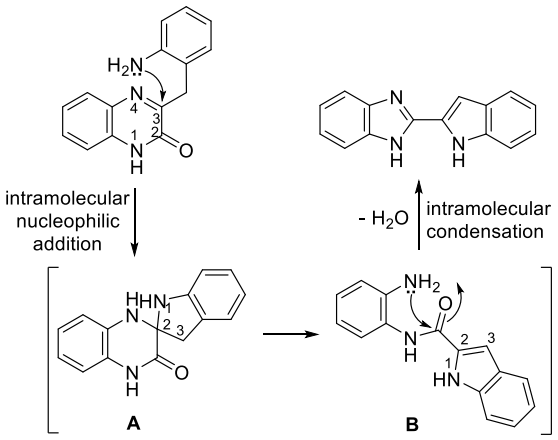
It is shown that the products of reduction of the nitro group in 3-(2-nitrobenzyl)quinoxalin-2-ones, and pyrido- and 1,2,5-oxadiazolo-fused 3-(2-nitrobenzyl)pyrazinones with sodium dithionite ($Na_2S_2O_4$) undergo in the first two cases in an acidic medium Mamedov rearrangement, and in the third case – intramolecular condensation with the formation of rare bi-, bis- and condensed heterocyclic systems, respectively, difficult to obtain by other methods.



Keywords: 3-(2-Nitrobenzyl)quinoxalin-2-ones, 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3-one, Mamedov rearrangement, 2-(indol-2-yl)benzimidazoles, bis(2-(imidazo[4,5-*b*]pyridin-2-yl)-indol-3-yl)methane, 4,11-dihydro[1,2,5]oxadiazolo[3',4':5,6]pyrazino[2,3-*b*]quinoline

Introduction

Recently, quinoxalinone derivatives have been of great importance in the synthesis of benzimidazole systems,[1-3] while Mamedov rearrangement[4] is a convenient way to obtain various biheterocycles with a benzimidazole fragment in the composition. Mamedov rearrangement assumes the presence of a functional group in the third position of the quinoxalinone system, in particular, in the synthesis of 2-(indole-2-yl)benzimidazoles, such a group is a benzyl fragment with an amino group in the *ortho* position.[5] Formation of a 2-(indole-2-yl)benzimidazole system from 3-(2-aminobenzyl)quinoxalin-2-ones is shown in Scheme 1. In this process, at the initial stage, the intramolecular nucleophilic addition of the amino group in the *ortho*-position of the benzyl fragment at the C3-N4 bond of the quinoxalinone fragment occurs and the indolylquinoxaline spirosystem **A** is formed, which is transformed into **B** as a result of the breaking of the C3-N4 bond of the quinoxaline part of the molecule, accompanied by the displacement of hydrogen atom from the third positions of the indole fragment to N4 of the quinoxalinone fragment and the formation of a double bond.

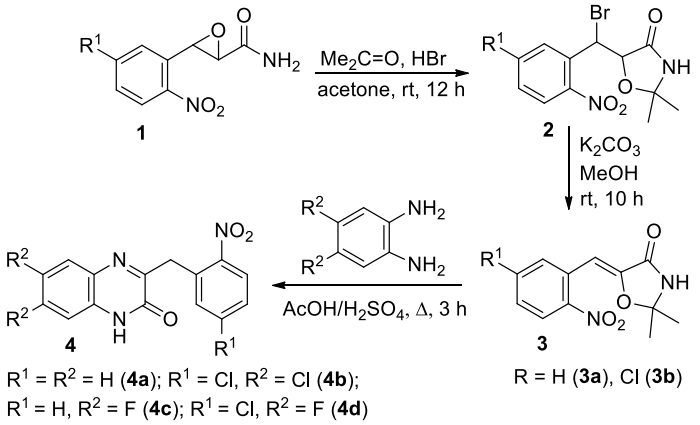


Scheme 1. Mamedov rearrangement in the synthesis of 2-(indol-2-yl)benzimidazole from 3-(2-aminobenzyl)quinoxalin-2-one.

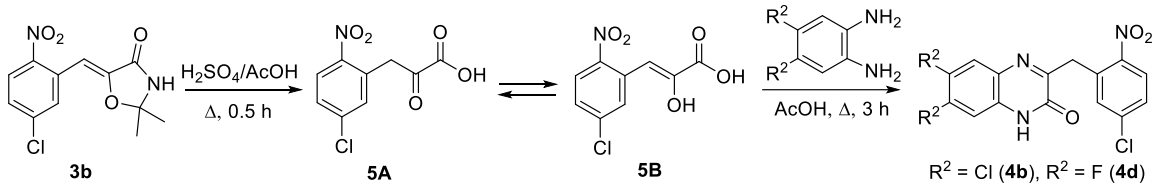
The synthesis of 2-(indol-2-yl)benzimidazoles with use of this method has long been limited by the unavailability of 3-(2-aminobenzyl)quinoxalin-2-ones or the 3-(2-nitrobenzyl)quinoxalin-2-ones preceding them, which are most often obtained as a result of the reaction of 1,2-diaminobenzenes with 2-nitrophenylpyruvic acid, synthesized in very moderate yields by the condensation of 2-nitrotoluenes with oxalates in the presence of a base.[5-7] Our research group has recently proposed a mild method for the synthesis of 2-nitrophenylpyruvic acid and its ester from 3-(2-nitrophenyl)oxirane-2,3-carboxamide *via* 5-(2-nitrobenzyliden)-2,2-dimethyl-1,3-oxazolidin-4-one,[8,9] and quite recently by the reaction of 5-(2-nitrobenzyliden)-2,2-dimethyl-1,3-oxazolidin-4-one with 1,2-diaminebenzenes were obtained 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones.[10] In this work we use the latest method for synthesizing 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones in order to obtain new representatives of 2-(indole-2-yl)benzimidazoles on their base, and also synthesize 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3(4*H*)-one and 2-(2-nitrobenzylidene)-1,2-dihydro-1,2,5-oxadiazolo[3,4-*b*]pyrazin-3(4*H*)-one in a similar way for further study of them under the processes of reduction and in the Mamedov rearrangement.[3,4]

Results and Discussion

The 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones used in the synthesis of 2-(indol-2-yl)benzimidazoles were prepared according to the method described in our previous work[10] (Schema 2). According to this method, 3-(2-nitroaryl)oxirane-2,3-carboxamides (**1**) by the action of hydrobromic acid and acetone were converted into 5-(*α*-bromo-2-nitrobenzyl)-2,2-dimethyl-1,3-oxazolidin-4-ones (**2**), which, in turn, under the action of K_2CO_3 in MeOH were converted into 5-(2-nitroarylidene)-2,2-dimethyl-1,3-oxazolidin-4-ones (**3**) and the reaction of the latter with 1,2-diaminobenzenes in boiling acetic acid with a small amount of H_2SO_4 led to the desired products **4**. In the last step of this synthesis, oxazolidinones **3** are first hydrolyzed to 3-arylpyruvic acids, which are further reacted with 1,2-diaminobenzenes. We have previously studied the process of hydrolysis of **3a** under the action of concd HCl.[8] In this work, we subjected oxazolidinone **3b** to hydrolysis in boiling mixture AcOH with H_2SO_4 (50:1 by volume) and isolated 3-(5-chloro-2-nitrophenyl)pyruvic acid (**5**), which was further successfully used in the syntheses of quinoxalinones **4b** and **4d** (Schema 3) under Hinsberg-Körner reaction condition.[1] The acid **5**, under the conditions of registration of NMR spectra in DMSO-d_6, existed in a mixture of two tautomeric forms **A** and **B** (Scheme 3) with a slight predominance of the latter (1:1.2).



Scheme 2. Synthesis of 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones (**4**) starting from 3-(2-nitroaryl)oxirane-2-carboxamides (**1**).

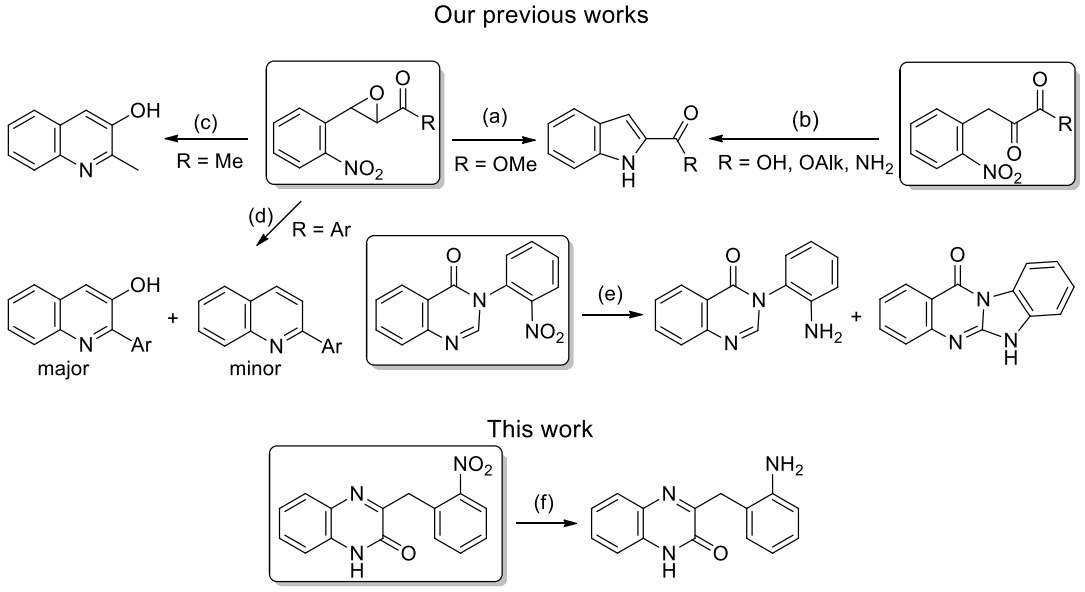


Scheme 3. Synthesis of 3-(5-chloro-2-nitrobenzyl)quinoxalin-2(1*H*)-ones (**4b** and **4d**) from 5-(5-chloro-2-nitrobenzylidene)-2,2-dimethyl-1,3-oxazolidin-4-one (**3b**).

We have previously shown that derivatives of glycidic and pyruvic acids, oxiranyl ethanone, oxiranylaryl ketone, and quinazoline, containing a 2-nitrophenyl group, under the action of sodium dithionite in a boiling water-dioxane solution, along with the reduction of the nitro group to the amino group, undergo further transformations leading to the formation of various heterocyclic systems depending on the nature of the functional groups in the initial compound (Scheme 4). Methyl 3-(2-nitrophenyl)oxirane-2-carboxylate, for

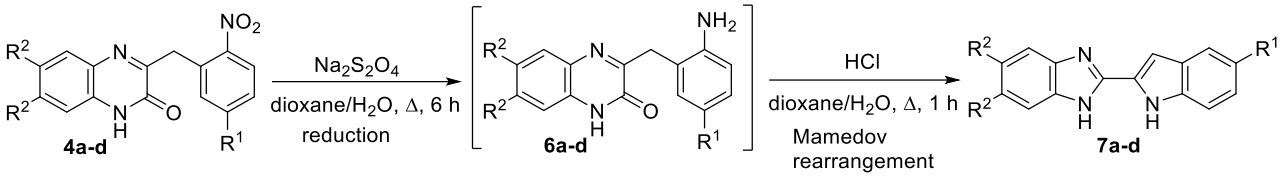
example, was converted to methyl indole-2-carboxylate[9] (Scheme 4a), and 3-(2-nitrophenyl)pyruvic acid and its esters and amide[9] experienced similar transformations (Scheme 4b). Under the same reaction conditions, 1-(3-(2-nitrophenyl)oxiran-2-yl)ethanone was converted to 3-hydroxy-2-methylquinoline[11] (Scheme 4c), and (3-(2-nitrophenyl)oxiran-2- yl)(aryl)methanones formed, along with 3-hydroxy-2-arylquinolines and unsubstituted in the third position 2-arylquinolines in small amounts[11,12] (Scheme 4d). The treatment of 3-(2-nitrophenyl)quinazolin-4-one with $Na_2S_2O_4$ resulted in the isolation of benzo[4,5]imidazo[2,1-b]quinazolin-12-one[13] along with the reduction product (Scheme 4e). In this work, it was shown that the reaction of 3-(2-nitrobenzyl)quinoxalinone **4a** with $Na_2S_2O_4$ in a boiling aqueous dioxane medium stops at the stage of formation of 2-aminobenzylquinoxalinone **6a** (Scheme 4f) – the desired starting compound for the synthesis of 2-(indol-2-yl)benzimidazole **7a** (Scheme 1). Boiling **6a** in dioxane in the presence of hydrochloric acid resulted in **7a** as a result of Mamedov rearrangement. Indolylbenzimidazole **7a** was also prepared directly from 3-(2-nitrobenzyl)quinoxalinone **4a** in a *one-pot* process involving a combination of reduction of nitro group and Mamedov rearrangement. This *one-pot* process has been extended to the synthesis of previously undescribed indolylbenzoimidazoles **7b-d** (Table 1).

In this work, we synthesized for the first time the aza-analogue of 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones (**4**) – 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3(4*H*)-one (**8**), as well as 2-(2-nitrobenzyliden)-1,2-dihydro-1,2,5-oxadiazolo[3,4-b]pyrazin-3(4*H*)-one (**9**), *via* the reaction of 5-(2-nitrobenzyliden)-2,2-dimethyl-1,3-oxazolidin-4-one (**3a**) with 2,3-diaminopyridine and 3,4-diamino-1,2,5-oxadiazole, respectively (Scheme 5). Compound **9**, under the NMR spectra removal conditions in DMSO-d_6, existed in the tautomeric form **B**, moreover, as one regioisomer, namely Z, which was established by 1D-NOESY NMR experiment (see Supporting Information).



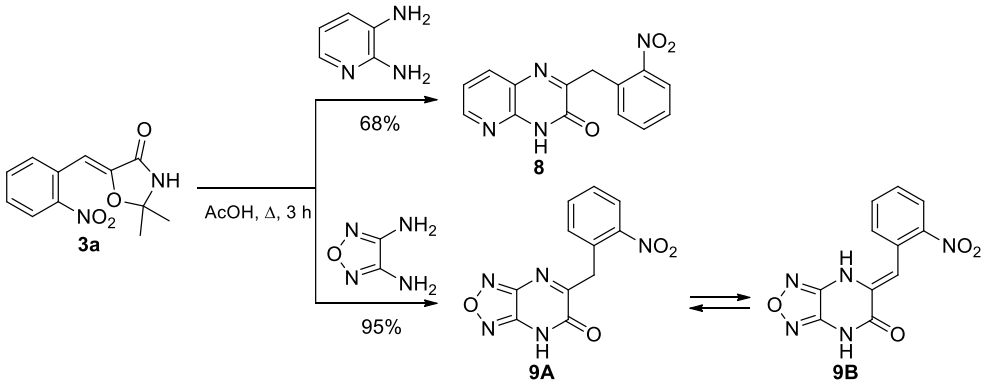
Scheme 4. Transformations of glycidic and pyruvic acids, oxiranyl ethanone, oxiranylaryl ketone, and quinazoline derivatives containing a 2-nitrophenyl group, when exposed to sodium dithionite.

Table 1. Synthesis of 2-(1*H*-indol-2-yl)-1*H*-benzo[*d*]imidazoles[a]



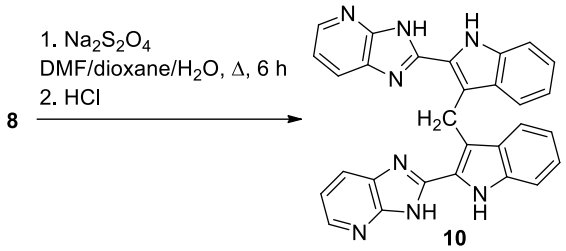
Entry	R^1	R^2	Product **7**	Yield (%)[b]
1	H	H	**7a**	59 (58[c])
2	Cl	Cl	**7b**	63
3	H	F	**7c**	65
4	Cl	F	**7d**	63

[a] The reaction were performed using 1 equiv. of 3-(2-nitrophenyl)quinoxalin-2(1*H*)-one **4**, 5 equiv. of sodium dithionite and about 10 equiv. HCl. [b] Yields of purified products. [c] Value in parenthesis indicate the isolated yield of **7a** in two-stage process with isolation of **6a**.



Scheme 5. Synthesis of 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3(4*H*)-one (**8**) and (Z)-2-(2-nitrobenzyliden)-1,2-dihydro-1,2,5-oxadiazolo[3,4-*b*]pyrazin-3(4*H*)-one (**9**).

Condensed derivatives of pyrazinones **8** and **9** were investigated under the action of $Na_2S_2O_4$ followed by treatment with HCl (Table 1). Compound **8** was poorly soluble in dioxane, so the reaction was carried out in a DMF-dioxane-H_2O medium, while to our pleasant surprise DMF played the role of not only a solvent, but also a reagent, as a supplier of a formyl group, which facilitates the addition of two molecules of 2-(indol-2-yl)imidazo[4,5-*b*]pyridines *via* the methylene group to unexpectedly form bis-(2-(imidazo[4,5-*b*]pyridin-2-yl)-indol-3-yl)methane (**10**) (Scheme 6). The formation of **10** is supported by the molecular peak $[M+H]^+$ = 481 in the MALDI-TOF mass spectrum and the characteristic signals of the methylene group, manifested in the ^{13}C DEPT spectrum by an antiphase peak (Figure 1) and in the DO spectrum triplet (see Supporting Information).



Scheme 6. Synthesis of bis-(2-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)-1*H*-indol-3-yl)methane (**10**).

The proposed mechanism for the formation of compound **10** is shown in Scheme 7. This cascade process proceeds with the involving the reduction of the nitro group of 2-(2-nitrobenzyl)pyridopyrazinone **8**, followed by the Mamedov rearrangement of 2-(2-aminobenzyl)pyridopyrazinone **11** with the formation of 2-(indol-2-yl)imidazo[4,5-*b*]pyridine **12**. Then, the modified Vilsmeier-Haack formylation to the third position of the indole fragment **12** with DMF and HCl, the reduction of the formyl group **13** to a hydroxymethyl group, and the condensation of the obtained compound **14** with the initial molecule of indolylimidazopyridine **12** occur.

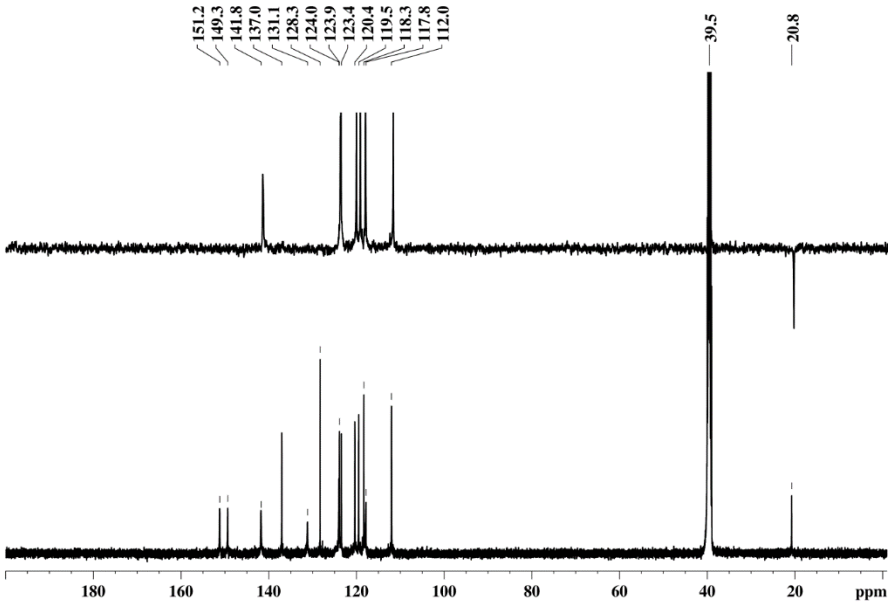
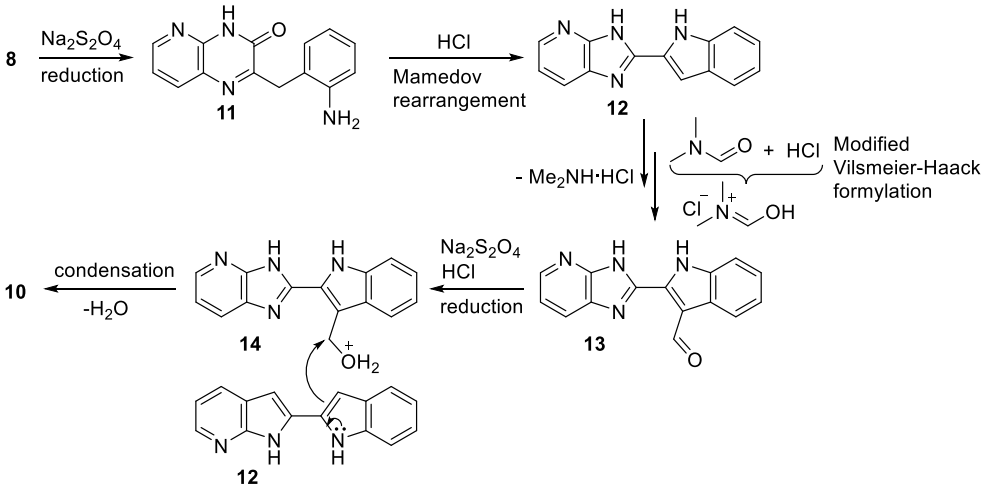
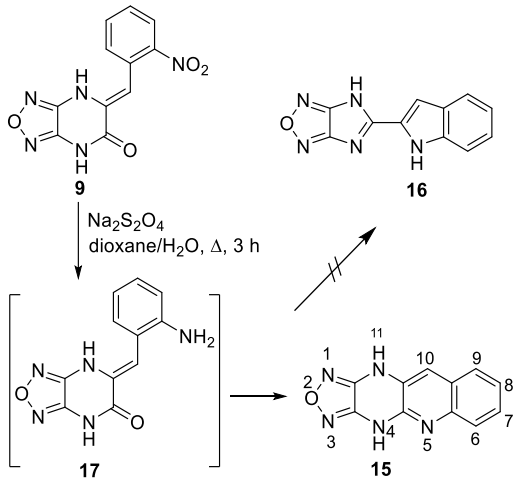


Figure 1. $^{13}C\{^1H\}$ (bottom) and DEPT (top) NMR spectra (126 MHz, DMSO, 303K) of **10**.



Scheme 7. Proposed mechanism for the conversion of 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3(4*H*)-one (**8**) to *bis*-(2-(imidazo[4,5-*b*]pyridin-2-yl)-indol-3-yl)methane (**10**) when exposed to sodium dithionite in DMF in the presence of HCl.

The reaction of oxadiazolopyrazinone **9** with $Na_2S_2O_4$ in a boiling aqueous medium of dioxane with or without subsequent HCl treatment resulted in the formation of a compound with m/z $[M+H]^+$ = 226.0720 (see Supporting Information), that corresponds to the compounds **15** and **16** in Scheme 8. Signals at 6.95 ppm in ^{1}H NMR spectrum and 209.6 ppm in ^{15}N NMR spectrum indicate the formation of the quinoline system and correspond to the signals of H10 and N5 in **15**, formed as a result of intramolecular condensation involving amino and carbonyl groups in the intermediate **17**.



Scheme 8. Synthesis of 4,11-dihydro-[1,2,5]oxadiazolo[3',4':5,6]pyrazino[2,3-*b*]quinoline (**15**).

The formation of 5-(indol-2-yl)imidazo[4,5-*c*][1,2,5]oxadiazole – the product of Mamedov rearrangement **17**, did not occur, apparently, due to the less electrophilicity of the C6 carbon atom responsible for the formation of a spiro-compound of type **A** (see Scheme 1) compared with the C5 carbon atom of the carbamoyl group, which makes the attack of the amino group on it more favorable with the formation of compound **15**.

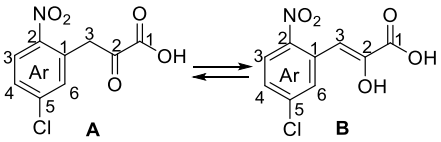
Conclusions

In conclusion, new representatives of the pharmacologically significant of 2-(indol-2-yl)-benzoimidazoles (**7b-d**) were synthesized from 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones **(4b-d**) in *one-pot* processes involving nitro group reduction and Mamedov rearrangement. The method used in this work for the synthesis of 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones (**4b-d**) was first used for the synthesis 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3(4*H*)-one (**8**) and 2-(2-nitrobenzyliden)-1,2-dihydro-1,2,5-oxadiazolo[3,4-*b*]pyrazin-3(4*H*)-one (**9**). Based on 2-(2-nitrobenzyl)pyridopyrazinone (**8)** and 2-(2-nitrobenzyliden)-1,2-dihydro-1,2,5-oxadiazolopyrazinone (**9)** in tandem processes, new heterocyclic structures were obtained – bis-(2-(imidazo[4,5-*b*]pyridin-2-yl)-indol-3-yl)methane (**10**) and 4,11-dihydro-[1,2,5]oxadiazolo[3',4':5,6]pyrazino[2,3-*b*]quinoline (**15**), respectively. The remarkable advantages of this method for the synthesis of bi- and bis-heterocyclic systems are simple experimental procedures, short reaction times, good yields, and ease of product isolation. Efforts to design and synthesize new *N*-fused heterocyclic chemical scaffolds for biological study are continuously being pursued in our laboratory.

Experimental Section

General. All solvent and reagents were obtained from commercial sources and were used without purification. The compounds **1-4** were synthetized as previously reported.[10] Melting points were determined on a hot-stage apparatus. Infrared spectra were recorded on a FT-IR spectrometer with reference KBr. All NMR experiments were performed on a Bruker AVANCE(III)-500 spectrometer (500 MHz for ^{1}H, 126 MHz for for ^{13}C, 51 MHz for ^{15}N). The spectrometer was equipped with a Bruker multinuclear z-gradient inverse probe head. The temperature for all measurements was set to 303 K. Chemical shifts (δ in ppm) are reffered to the solvent DMSO-d_6 (2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C NMR spectra), to external CD_3NO_2 (380.2 ppm) for ^{15}N NMR spectra. Values of NOE were acquired from DPFGNOE spectra [12 Stott K]. DPFGNOE Spectra for **15** were obtained using a spectral width of 33.87 ppm (20325.20 Hz) to give a digital resolution of 0.62 Hz per point, an RD of 8.00 s and an AT of 1.36 s. A Hermite-shaped pulse was used for selective irradiation. The MALDI mass-spectra for **10** was obtained on an UltraFlex III TOF-TOF instrument in positive mode. The device is equipped with a solid-state laser Nd:YAG laser (λ = 355 nm, repetition rate 66.7 Hz). Measurements were made in the range *m*/*z* 200-2000. A mixture of the sample (2 mg/mL, DMSO) was prepared to determine the mass values. *para*-Nitroaniline (10 mg/mL, CH_3CN) was used as a matrix. Portions (0.5 µL) of the matrix solution and the analyzed mixture were sequentially applied to the target and evaporated. The metal target MTP AnchorChipTM was used. The m/z values of monoisotopic ions are given in the descriptions. The data was obtained using the FlexControl program (Bruker Daltonik GmbH, Germany) and processed using the FlexAnalysis 3.0 program (Bruker Daltonik GmbH, Germany). The high resolution mass spectra (HRMS) of **15** was obtained on an Impact II ESI-QTOF (Bruker Daltonic GmbH, Germany) mass spectrometer. Measurement was made in the range m/z 50-1900. The instrument was calibrated with Sodium formate. The sample was dissolved in DMF and redissolved in acetonitrile/water solution (70:30). An acetonitrile/water solution was used at a flow rate of 0.3 mL/min by binary pump. The specified composition allowed to provide the relative error in determining the masses no more than 2.0 ppm. The elemental analyses for C, H, N were performed on an EVROVECTOR 3000 analyser, and the total content of halogens was determined by the gravimetric method of burning it in an oxygen flow.

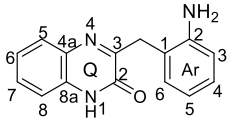
Procedure for synthesis of 3-(2-nitro-5-chlorophenyl)pyruvic acid (5)



Oxazolidinone **3b** (1.00 g, 4 mmol) was boiled in a mixture of AcOH (25 mL) and H_2SO_4 (0.5 mL) for 30 min. The formed after cooling the reaction mixture precipitate was filtered off, washed with water (2 × 10 mL) and dried in air. Brown solid; yield 0.87 g (89%); mp 147-149 °C; IR (KBr) ν_{max} 3117, 1721, 1676, 1520, 1336, 1297, 1240 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) for **5A** (45%) δ 4.58 (s, 2H, CH_2), 7.66 (d, *J* 8.6 Hz, 1H, H4-Ar), 7.67 (s, 1H, H6-Ar), 8.14 (d, *J* 8.6 Hz, 1H, H3-Ar), 10.26 (s, 1H, OH); for **5B** (55%) δ 6.59 (s, 1H, CH), 7.52 (d, *J* 8.2 Hz, 1H, H4-Ar), 7.97 (d, *J* 8.3 Hz, 1H, H3-Ar), 8.26 (s, 1H, H6-Ar); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz) for **5A** (45%) δ 191.5 (C2=O), 161.6 (COOH), 147.0 (C2-Ar), 138.4 (C5-Ar), 133.4 (C6-Ar), 132.1 (C1-Ar), 128.7 (C4-Ar), 126.8 (C3-Ar), 43.2 (CH_2); for **5B** (55%) δ 165.2 (COOH), 146.4 (C2-Ar), 145.9 (C2-OH), 137.3 (C5-Ar), 130.5 (C1-Ar), 130.0 (C6-Ar), 127.5 (C4-Ar), 126.2 (C3-Ar), 100.5 (CH=); anal. calcd for $C_9H_6ClNO_5$: C, 44.37; H, 2.48; Cl, 14.55; N, 5.75; found: C, 44.29; H, 2.51; Cl, 14.79; N, 5.63.

Procedure for synthesis of 6,7-dichloro-3-(2-nitro-5-chlorobenzyl)quinoxalin-2(1*H*)-one 4b and 6,7-difluoro-3-(5-chloro-2-nitrobenzyl)quinoxalin-2(1*H*)-one 4d from 5. Mixture of acid **5** (0.37 g, 1.5 mmol) and corresponding 1,2-diaminebenzene (1.5 mmol) was boiled in AcOH for 6 h, and then kept at room temperature for 12 h. Water (20 mL) and 2% $NaHCO_2$ solution (10 mL) were added to the reaction mixture. The resulting precipitate was filtered off, washed with water (3 × 5 mL) and acetone (2 mL). Yield 0.47 g (81%) and 0.39 g (73%) for **4b** and **4d**, respectively. The characteristics of **4b** and **4d** matched those when compounds were prepared from 5-(5-chloro-2-nitrobenzylidene)-2,2-dimethyl-1,3-oxazolidin-4-one (**3b**) according to the method described by us earlier.[10]

Procedure for synthesis of 3-(2-aminobenzyl)quinoxalin-2(1*H*)-one (6a)



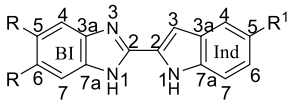
A solution of $Na_2S_2O_4$ (5.22 g, 30 mmol) in H_2O (350 mL) was added to a solution of **4a** (1.69 g, 6 mmol) in dioxane (350 mL). The reaction mixture was boiled for 6 h, and then poured into water (800 mL). The resulting precipitate was filtered off, washed with water (2 × 70 mL) and dried in air. Tan solid; yield 1.07 g (71%); mp 190-191 °C (185-187 °C[16]); IR (KBr) ν_{max} 3487, 3407, 3330, 2964, 2893, 2847, 1655 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.97 (s, 2H, CH_2), 6.54 (dd, *J* 7.5, 7.4 Hz, 1H, H5-Ar), 6.67 (d, *J* 7.7 Hz, 1H, H3-Ar), 6.94 (dd, *J* 7.7, 7.6 Hz, 1H, H4-Ar), 7.08 (d, *J* 7.3 Hz, 1H, H6-Ar), 7.25 (dd, *J* 8.0, 7.9 Hz, 1H, H6-Q), 7.28 (d, *J* 8.0, 8.0 Hz, 1H, H8-Q), 7.48 (dd, *J* 7.9, 7.7 Hz, 1H, H7-Q), 7.70 (d, *J* 7.9 Hz, 1H, H5-Q), 12.41 (s, 1H, NH-Q); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 159.9 (C2-Q), 154.8 (C3-Q), 146.4 (C2-Ar), 131.8 (C8a-Q), 131.5 (C4a-Q), 130.7 (C6-Ar), 129.7 (C7-Q), 128.1 (C5-Q), 127.3 (C4-Ar), 123.2 (C6-Q), 120.9 (C1-Ar), 116.8 (C5-Ar), 115.4 (C3-Ar), 115.3 (C8-Q), 35.0 (CH_2); anal. calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72; found: C, 71.63; H, 5.28; N, 16.58.

Procedure for synthesis of 2-(indol-2-yl)-benzimidazole (7a) from 6a

Concd HCl (1.5 mL, approximately 15.9 mmol) was added to a solution of **6a** (0.4 g, 1.59 mmol) in dioxane (30 mL), and the mixture was boiled for 1 h. The resulting precipitate was filtered off, washed with water (3 × 10

mL) and dried in air. Brown solid; yield 0.21 g (58%); mp 254-256 °C (282-283 °C,[5] 250-252 °C[14]); spectral data matched previously described.[5]

General procedure for the synthesis of 2-(indol-2-yl)-benzimidazoles 7a-d



A solution of $Na_2S_2O_4$ (5.22 g, 30 mmol) in H_2O (120 mL) was added to a solution of corresponding 3-benzylquinoxalin-2-ones **4** (6 mmol) in dioxane (120 mL). The reaction mixture was boiled for 6 h, then concd HCl (5.7 mL, approximately 60 mmol) was added, and boiling was continued for 1 h. The resulting precipitate was filtered off, washed with water (2 × 70 mL) and dried in air.

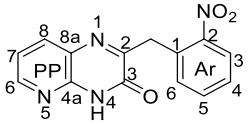
2-(Indol-2-yl)-benzoimidazole (7a). Brown solid; yield 0.82 g (59%); mp 255-256 °C; spectral data matched previously described.[5]

5,6-Dichloro-2-(5-chloroindol-2-yl)-benzimidazole (7b). Brown solid; yield 1.27 g (63%); mp 214-215 °C; IR (KBr) ν_{max} 3154, 1632, 1451 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.19 (dd, *J* 8.7, 2.0 Hz, 1H, H6-Ind), 7.24 (s, 1H, H3-Ind), 7.47 (d, *J* 8.7 Hz, 1H, H7-Ind), 7.72 (d, *J* 2.0 Hz, 1H, H4-Ind), 7.85 (s, 2H, H4,7-BI), 12.19 (s, 1H, NH-Ind); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 148.1 (C2-BI), 138.7 (C3a,7a-BI), 135.9 (C7a-Ind), 129.1 (C2-Ind), 128.8 (C3a-Ind), 124.9 (C5,6-BI), 124.6 (C5-Ind), 123.4 (C6-Ind), 120.2 (C4-Ind), 116.2 (C4,7-BI), 113.7 (C7-Ind), 102.5 (C3-Ind); anal. calcd for $C_{15}H_8Cl_3N_3$: C, 53.52; H, 2.40; Cl, 31.60; N, 21.48; found: C, 53.29; H, 2.44; Cl, 31.72; N, 21.31.

5,6-Difluoro-(indol-2-yl)-benzimidazole (7c). Black solid; yield 1.05 g (65%); mp 310-312 °C; IR (KBr) ν_{max} 2923, 1643, 1486, 1173 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.08 (dd, *J* 7.8, 7.6 Hz, 1H, H6-Ind), 7.23 (dd, *J* 7.8, 7.6 Hz, 1H, H5-Ind), 7.32 (s, 1H, H3-Ind), 7.51 (d, *J* 7.8 Hz, 1H, H4-Ind), 7.66 (d, *J* 7.8 Hz, 1H, H7-Ind), 7.72 and 7.74 (2d, *J* 8.5 and 8.6 Hz, 2H, H4,7-BI), 11.84 (s, 1H, NH-Ind); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 147.8 (d, J_{CF} = 242.7 Hz, C5-BI), 147.6 (d, J_{CF} = 242.5 Hz, C6-BI), 147.1 (C2-BI), 137.8 (C7a-Ind), 132.3 (C3a,7a-BI), 127.7 (C3a-Ind), 125.5 (C2-Ind), 124.3 (C5-Ind), 121.5 (C4-Ind), 120.6 (C6-Ind), 112.5 (C7-Ind), 104.7 (C3-Ind), 102.8 (d, J_{CF} = 14.9, C4-BI), 102.7 (d, J_{CF} = 14.9, C7-BI); anal. calcd for $C_{15}H_9F_2N_3$: C, 66.91; H, 3.37; F, 14.11; N, 15.61; found: C, 66.31; H, 3.39; F, 14.28; N, 15.32.

5,6-Difluoro-2-(5-chloroindol-2-yl)-benzimidazole (7d). Brown solid; yield 1.15 g (63%); mp 309-311 °C; IR (KBr) ν_{max} 3074, 1642, 1513, 1488 cm^{-1}; NMR (500 MHz, DMSO-d_6) δ 7.20 (dd, *J* 8.6, 1.8 Hz, 1H, H6-Ind), 7.29 (s, 1H, H3-Ind), 7.49 (d, *J* 8.6 Hz, 1H, H7-Ind), 7.69 and 7.71 (2d, *J* 8.8 and 8.7 Hz, 2H, H4,7-BI), 7.727 (d, 1H, *J* 1.7 Hz, H4-Ind), 12.21 (s, 1H, NH-Ind); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 147.5 (d, J_{CF} = 242.6 Hz, C5-BI), 147.1 (d, J_{CF} = 242.5 Hz, C6-BI), 146.9 (C2-BI), 135.9 (C7a-Ind), 133.2 (C3a,7a-BI), 128.8 (C3a-Ind), 128.2 (C2-Ind), 124.7 (C5-Ind), 123.7 (C6-Ind), 120.3 (C4-Ind), 113.8 (C7-Ind), 103.1 (C3-Ind), 102.7 (C4,7-BI); anal. calcd for $C_{15}H_8ClF_2N_3$: C, 59.32; H, 2.66; Cl, 11.67; F, 12.51 (Cl+F = 24.18); N, 13.84; found: C, 59.67; H, 2.62; Cl+F = 24.33; N, 13.61.

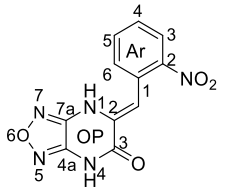
Procedure for the synthesis of 2-(2-nitrobenzyl)pyrido[2,3-*b*]pyrazin-3(4*H*)-one (8)



Mixture of oxazolidine **3a** (0.99 g, 4 mmol), 2,3-diaminopyridine (0.44 g, 4 mmol), AcOH (25 mL) and concd H_2SO_4 (0.5 mL) was boiled for 3 h, and then kept at room temperature for 12 h. Water (50 mL) and 2% $NaHCO_3$ solution (25 mL) were added to this mixture. The resulting precipitate was filtered off, washed with water (2 × 25 mL)

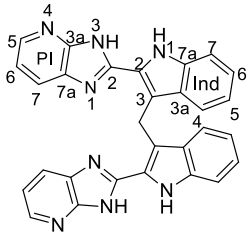
and acetone (5 mL). Brown solid; yield 0.77 g (68%); mp 233-235 °C; IR (KBr) ν_{max} 2879, 2776, 1672, 1532 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.54 (s, 2H, CH_2), 7.27 (dd, *J* 7.7, 4.7 Hz, 1H, H7-PP), 7.56 (ddd, *J* 8.1, 7.6, 1.4 Hz, 1H, H4-Ar), 7.58 (dd, *J* 7.5, 1.4 Hz, 1H, H6-Ar), 7.71 (ddd, *J* 7.6, 7.5, 1.3 Hz, 1H, H5-Ar), 7.88 (d, *J* 7.7, 1.6 Hz, 1H, H8-PP), 8.06 (dd, *J* 8.1, 1.2 Hz, 1H, H3-Ar), 8.46 (dd, *J* 4.7, 1.6 Hz, 1H, H6-PP), 12.92 (s, 1H, NH); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz) δ 160.3 (C3-PP), 155.6 (C2-PP), 149.6 (C6-PP), 149.2 (C2-Ar), 143.7 (C4a-PP), 136.1 (C8-PP), 133.6 (C5-Ar), 133.5 (C6-Ar), 131.8 (C1-Ar), 128.3 (C4-Ar), 126.4 (C8a-PP), 124.7 (C3-Ar), 119.7 (C7-PP), 36.7 (CH_2); anal. calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85; found: C, 59.67; H, 3.59; N, 19.81.

Procedure for the synthesis of (*Z*)-2-(2-nitrobenzyliden)-1,2-dihydro-1,2,5-oxadiazolo[3,4-*b*]pyrazin-3(4*H*)-one (9)



Mixture of oxazolidine **3a** (0.99 g, 4 mmol), 3.4-diamino-1,2,5-oxadiazole (0.40 g, 4 mmol), AcOH (25 mL) and concd H_2SO_4 (0.5 mL) was boiled for 3 h, and then kept at room temperature for 12 h. Water (50 mL) and 2% $NaHCO_3$ solution (25 mL) were added to this mixture. The resulting precipitate was filtered off, washed with water (2 × 25 mL) and acetone (5 mL). Yellow solid; yield 1.04 g (95%); mp 257 °C; IR (KBr) ν_{max} 3232, 3154, 1710, 1630, 1522, 1339 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.841 (s, 1H, CH=), 7.57 (ddd, *J* 7.8, 7.5, 1.3 Hz, 1H, H4-Ar), 7.73 (dd, *J* 7.1, 1.2 Hz, 1H, H6-Ar), 7.78 (dd, *J* 7.7, 7.2 Hz, 1H, H5-Ar), 8.11 (d, *J* 7.5 Hz, 1H, H3-Ar), 10.53 (s, 1H, NH4-OP), 12.37 (s, 1H, NH1-OP); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz) δ 158.2 (C3-OP), 147.8 (C2-Ar), 144.5 (C7a-OP), 143.9 (C4a-OP), 133.9 (C5-Ar), 131.2 (C6-Ar), 129.1 (C1-Ar), 128.7 (C4-Ar), 128.6 (C2-OP), 124.7 (C3-Ar), 106.7 (C=); ^{15}N NMR (DMSO-d_6, 51 MHz) δ 80.2 (N1-OP), n/o (N4-OP), n/o (N5-OP), n/o (N7-OP), 374.1 (NO_2); anal. calcd for $C_{11}H_7N_5O_4$: C, 48.36; H, 2.58; N, 25.63; found: C, 48.44; H, 2.59; N, 25.68.

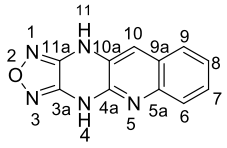
Procedure for synthesis of bis-(2-(imidazo[4,5-*b*]pyridin-2-yl)-indol-3-yl)methane (10)



A solution of $Na_2S_2O_4$ (5.22 g, 30 mmol) in H_2O (120 mL) was added to a solution of pyridopyrazinone **8** (1.69 g, 6 mmol) in the mixture dioxane and DMF (120 mL, 3:1 by volume). The reaction mixture was heated at reflux for 6 h, then concd HCl (5.7 mL, approximately 60 mmol) was added, and the heating was continued for 1 h. The resulting precipitate was filtered off, washed with water (2 × 70 mL) and dried in air. Brown solid; yield 0.96 g (67%); mp 286-287 °C; IR (KBr) ν_{max} 3182, 1568, 1342 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 5.40 (s, 2H, CH_2), 6.79 (dd, *J* 8.0, 7.8 Hz, 2H, 2H6-Ind), 7.12 (dd, *J* 8.0, 7.8 Hz, 2H, 2H5-Ind), 7.31 (d, *J* 8.0 Hz, 2H, 2H4-Ind), 7.41 (dd, *J* 7.9 Hz, *J* 4.7 Hz, 2H, 2H6-PI), 7.45 (d, *J* 8.0 Hz, 2H, 2H7-Ind), 8.16 (d, *J* 7.8 Hz, 2H, 2H5-PI), 8.45 (d, *J* 4.6 Hz, 2H, 2H4-PI), 11.62 (s, 2H, 2NH-Ind); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz) δ 151.1 (C3a-PI), 149.6 (C2-PI), 141.6 (C5-PI), 137.2 (C7a-Ind), 131.2 (C7a-PI), 128.3 (C3a-Ind), 124.3 (C7-PI), 124.1 (C5-Ind), 123.4 (C2-Ind), 120.4 (C4-Ind),

119.8 (C6-Ind), 118.5 (C6-PI), 118.1 (C3-Ind), 112.2 (C7-Ind), 20.8 (s, CH_2); MS (MALDI-TOF), *m/z*: $[M + H]^+$ = 481; anal. calcd for $C_{29}H_{20}N_8$: C, 72.49; H, 4.20; N, 23.32; found: C, 72.02; H, 4.23; N, 23.47.

Procedure for synthesis of 4,11-dihydro-[1,2,5]oxadiazolo[3',4':5,6]pyrazino[2,3-*b*]quinoline (15)



A solution of $Na_2S_2O_4$ (2.61 g, 15 mmol) in H_2O (60 mL) was added to a solution of oxadiazolopyrazinone **9** (0.82 g, 3 mmol) in dioxane (60 mL). The reaction mixture was heated at reflux for **3** h and the resulting precipitation was filtered off, washed with water (2 × 70 mL) and dried in air. Yellow solid; yield 0.66 g (97%); mp 287-289 °C; IR (KBr) ν_{max} 3431, 3063, 2924, 1664, 1563 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.95 (s, 1H, H10), 7.17 (dd, *J* 7.6, 7,5 Hz, 1H, H8), 7.31 (dd, *J* 7.6, 7.5 Hz, 1H, H7), 7.37 (d, *J* 7.7 Hz, 1H, H6), 7.49 (d, *J* 7.7 Hz, 1H, H9), 10.63 (s, 1H, H11), 11.59 (s, 1H, H4); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz) δ 149.6 (C3a), 147.5 (C4a), 145.7 (C11a), 139.0 (C5a), 127.1 (C6,7), 126.3 (C10a), 125.8 (C9), 124.5 (C9a), 124.0 (C8), 112.9 (C10); ^{15}N NMR (DMSO-d_6, 51 MHz) δ n/o (N1), n/o (N3), n/o (N4), 80.2 (N11), 209.6 (N5); MS (ESI-QTOF), *m/z*: $[M+H]^+$ calc. 226.0724, found 226.0720; anal. calcd for $C_{11}H_7N_5O$: C, 58.67; H, 3.13; N, 31.10; found: C, 58.94; H, 3.56; N, 30.98.

Acknowledgements

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Supplementary Material

Copies of ^1H and ^{13}C NMR spectra for all new compounds, 1D DPFGNOE Spectrum for (Z)-2-(2-nitrobenzylidene)-1,2-dihydro-1,2,5-oxadiazolo[3,4-*b*]pyrazin-3(4*H*)-one (**9**) and mass spectra for *bis*(2-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)-1*H*-indol-3-yl)methane (**10**) and 4,11-dihydro-[1,2,5]oxadiazolo[3',4':5,6]pyrazino[2,3-*b*]quinoline (**15**) are given in the Supplementary Material file associated with the manuscript.

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