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Reductive acid-catalyzed rearrangement of 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones in the presence of $Na_2S_2O_4$ – effective method for the synthesis of 2-(indol-2-yl)benzimidazoles

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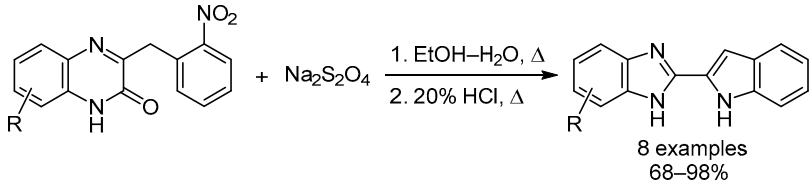


An effective one-step method is proposed for the synthesis of 2-(indol-2-yl)benzimidazoles from 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones without using metal catalysts and reagents. This method is based on the Mamedov rearrangement of 3-(2-aminobenzyl)quinoxalin-2(1*H*)-ones, formed *in situ* by the action of $Na_2S_2O_4$, giving 2-(indol-2-yl)benzimidazoles as the products.

Keywords: 3-(2-aminobenzyl)quinoxalin-2(1*H*)-ones, 1',4'-dihydro-3'*H*-spiro(indoline-2,2'-quinoxalin)-3'-ones, 2-(indol-2-yl)benzimidazoles, 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones, Mamedov rearrangement.

Benzo-fused nitrogen-containing heterocyclic compounds have a major importance in drug discovery efforts. Of particular interest are benzimidazole derivatives, the best known of which is *N*-ribosyldimethylbenzimidazole, the axial ligand present in B_{12} vitamin, which is involved in the coordination of cobalt ion.[1] Some authors have recognized it as an example of the so-called privileged molecules,[2] compounds that exhibit several types of activity and are widely used in the search for biologically active substances. Benzimidazole and its various derivatives serve as an optimal starting point for the design of new drug molecules. A series of benzimidazole hetaryl derivatives have been shown to possess various types of pharmaceutical activity, such as antimicrobial,[3] antitumor,[4] antiviral,[5] anthelmintic,[6] antioxidant,[7] antiulcer,[8] antihypertensive,[9] and tuberculostatic[10] effects. For example, the benzimidazole-quinoline conjugate dovitinib (Fig. 1) is a powerful inhibitor of EGFR-3, and is currently in phase III clinical trials for the treatment of metastatic renal cancer.[11] The thiazolylbenzimidazole derivative thiabendazole acts as anthelmintic drug,[12] while the pyridazinonylbenzimidazole derivative pimobendan is used as a vasoconstrictor medication for the treatment of cardiomyopathy in dogs.[13a–c] The Hoechst dye, which contains two benzimidazole rings, is widely used for staining of DNA in fluorescent microscopy, immunohistochemistry, and flow cytometry[13d] (Fig. 1).

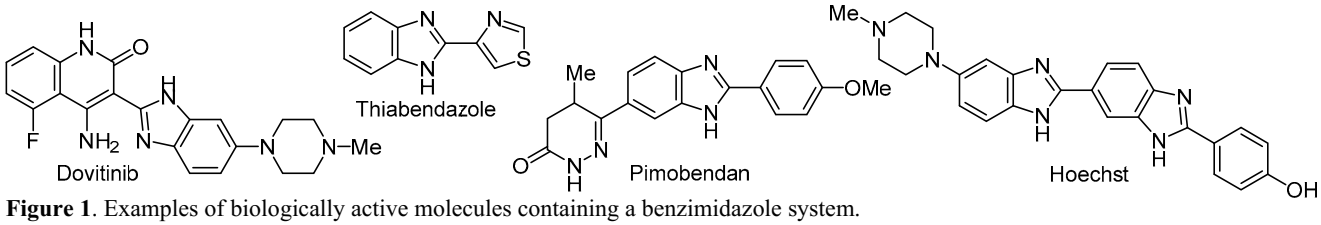


Figure 1. Examples of biologically active molecules containing a benzimidazole system.

Due to the major importance of benzimidazoles in the search for new drugs, significant efforts have been devoted to the development of short and simple methods for the synthesis of new benzimidazole derivatives.[14] The standard approach is based on the use of Weidenhagen reaction – condensation of *o*-phenylenediamines with aldehydes or ketones in the presence of an acidic, basic,[15] or metal catalyst.[16] Another approach involves the use of Phillips–Ladenburg reaction – condensation of *o*-phenylenediamines with carboxylic acids, nitriles, and orthoesters under dehydrating conditions. The dehydration reactions of *N*-acylated *o*-phenylenediamines by using acetic acid,[17a–c] *p*-TSA,[17d] or Amberlyst-15[17e] also have been shown to provide benzimidazoles.

Even though the described methods are effective and often used, it is also important to note their limitations. For example, the condensation of *o*-phenylenediamine and aldehyde in the presence of an acid or base requires a longer reaction time and leads to *N*-1 benzylated benzimidazoles as undesirable by-products, which are often very difficult to separate from the desired reaction products.[18] Metal-catalyzed condensation reactions often require high temperatures, while the residual metal impurities present in the product can cause toxic effects during the pharmaceutical use.[19] The main drawback of these methods is the impossibility of using them in the synthesis of biheterocyclic systems, which would require laborious multistep processes that would result in decreased yields of the final products. This may be the reason why we did not find any indolylbenzimidazole derivatives among the many biheterocyclic systems with useful properties, even though biaryl structures containing an indole nucleus are present in many pharmaceutical substances, biologically active compounds, and functional materials, thus attracting significant attention of synthetic chemists to the reactions of indole-arene cross coupling.[20] In particular, methods based on direct C–H-functionalization[21] enable the cross coupling of unactivated indoles and could serve as alternatives to the more common cross-coupling reactions of halides or metal-catalyzed reactions.[22] However, the methods of direct C–H-functionalization usually require the use of expensive palladium catalysts in combination with the copper- or silver-based oxidants that are needed for these reactions. With regard to the cross-coupling reactions in the synthesis of biheterocyclic compounds, their success primarily depends on the availability of the necessary aryl halides and organometallic derivatives of the other aromatic compound, which together serve as electrophilic and nucleophilic reagents, respectively.

Despite certain achievements in the synthesis of biheterocyclic systems by using metal catalysts, we have found only a few examples for the synthesis of similar compounds with benzimidazole ring system where the yields exceeded 50%. For example, the synthesis of 4-hetarylquinolines *via* Pd/Cu-catalyzed coupling reaction of 1-methylbenzimidazole and 2-oxoquinolin-4-yl triflate, in contrast to the effective coupling with benzothiazoles, benzoxazoles, thiazoles, and oxazoles, gave only a 56% yield.[23] The copper-catalyzed cross-coupling reaction of indoles with 1,3-azoles using a double C–H-activation and chelation of pyridine group at the indole ring nitrogen atom also generally proceeded relatively smoothly with the formation of the desired products, but the yield was merely 28% in the case of methylbenzimidazole.[24] When the Cu(I)- or Pd(II)-catalyzed cross coupling of geminal dihaloalkenes with azoles, proceeding *via* the tandem process of C–heteroatom coupling and C–H-activation, was applied for the preparation of benzo-fused hetarylazoles, the yields of 2-(5-chlorobenzofuran-2-yl)methylbenzimidazole and 2-(6-methylbenzofuran-2-yl)methylbenzimidazole reached 64 and 66%, respectively.[25] We did not find any examples of such metal-catalyzed reaction for *N*-unsubstituted benzimidazole derivatives.

Hetaryl derivatives of benzimidazole can be easily obtained using acid-catalyzed rearrangement of quinoxaline derivatives by the action of nucleophilic reagents (the Mamedov rearrangement).[26] As shown in the general scheme below, "any spiro derivative of 1,2,3,4-tetrahydroquinoxalin-3-one with at least one acidic hydrogen atom in its spiro-forming component is on the pathway to benzimidazole derivatives with a spiro-forming component at position 2" (Fig. 2),[26b,c] – this is one of the variants of Mamedov rearrangement, a reaction that is used for the introduction of heterocyclic moiety at position 2 of benzimidazole ring system. In order to achieve this, it is necessary to first synthesize the respective functionalized derivatives of quinoxalinones, which allow to introduce the given heterocyclic nucleus at position 2 as the spiro-forming moiety, with subsequent acid-catalyzed rearrangement providing the desired product.

In order to obtain 2-(indol-2-yl)benzimidazoles **4**, it was necessary to synthesize a quinoxalinone derivative with such a functional group (for example, compound **2**) that would allow *in situ* introduction of an indole moiety into the quinoxalinone molecule, with the C-2 carbon atom serving as the spiro-forming site for both heterocycles (compound **3**, Scheme 1). Among the many possible approaches to the synthesis of indoles,[27] we selected the Reissert reaction as the method for introducing the spiro-forming moiety at position 2 of indole nucleus,[28] by considering 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one derivatives **1** as hetero analogs of *o*-nitrophenylpyruvate esters **5** (Scheme 1),[26b] with compounds **1** readily formed by an interaction of the latter with *o*-phenylenediamine and its

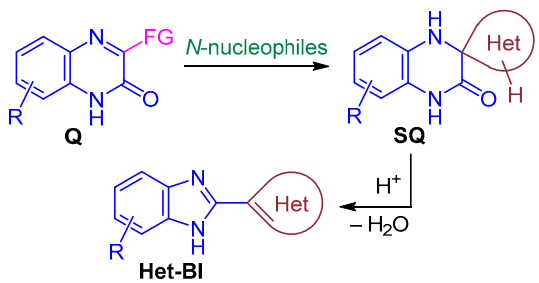
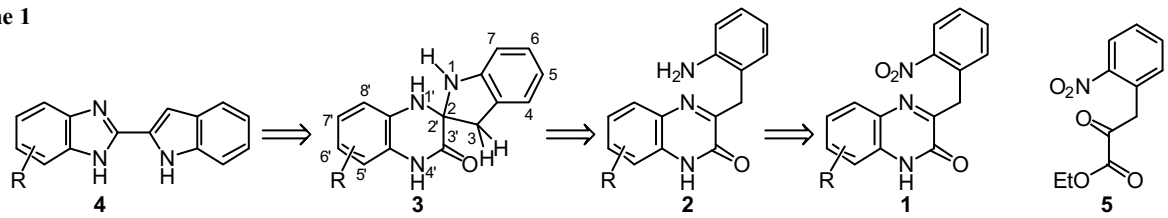


Figure 2. The general scheme for one of the variants of the Mamedov rearrangement.

Scheme 1



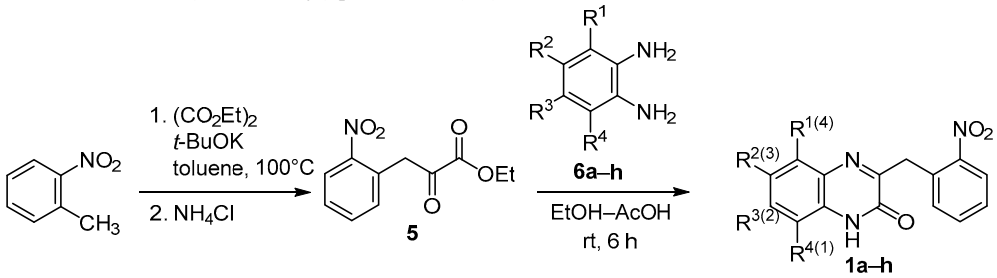
derivatives substituted in the benzene ring, according to the Körner-Hinsberg reaction (Table 1).[29]

At the same time, it should be noted that the synthesis of ethyl *o*-nitrophenylpyruvate **5** was accomplished by following a slightly modified procedure involving the reaction of *o*-nitrotoluene with diethyl oxalate in the presence of *t*-BuOK in toluene, but not in Et_2O, as described in the literature.[30a] The reaction proceeded smoothly and gave good yields, producing compound **5** that was suitable for use without additional purification in the synthesis of quinoxalin-2(1*H*)-ones by a reaction with 1,2-diaminobenzenes (Table 1).[30b,c]

The reactions of pyruvate **5** with monosubstituted 1,2-diaminobenzenes **6d**–**h**, in contrast to the reactions of 2-diaminobenzene **6a** and its symmetrically substituted derivatives **6b**,**c**, proceeded with the formation of a mixture of regioisomers **A** and **B** in the case of starting compounds **1d**,**f**–**h** (Scheme 2a), or a mixture of regioisomers **E** and **F** at various ratios (Scheme 1) in the case of compound **1e** as the starting material (Scheme 2b). Furthermore, in the case of monosubstituted 1,2-diaminobenzenes **6g**,**h**, according to ^{1}H NMR spectral data, a DMSO-d_6 solution contained besides the imine forms of regioisomers **A** and **B** also the respective enamine forms **C** and **D** of these regioisomers (Scheme 2).

The presence of *o*-nitrobenzyl moiety at the C-3 imine carbon atom of quinoxalin-2(1*H*)-one system allowed to introduce an indole system at this position under the conditions of nitro group reduction with $Na_2S_2O_4$ according to the Reissert reaction. The imino group participated in this reaction as a hetero analog of carbonyl group in the *o*-nitrophenylpyruvate esters **5**. Refluxing of the reaction mixture in the presence of HCl led to a rearrangement with the formation of 2-(indol-2-yl)benzimidazoles **4a**–**h**. In the case when derivatives **1d**–**h** were used, the presence of benzimidazole tautomerism led to indistinguishable (by ^{1}H NMR spectroscopy) regioisomers of compounds **4d**–**h**. This occurred regardless of the ratio of regioisomers **A** and **B** in the starting compounds **1d**,**f**–**h**, as well as their tautomeric forms **C** and **D** in solutions of compounds **1g**,**h** or regioisomers **E** and **F** in compound **1e**. At the same time, it should be noted that in the case when dinitro derivative **1g** was used, the reduction of both nitro groups under the reaction conditions led to the formation of 6-amino-2-(indol-2-yl)benzimidazole **4g**, instead of its nitro analog (Scheme 3).

Table 1. Synthesis of substituted 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones **1a**–**h**

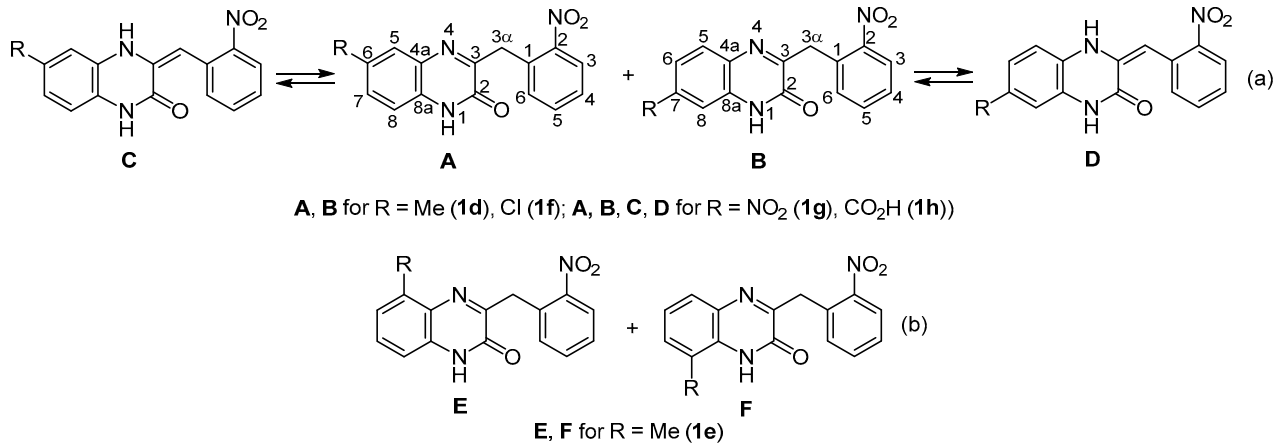


Compound	R^1	R^2	R^3	R^4	Product*	Yield**, %
6a	H	H	H	H	**1a**	96
6b	H	Me	Me	H	**1b**	92
6c	H	Cl	Cl	H	**1c**	96
6d	H	Me	H	H	**1dA** + **1dB**	71 (53:47)
6e	Me	H	H	H	**1eE** + **1eF**	51 (72:28)
6f	H	Cl	H	H	**1fA** + **1fB**	88 (58:42)
6g	H	NO_2	H	H	**1gB** + **1gA** + **1gD** + **1gC**	82 (45:25:30:traces)
6h	H	CO_2H	H	H	**1hB** + **1hA** + **1hD** + **1hC**	86 (58:37:5:traces)

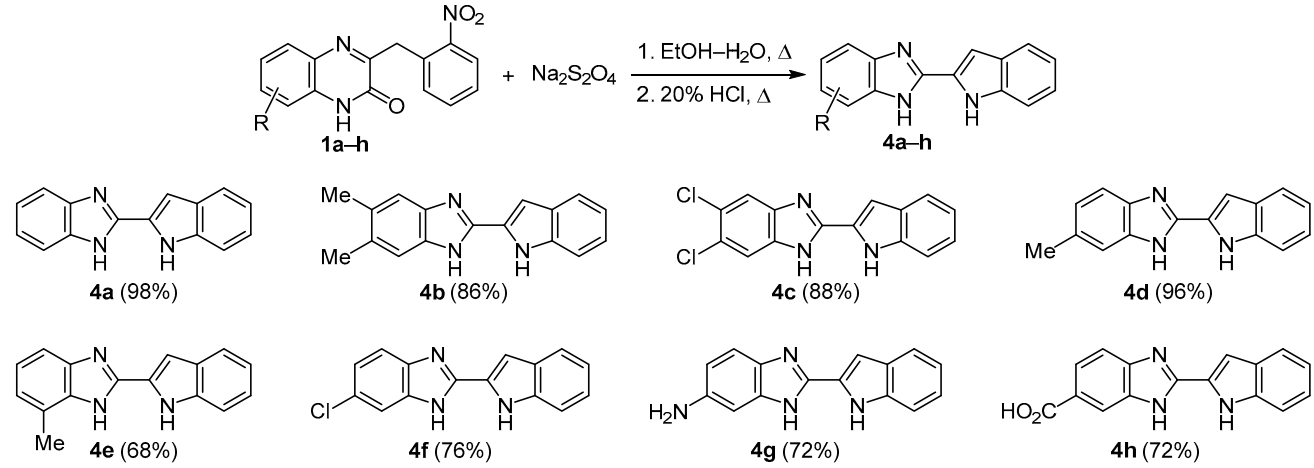
* Lower case letters indicate the substituents in the benzene ring of the quinoxalinone system, upper case letters – regioisomers and their tautomeric forms (Scheme 2).

** The ratio of isomers was calculated from ^{1}H NMR spectra.

Scheme 2



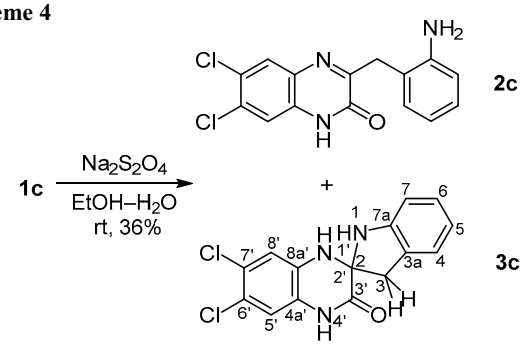
Scheme 3



The described transformation is an acid-catalyzed process. The use of a large excess of acid allowed to isolate the reaction products without additional steps, except for the treatment of reaction mixture with water. Thus, the acid in this process served as a catalyst and facilitated the conversion of excess sodium dithionite into water-soluble inorganic salts.

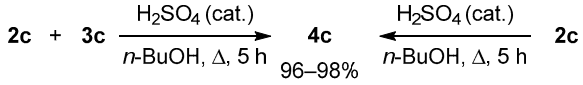
The analysis of ^{1}H NMR spectrum of the reaction mixture formed upon treatment of 6,7-dichloro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (**1c**) with a sixfold excess of $Na_2S_2O_4$ (dithionite was added to the reaction mixture in three portions at 3 h intervals) prior to refluxing in the presence of hydrochloric acid indicated that the reaction mixture contained only the respective amine **2c** and spiro compound **3c** without any impurities of other organic compounds (Scheme 4). The formation of compound **2c** was evidenced by the presence of a singlet signal due to methylene group (3.97 ppm) along with the signals of benzene ring protons, while the formation of compound **3c** was indicated by the presence of two doublet signals of pyrroline ring methylene group (2.92 and 3.89 ppm) with a geminal spin-spin coupling constant of 16.3 Hz, besides the benzene ring proton signals of the quinoxaline and indole systems. The structure of compound **3c** was established conclusively by using two-dimensional COSY, ^{13}C–^{1}H HSQC, ^{13}C–^{1}H HMBC, ^{15}N–^{1}H HSQC, and ^{15}N–^{1}H HMBC experiments. The signals of spiro moiety were assigned by using a sequence of cross correlations (cross peaks) starting from the characteristic 3-CH_2 signal at the 3-C atom (38.9 ppm). The spiro and quinoxaline fragments were linked by cross peaks between the 3-CH_2 signal and N-1' atom (88.9 ppm) and the 3'-C atom (164.4 ppm). The further chain linked the 1'-NH group (7.52 (^{1}H) and 88.9 (^{15}N) ppm) to the C-8' carbon atom (115.0 ppm) and then with the singlet signal of H-8' proton (6.93 ppm). This interpretation overlapped and was confirmed by the cross peaks of 4'-H proton (10.76 ppm) and the 3'-C carbon atom (164.4 ppm) (a weak cross peak) and 2'-C (2-C) carbon atom (75.7 ppm) (a strong cross peak), and to the other side between the C-5' (115.4 ppm) and C-8a' (132.5 ppm) atoms, the latter of which gave a weak cross peak with the H-8' proton signal.

Scheme 4



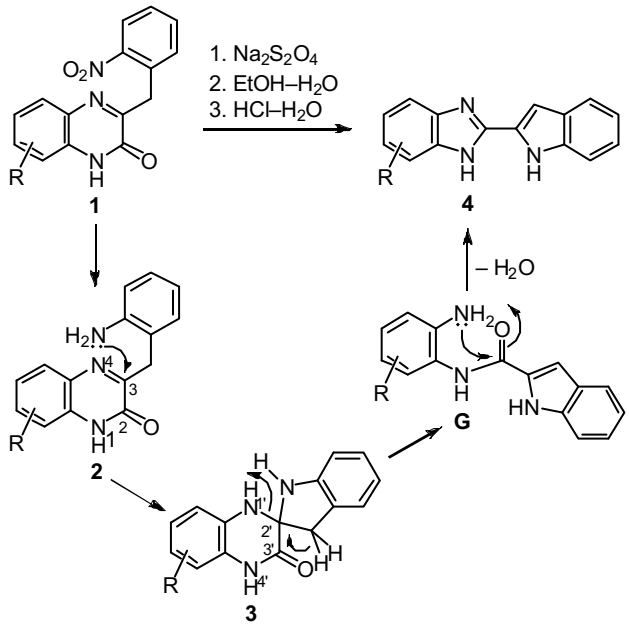
The main amount of amine **2c**, in contrast to the spiro compound **3c**, was easily isolated from the product mixture as a pure sample by extraction with EtOAc. Both the refluxing of pure amine **2c**, as well as the mixture of compounds **2c** and **3c** in butanol in the presence of catalytic amounts of H_2SO_4 led to a high yield of the rearrangement product **4c** (Scheme 5).

Scheme 5



On the basis of known data from the chemistry of nitro-compounds,[31] amines,[32] imines,[33] quinoxalines,[29,34] also including our own previously reported results[26b,c] and observations from this study, the following scheme can be proposed for the formation of 2-(indol-2-yl)benzimidazoles. The first step involves the reduction of nitro group to amino group, with the formation of compound **2**, which undergoes an intramolecular nucleophilic addition with the participation of amine nitrogen atom and the imine C-3 carbon atom of the quinoxalinone system, forming the spiro derivative – compound **3**. This intermediate then undergoes a series of cascade transformations: a) ring opening with the cleavage of N(1')–C(2') bond in the spiro compound **3**, giving the indole derivative **G**, b) intramolecular nucleophilic attack by amino group at the carbonyl carbon atom, followed by elimination of a water molecule and formation of final product **4** (Scheme 6).

Scheme 6



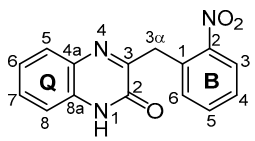
Thus, we have proposed an effective one-step method for the synthesis of 2-(indol-2-yl)benzimidazoles from 3-(2-nitrobenzyl)quinoxalin-2(1*H*)-ones. This method is based on the transformation of 3-(2-aminobenzyl)quinoxalin-2(1*H*)-ones, which are formed *in situ* by the action of $Na_2S_2O_4$, according to the scheme of the Mamedov rearrangement, including the formation of 1'*H*-spiro(indolino-2,2'-quinoxalin)-3'(4'*H*)-ones as a result of intramolecular nucleophilic addition of amine nitrogen atom at the imine C-3 carbon atom of quinoxalinone system. It is expected that the proposed method can serve as the synthetic basis for expanding the libraries of biheterocyclic systems of indole and benzimidazole series, which are applicable for the design of potential new medicinal compounds. The synthetic approaches to such systems are currently being developed at our laboratory.

Experimental

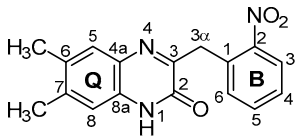
IR spectra in the range of 4000–400 cm^{-1} were recorded for KBr pellets on a Bruker Tensor 27 spectrometer with optical resolution of 4 cm^{-1} and accumulation of 64 scans. ^1H NMR spectra were acquired on Bruker Avance II 400 (400 MHz), Avance III 500 (500 MHz), or Avance 600 (600 MHz) spectrometers, while ^{13}C NMR spectra were acquired on a Bruker Avance III 500 spectrometer (125 MHz) in DMSO-d_6 solution, with the solvent signals as internal standards (2.5 ppm for ^1H nuclei, 39.5 ppm for ^{13}C nuclei). NMR experiments with compounds **1d**–**g**, **4a**,**c**–**h**, and **3c** were performed on a Bruker Avance III 500 spectrometer (^{15}N NMR at 51 MHz) at 303 K temperature in DMSO-d_6 solution. The spectrometer had a 5 mm two-channel gradient sensor with magnetic field pulse gradient of 53.5 G cm^{-1} in the z-direction. ^{15}N NMR chemical shifts are given in the δ scale relative to external standard – CD_3NO_2 (380.2 ppm for ^{15}N nuclei). The typical parameters for ^1H NMR spectra – spectral width 12020 Hz, pulse length (π/3) 3.7 μs, acquisition time 2 s, and relaxation delay 2 s. The following parameters were used for ^{13}C NMR spectra – spectral width 27 kHz, pulse length (π/3) 3.2 μs, acquisition time 1 s, and relaxation delay 4 s; WALTZ-16 scheme was used for broadband proton decoupling. The assignment of NMR signals was achieved by relying on a set of two-dimensional NMR experiments – COSY, ^1H–^{13}C gs-HSQC and gs-HMBC, as well as ^1H–^{15}N gs-HSQC and gs-HMBC. The two-dimensional NMR experiments were performed and processed by using the standard software suite provided for NMR spectrometers by Bruker. The main parameters for ^1H–^{13}C gs-HSQC and gs-HMBC spectra were the following: spectral width 8000 Hz for ^1H nuclei and 25 kHz for ^{13}C nuclei, the number of scans was 8 for the gs-HMQC spectra and 16 for the gs-HMBC spectra, and the relaxation delay was 3 s. ^1H–^{13}C HSQC spectra were optimized for $^1J_{CH}$ = 145 Hz, ^1H–^{13}C HMBC – for $^1J_{CH}$ = 145 and $^nJ_{CH}$ = 8 Hz. For the ^1H–^{15}N two-dimensional NMR spectra, the spectral width was 8000 Hz for ^1H nuclei, 10.5 kHz for ^{15}N nuclei in gs-HSQC experiments, 28 kHz for ^{15}N nuclei in gs-HMBC experiments with the number of scans equal to 8 (gs-HMQC) or 32 (gs-HMBC), and the relaxation delay was 23 s. ^1H–^{15}N HMBC spectra were optimized for $^1J_{NH}$ = 96 Hz and $^nJ_{NH}$ = 6 Hz. In gs-HSQC spectra, decoupling from the X-nuclei was achieved by GARP-modulation. Prior to the Fourier transform, the FID data were supplemented by zeroes along both axes to obtain a data array of 4024 × 2048 elements, using a weighting function with $\sin^2$ along both axes. MALDI mass spectra were recorded

on an UltraFlex III TOF/TOF mass spectrometer (Bruker Daltonik GmbH). In order to obtain mass spectra in high resolution mode and to determine the accurate mass values of molecular ions, the mass spectra were recorded in reflectron mode (resolution 10000) with the registration of positively charged ions while using a metallic target. The data were processed using the FlexAnalysis 3.0 program (Bruker Daltonik GmbH). 2,5-Dihydroxybenzoic acid (DHB) or *p*-nitroaniline (*p*-NA) were used as the matrix compounds. Mass spectra with accurate mass values were obtained by using a mixture consisting of the sample in DMF (5 mg/ml) and a reference compound in MeCN (1 mg/ml, PEG-400) in 1:5 ratio, followed by coating on the target and evaporation of 0.5 μl of matrix solution (10 mg/ml) in MeCN and 0.5 μl of the mixture. The indicated composition allowed to ensure that the absolute error of mass determination did not exceed 0.0030 amu. Melting points were determined in glass capillaries on an Electrothermal IA9200 apparatus.

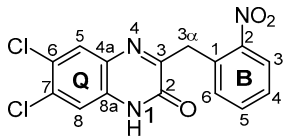
Synthesis of compounds 1a–h (General method). A solution of *o*-nitrotoluene (0.96 g, 7 mmol) and diethyl oxalate (5.11 g, 35 mmol) in toluene (20 ml) was stirred at 50°C and treated by the addition of *t*-BuOK (0.78 g, 7 mmol). The temperature was then increased to 100°C and stirring was continued for another 2 h. After the reaction was complete (the reaction progress was controlled by TLC (EtOAc–hexane, 1:1)), the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (10 ml) and extracted with toluene (3×50 ml). The combined organic layer was dried over $MgSO_4$, filtered, the solvent was evaporated under water aspirator vacuum, resulting in the isolation of crude product (7.15 g) containing 17.5% of ethyl *o*-nitrophenylpyruvate, 58.0% of diethyl oxalate, and 24.5% of toluene according to the data of ^{1}H NMR spectroscopy, pointing to the formation of the desired product **5** (1.25 g, 75%), which was not isolated from the mixture. A characteristic ^{1}H NMR feature for ethyl *o*-nitrophenylpyruvate **5** was the singlet of CH_2 group at 4.49 ppm, which was in agreement with the literature data.[30a] Part of the reaction mixture (2.7 g) containing compound **5** (0.47 g, 2 mmol) was dissolved in a 10:1 mixture of EtOH–AcOH, the appropriate 1,2-diaminobenzene **6** (2 mmol) was added, and the mixture was stirred at room temperature for 6 h. The precipitate that formed was filtered off, providing compounds **1a**–**h**.



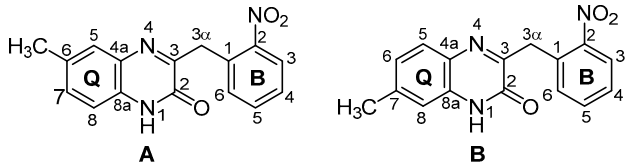
3-(2-Nitrobenzyl)quinoxalin-2(1*H*)-one (1a) was obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and *o*-phenylenediamine (**6a**) (0.22 g, 2 mmol). Yield 0.54 g (96%), beige powder, mp 232–234°C (mp 232–234°C[30b]). IR spectrum, ν, cm^{-1}: 3105, 2966, 2841, 1657, 1611, 1568, 1516, 1350, 1142, 1108, 902, 861, 948, 756, 723, 703, 687, 595. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 4.53 (2H, s, 3α-CH_2); 7.21 (1H, ddd, *J* = 7.7, *J* = 7.5, *J* = 1.1, H-6 Q); 7.29 (1H, d, *J* = 7.9, H-8 Q); 7.44–7.48 (2H, m, H-5,7 Q); 7.54–7.59 (2H, m, H-4,6 B); 7.70 (1H, ddd, *J* = 8.1, *J* = 5.7, *J* = 1.2, H-5 B); 8.05 (1H, dd, *J* = 6.7, *J* = 1.0, H-3 B); 12.44 (1H, s, NH). Found, *m*/*z*: 413.9837 $[M+Cs]^+$. $C_{15}H_{11}CsN_3O_3$. Calculated, *m*/*z*: 413.9849.



6,7-Dimethyl-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1b) was obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 4,5-dimethyl-*o*-phenylenediamine (**6b**) (0.27 g, 2 mmol). Yield 0.57 g (92%), pink powder, mp 274–275°C (mp 215–217°C[30c]). IR spectrum, ν, cm^{-1}: 3445, 3154, 2918, 2866, 2792, 1655, 1630, 1556, 1520, 1496, 1444, 1358, 1208, 1003, 934, 859, 796, 737, 724, 594. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.20 (3H, s, CH_3); 2.27 (3H, s, CH_3); 4.50 (2H, s, 3α-CH_2); 7.04 (1H, s, H-5 Q); 7.23 (1H, s, H-8 Q); 7.54–7.58 (2H, m, H-4,6 B); 7.70 (1H, ddd, *J* = 8.1, *J* = 7.0, *J* = 1.1, H-5 B); 8.05 (1H, d, *J* = 8.4, H-3 B); 12.29 (1H, s, NH). Found, *m*/*z*: 442.0161 $[M+Cs]^+$. $C_{17}H_{15}CsN_3O_3$. Calculated, *m*/*z*: 442.0162.



6,7-Dichloro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1c) was obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 4,5-dichloro-*o*-phenylenediamine (**6c**) (0.35 g, 2 mmol). Yield 0.67 g (96%), beige powder, mp 271–272°C. IR spectrum, ν, cm^{-1}: 3144, 3044, 2977, 2888, 2809, 1665, 1607, 1562, 1526, 1467, 1384, 1361, 1274, 1203, 1117, 914, 886, 859, 789, 730. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 4.53 (2H, s, 3α-CH_2); 7.44 (1H, br. s, H-5(8) Q); 7.55–7.59 (2H, m, H-4,6 B); 7.68 (1H, br. s, H-8(5)); 7.71 (1H, dd, *J* = 7.7, *J* = 7.4, H-5 B); 8.07 (1H, br. d, *J* = 8.2, H-3 B); 12.59 (1H, s, NH). Found, *m*/*z*: 371.9902 $[M(^{35}Cl)+Na]^+$. $C_{15}H_9Cl_2N_3NaO_3$. Calculated, *m*/*z*: 371.9913. Found, *m*/*z*: 373.9877 $[M(^{37}Cl)+Na]^+$. $C_{15}H_9Cl_2N_3NaO_3$. Calculated, *m*/*z*: 373.9886.

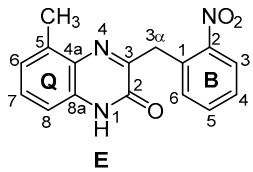


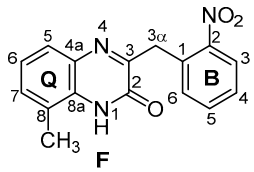
A **B**

6-Methyl-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1dA) and 7-methyl-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1dB)

(53:47 mixture of isomers) was obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 3,4-diaminotoluene (**6d**) (0.24 g, 2 mmol). The overall yield was 0.42 g (71%), light-pink powder, mp 225–226°C. IR spectrum, ν, cm^{-1}: 3307, 2922, 2861, 1660, 1624, 1556, 1524, 1400, 1338, 1318, 1271, 1164, 896, 862, 816, 796, 731, 671. Regioisomer **A** (53%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 4.53 (2H, s, 3α-CH_2); 7.18 (1H, d, *J* = 8.1, H-8 Q); 7.26 (1H, s, H-5 Q); 7.29 (1H, dd, *J* = 8.1, *J* = 1.3, H-7 Q); 7.55–7.57 (1H, m, H-4 B); 7.56–7.58 (1H, m, H-6 B); 7.70–7.72 (1H, m, H-5 B); 8.04 (1H, dd, *J* = 7.5, *J* = 1.1, H-3 B); 12.36 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm 158.6 (C-3 Q); 154.1 (C-2 Q); 149.3 (C-2 B); 133.4 (C-5 B); 133.4 (C-6 B); 132.6 (C-6 Q); 132.1 (C-1 B); 131.1 (C-4a Q); 130.8 (C-7 Q); 129.4 (C-8a Q); 128.1 (C-4 B); 127.7 (C-5 Q); 124.5 (C-3 B); 115.0 (C-8 Q); 36.6 (3α-C); 20.1 (CH_3). ^{15}N NMR spectrum (51 MHz), δ, ppm: 149.8 (N-1 Q); 324.6 (N-4 Q); 376.5 (NO_2 B).

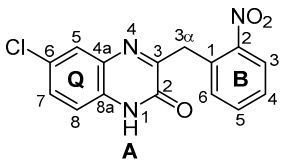
Regioisomer **B** (47%): ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3); 4.51 (2H, s, 3α-CH_2); 7.02 (1H, dd, *J* = 8.2, *J* = 1.3, H-6 Q); 7.06 (1H, s, H-8 Q); 7.34 (1H, d, *J* = 8.2, H-5 Q); 7.54–7.56 (1H, m, H-4 B); 7.57–7.59 (1H, m, H-6 B); 7.70–7.72 (1H, m, H-5 B); 8.04 (1H, dd, *J* = 7.5, *J* = 1.1, H-3 B); 12.36 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 157.4 (C-3 Q); 154.3 (C-2 Q); 149.4 (C-2 B); 139.8 (C-7 Q); 133.4 (C-5 B); 133.3 (C-6 B); 132.0 (C-1 B); 131.6 (C-8a Q); 129.4 (C-4a Q); 128.1 (C-4 B); 127.8 (C-5 Q); 124.5 (C-3 B); 124.4 (C-6 Q); 114.9 (C-8 Q); 36.4 (3α-C); 21.1 (CH_3). ^{15}N NMR spectrum (51 MHz), δ, ppm: 149.2 (N-1 Q); 324.7 (N-4 Q); 376.5 (NO_2 B). Found, *m*/*z*: 428.0014 $[M+Cs]^+$. $C_{16}H_{13}CsN_3O_3$. Calculated, *m*/*z*: 428.0006.

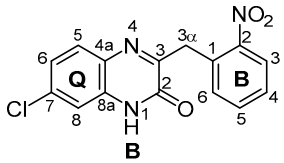




5-Methyl-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1eE) and 8-methyl-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1eF) (72:28 mixture of isomers) were obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 2,3-diaminotoluene (**6e**) (0.24 g, 2 mmol). The overall yield 0.30 g (51%), light-brown powder, mp 203–204°C. IR spectrum, ν, cm^{-1}: 3437, 3103, 2976, 2921, 2849, 1665, 1610, 1524, 1355, 1130, 866, 787, 778, 706, 666, 543. Regioisomer **E** (72%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.20 (3H, s, CH_3); 4.57 (2H, s, 3α-CH_2); 7.05 (1H, d, *J* = 7.1, H-6 Q); 7.11 (1H, d, *J* = 7.1, H-8 Q); 7.33 (1H, d, *J* = 7.1, H-7 Q); 7.55–7.57 (1H, m, H-6 B); 7.57–7.59 (1H, m, H-4 B); 7.69–7.71 (1H, m, H-5 B); 8.08 (1H, dd, *J* = 7.5, *J* = 1.1, H-3 B); 12.38 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 156.5 (C-3 Q); 154.2 (C-2 Q); 149.7 (C-2 B); 136.2 (C-4a Q); 133.4 (C-4 B); 133.4 (C-5 B); 131.9 (C-1 B); 131.7 (C-8a Q); 129.6 (C-5 Q); 129.5 (C-7 Q); 128.1 (C-6 B); 124.4 (C-3 B); 124.0 (C-6 Q); 113.1 (C-8 Q); 37.0 (3α-C); 16.1 (CH_3). ^{15}N NMR spectrum (51 MHz), δ, ppm: 149.3 (N-1 Q); 321.7 (N-4 Q); 376.6 (NO_2 B).

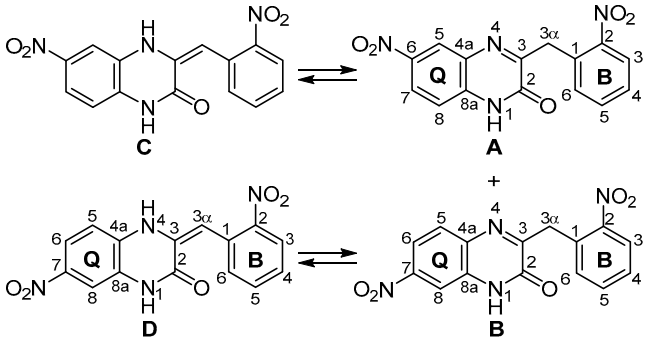
Regioisomer **F** (28%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 4.55 (2H, s, 3α-CH_2); 7.09–7.11 (1H, m, H-6 Q); 7.29 (1H, d, *J* = 8.0, H-5 Q); 7.30 (1H, d, *J* = 8.0, H-7 Q); 7.56–7.58 (1H, m, H-6 B); 7.58–7.60 (1H, m, H-4 B); 7.71–7.73 (1H, m, H-5 B); 8.06 (1H, dd, *J* = 7.8, *J* = 1.3, H-3 B); 11.78 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 158.2 (C-3 Q); 154.7 (C-2 Q); 149.4 (C-2 B); 143.9 (C-4a Q); 133.4 (C-4 B); 133.3 (C-5 B); 131.9 (C-1 B); 131.3 (C-8 Q); 130.8 (C-7 Q); 128.6 (C-6 B); 126.1 (C-5 Q); 124.5 (C-3 B); 124.0 (C-8a Q); 122.7 (C-6 Q); 36.5 (3α-C); 16.7 (CH_3). ^{15}N NMR spectrum (51 MHz), δ, ppm: 149.3 (N-1 Q); 325.9 (N-4 Q); 376.5 (NO_2 B). Found, *m*/*z*: 428.0020 $[M+Cs]^+$. $C_{16}H_{13}CsN_3O_3$. Calculated, *m*/*z*: 428.0006.





6-Chloro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1fA) and 7-chloro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1fB) (58:42 mixture of isomers) were obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 4-chloro-*o*-phenylenediamine (**6f**) (0.29 g, 2 mmol). The overall yield 0.56 g (88%), dark-pink powder, mp 248–249°C. IR spectrum, ν, cm^{-1}: 3442, 2989, 2918, 2833, 1667, 1612, 1522, 1485, 1344, 1310, 1116, 1079, 946, 862, 822, 726, 564. Regioisomer **A** (58%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 4.54 (2H, s, 3α-CH_2); 7.29 (1H, d, *J* = 8.9, H-8 Q); 7.46 (1H, d, *J* = 2.3, H-5 Q); 7.51 (1H, dd, *J* = 8.9, *J* = 2.3, H-7 Q); 7.55–7.57 (1H, m, H-4 B); 7.58–7.60 (1H, m, H-6 B); 7.69–7.71 (1H, m, H-5 B); 8.06 (1H, d, *J* = 7.5, H-3 B); 12.57 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 160.4 (C-3 Q); 154.0 (C-2 Q); 149.3 (C-2 B); 133.5 (C-5 B); 133.4 (C-6 B); 131.7 (C-1 B); 130.6 (C-4a Q); 130.7 (C-8a Q); 129.6 (C-7 Q); 128.3 (C-4 B); 127.0 (C-5 Q); 126.8 (C-6 Q); 124.6 (C-3 B); 117.0 (C-8 Q); 36.7 (3α-C). ^{15}N NMR spectrum (51 MHz), δ, ppm: 148.5 (N-1 Q); 321.5 (N-4 Q); 377.0 (NO_2 B).

Regioisomer **B** (42%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 4.52 (2H, s, 3α-CH_2); 7.21 (1H, dd, *J* = 8.8, *J* = 2.3, H-6 Q); 7.28 (1H, s, H-8 Q); 7.45 (1H, d, *J* = 8.8, H-5 Q); 7.55–7.57 (1H, m, H-4 B); 7.58–7.60 (1H, m, H-6 B); 7.69–7.71 (1H, m, H-5 B); 8.06 (1H, d, *J* = 7.5, H-3 B); 12.51 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 159.3 (C-3 Q); 154.0 (C-2 Q); 149.3 (C-2 B); 133.7 (C-7 Q); 133.5 (C-5 B); 133.4 (C-6 B); 131.8 (C-8a Q); 131.7 (C-1 B); 129.9 (C-4a Q); 129.7 (C-5 Q); 128.2 (C-4 B); 124.6 (C-3 B); 123.2 (C-6 Q); 114.6 (C-8 Q); 36.6 (3α-C). ^{15}N NMR spectrum (51 MHz), δ, ppm: 148.3 (N-1 Q); 322.3 (N-4 Q); 377.0 (NO_2 B). Found, *m*/*z*: 447.9461 $[M(^{35}Cl)+Cs]^+$. $C_{15}H_{10}ClCsN_3O_3$. Calculated, *m*/*z*: 447.9460.

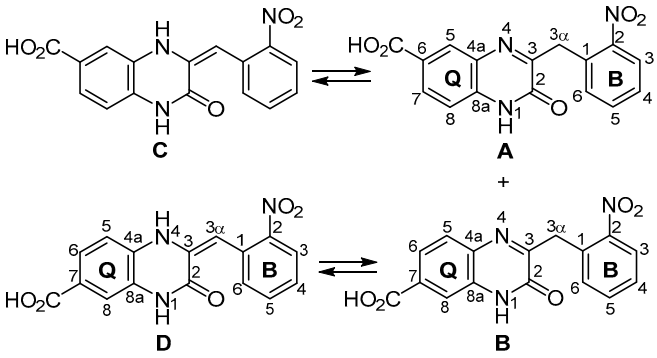


7-Nitro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1gB), 6-nitro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (1gA), (3*E*)-7-nitro-3-(2-nitrobenzylidene)-3,4-dihydroquinoxalin-2(1*H*)-one (1gD), (3*E*)-6-nitro-3-(2-nitrobenzylidene)-3,4-dihydroquinoxalin-2(1*H*)-one (1gC) (45:25:30 mixture of isomers, tautomer C was present in trace amounts) were obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 4-nitro-*o*-phenylenediamine (**6g**) (0.31 g, 2 mmol). The overall yield 0.54 g (82%), light-orange powder, mp 225–227°C. IR spectrum, ν, cm^{-1}: 3083, 2932, 2858, 2807, 1669 (br), 1614, 1573, 1525, 1414, 1402, 1342, 1141, 1112, 1087, 1078, 922, 886, 865, 845, 790, 738, 723, 714.

Regioisomer **B** (45%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 4.59 (2H, s, 3α-CH_2); 7.58–7.60 (1H, m, H-4 B); 7.59–7.61 (1H, m, H-6 B); 7.65 (1H, d, *J* = 8.8, H-5 Q); 7.75–7.77 (1H, m, H-5 B); 7.96 (1H, dd, *J* = 8.8, *J* = 1.9, H-6 Q); 8.07–8.09 (1H, m, H-3 B); 8.09–8.10 (1H, m, H-8 Q); 12.78 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 163.1 (C-2 Q); 153.9 (C-3 Q); 149.2 (C-2 B); 146.8 (C-7 Q); 134.6 (C-4a Q); 133.6 (C-5 B); 133.6 (C-6 B); 132.1 (C-8a Q); 131.4 (C-1 B); 129.4 (C-5 Q); 128.4 (C-4 B); 124.7 (C-3 B); 117.4 (C-6 Q); 110.9 (C-8 Q); 37.0 (3α-C). ^{15}N NMR spectrum (51 MHz), δ, ppm: 149.2 (N-1 Q); 319.7 (N-4 Q); 375.9 (NO_2 B).

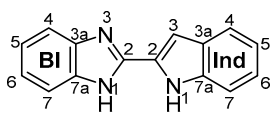
Regioisomer **A** (25%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 4.57 (2H, s, 3α-CH_2); 7.44 (1H, d, *J* = 9.1, H-8 Q); 7.58–7.60 (1H, m, H-4 B); 7.59–7.61 (1H, m, H-6 B); 7.74–7.76 (1H, m, H-5 B); 8.07–8.09 (1H, m, H-3 B); 8.15 (1H, d, *J* = 2.5, H-5 Q); 8.30 (1H, dd, *J* = 9.1, *J* = 2.5, H-7 Q); 12.96 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 161.7 (C-2 Q); 154.2 (C-3 Q); 149.3 (C-2 B); 142.8 (C-4a Q); 137.0 (C-8a Q); 133.7 (C-5 B); 133.5 (C-6 B); 131.3 (C-1 B); 130.0 (C-6 Q); 128.1 (C-4 B); 124.7 (C-3 B); 124.4 (C-7 Q); 123.4 (C-5 Q); 116.8 (C-8 Q); 36.7 (3α-C). ^{15}N NMR spectrum (51 MHz), δ, ppm: 151.5 (N-1 Q); 321.2 (N-4 Q); 375.9 (NO_2 B).

Regioisomer **D** (30%). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 6.62 (1H, s, 3α-CH); 7.09 (1H, d, *J* = 8.9, H-5 Q); 7.53–7.55 (1H, m, H-4 B); 7.75 (1H, s, H-8 Q); 7.76 (1H, ddd, *J* = 7.3, *J* = 7.3, *J* = 1.1, H-5 B); 7.81 (1H, d, *J* = 7.3, H-6 B); 7.81 (1H, d, *J* = 8.9, H-6 Q); 8.07–8.09 (1H, m, H-3 B); 10.16 (1H, s, 4-NH Q); 11.41 (1H, s, 1-NH Q). ^{13}C NMR spectrum, δ, ppm: 157.3 (C-2 Q); 147.8 (C-2 B); 139.2 (C-7 Q); 134.2 (C-4a Q); 133.6 (C-5 B); 130.8 (C-6 B); 130.6 (C-2 Q); 129.6 (C-1 B); 128.1 (C-4 B); 125.1 (C-8a Q); 124.7 (C-3 B); 119.6 (C-6 Q); 113.3 C-5 Q); 109.8 (C-8 Q); 100.6 (3α-C). ^{15}N NMR spectrum (51 MHz), δ, ppm: 104.5 (N-4 Q); 134.1 (N-1 Q); 368.0 (NO_2 B). Found, *m*/*z*: 349.0534 $[M+Na]^+$. $C_{15}H_{10}N_4NaO_5$. Calculated, *m*/*z*: 349.0543.



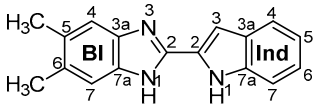
2-(2-Nitrobenzyl)-3-oxo-3,4-dihydroquinoxaline-6-carboxylic acid (1hB), 3-(2-nitrobenzyl)-2-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (1hA), (3*E*)-2-(2-nitrobenzylidene)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (1hD), (3*E*)-3-(2-nitrobenzylidene)-2-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (1hC) (58:37:5 mixture of isomers, tautomer C was present in trace amounts) were obtained from ethyl *o*-nitrophenylpyruvate **5** (0.47 g, 2 mmol) and 3,4-diaminobenzoic acid (**6h**) (0.30 g, 2 mmol). The overall yield 0.56 g (86%), beige powder, mp 278–279°C. IR spectrum, ν, cm^{-1}: 3069, 2846, 1694, 1665, 1612, 1561, 1525, 1428, 1415, 1344, 1302, 1277, 1139, 1116, 927, 856, 787, 770, 757, 724, 710, 611. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 4.55 (2H, s, 3α-CH_2 A); 4.56 (2H, s, 3α-CH_2 B); 6.51 (1H, s, 3α-CH_2 D); 7.05 (1H, d, *J* = 8.5, H-5 Q D); 7.34 (1H, d, *J* = 8.5, H-8 Q A); 7.51 (1H, d, *J* = 8.5, H-5 Q B); 7.46–7.59 (6H, m); 7.69–7.72 (4H, m); 7.82 (1H, d, *J* = 7.7, H-6 Q B or H-6 Q D); 7.89 (1H, d, *J* = 1.4, H-8 Q B); 7.92 (1H, d, *J* = 1.7, H-5 Q A); 7.98 (1H, dd, *J* = 8.5, *J* = 1.8, H-7 Q A); 8.02–8.07 (4H, m); 9.83 (1H, s, H-4 Q D); 11.25 (1H, s, NH D); 12.59 (1H, s, NH B); 12.70 (1H, s, NH A). Found, *m*/*z*: 457.9736 $[M+Cs]^+$. $C_{16}H_{11}CsN_3O_5$. Calculated, *m*/*z*: 457.9748.

Synthesis of compounds 4a–h (General method). A solution of compound **1** (2 mmol) in a mixture of EtOH (5 ml) and H_2O (5 ml) was stirred and treated by the addition of $Na_2S_2O_4$ (8 mmol), then refluxed for 3 h and treated with with another 4 mmol of $Na_2S_2O_4$. Refluxing was then continued for additional 3 h. The reaction mixture was quenched with 20% HCl solution (10 ml) and refluxed for additional 3 h, then left overnight. The reaction mixture was poured into H_2O (100 ml), the crystals that precipitated were seperated by filtration after 4 h, and recrystallized from EtOH if necessary.

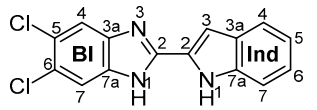


2-(1*H*-Indol-2-yl)-1*H*-benzimidazole (4a). Yield 0.46 g (98%), light-orange powder, mp 282–283°C (mp 328–329°C[35a], 160–162°C[35b]). ^{1}H NMR spectrum (500 MHz), δ, ppm

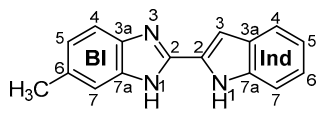
(*J*, Hz): 7.17 (1H, ddd, *J* = 7.2, *J* = 7.2, *J* = 0.9, H-5 Ind); 7.35 (1H, ddd, *J* = 7.5, *J* = 6.7, *J* = 0.9, H-6 Ind); 7.53–7.54 (2H, m, H-5,6 BI); 7.58 (1H, dd, *J* = 7.8, *J* = 1.0, H-7 Ind); 7.74 (1H, d, *J* = 1.0, H-3 Ind); 7.78 (1H, d, *J* = 7.8, H-4 Ind); 7.81–7.82 (2H, m, H-4,7 BI); 12.46 (1H, s, Ind). ^{13}C NMR spectrum, δ, ppm: 143.0 (C-2 BI); 137.9 (C-7a Ind); 131.9 (C-3a,7a BI); 127.1 (C-3a Ind); 125.6 (C-5,6 BI); 125.5 (C-6 Ind); 122.0 (C-4 Ind); 121.4 (C-2 Ind); 121.0 (C-5 Ind); 113.7 (2C, C-4,7 BI); 112.3 (C-7 Ind); 108.2 (C-3 Ind). ^{15}N NMR spectrum (51 MHz), δ, ppm: 133.9 (N-1 Ind). Found, *m*/*z*: 234.1025 $[M+H]^+$. $C_{15}H_{11}N_3$. Calculated, *m*/*z*: 234.1026.



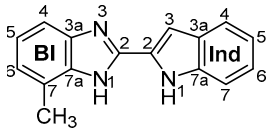
2-(1*H*-Indol-2-yl)-5,6-dimethyl-1*H*-benzimidazole (4b). Yield 0.45 g (86%), light-red powder, mp 236–238°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 2.26 (6H, s, CH_3); 7.08 (1H, dd, *J* = 7.3, *J* = 7.2, H-5 Ind); 7.22 (1H, s, H-4(7) BI); 7.24 (1H, dd, *J* = 8.2, *J* = 7.2, H-6 Ind); 7.39 (1H, s, H-4(7) BI); 7.49 (1H, d, *J* = 8.1, H-7 Ind); 7.57 (1H, s, H-3 Ind); 7.68 (1H, d, *J* = 8.1, H-4 Ind); 10.48 (1H, s, NH BI); 11.77 (1H, s, NH Ind). Found, *m*/*z*: 262.1330 $[M+H]^+$. $C_{17}H_{15}N_3$. Calculated, *m*/*z*: 262.1339.



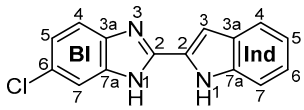
5,6-Dichloro-2-(-1*H*-indol-2-yl)-1*H*-benzimidazole (4c). Yield 0.53 g (88%), orange powder, mp >370°C. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 7.07 (1H, ddd, *J* = 7.5, *J* = 7.2, *J* = 0.9, H-5 Ind); 7.21 (1H, ddd, *J* = 7.9, *J* = 7.5, *J* = 0.9, H-6 Ind); 7.32 (1H, d, *J* = 1.4, H-3 Ind); 7.48 (1H, d, *J* = 7.9, H-7 Ind); 7.66 (1H, d, *J* = 8.1, H-4 Ind); 7.86 (2H, s, H-4,7 BI); 12.048 (1H, s, NH Ind). ^{13}C NMR spectrum, δ, ppm: 142.3 (C-2 BI); 138.2 (C-3a,7a BI); 137.5 (C-7a Ind); 127.6 (C-3a Ind); 126.9 (C-2 Ind); 124.8 (C-5,6 BI); 123.5 (C-6 Ind); 121.1 (C-4 Ind); 120.0 (C-5 Ind); 115.9 (C-4,7 BI); 112.1 (C-7 Ind); 103.5 (C-3 Ind). ^{15}N NMR spectrum (51 MHz), δ, ppm: 134.2 (N-1 Ind). Found, *m*/*z*: 302.0248 $[M(^{35}Cl)+H]^+$. $C_{15}H_9Cl_2N_3$. Calculated, *m*/*z*: 302.0246. Found, *m*/*z*: 304.0225 $[M(^{37}Cl)+H]^+$. $C_{15}H_9Cl_2N_3$. Calculated, *m*/*z*: 304.0219.



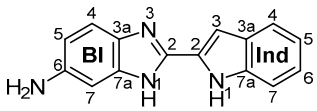
2-(1*H*-Indol-2-yl)-6-methyl-1*H*-benzimidazole (4d). Yield 0.47 g (96%), orange powder, mp 254–256°C (mp 148–150°C[35b]). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.50 (3H, s, CH_3); 7.17 (1H, ddd, *J* = 7.1, *J* = 6.9, *J* = 1.1, H-5 Ind); 7.34 (1H, ddd, *J* = 7.5, *J* = 7.5, *J* = 1.1, H-6 Ind); 7.35 (1H, d, *J* = 8.1, H-5 BI); 7.57 (1H, dd, *J* = 8.2, *J* = 1.1, H-7 Ind); 7.60 (1H, s, H-7 BI); 7.68 (1H, d, *J* = 8.2, H-4 BI); 7.69 (1H, s, H-3 Ind); 7.77 (1H, d, *J* = 7.8, H-4 Ind); 12.42 (1H, s, NH Ind). ^{13}C NMR spectrum, δ, ppm: 142.7 (C-2 BI); 137.8 (C-7a Ind); 135.5 (C-6 BI); 132.3 (C-7a BI); 130.2 (C-3a BI); 127.1 (C-5 BI); 127.0 (C-3a Ind); 125.3 (C-6 Ind); 121.9 (C-4 Ind); 121.8 (C-2 Ind); 120.9 (C-5 Ind); 113.4 (C-4 BI); 113.2 (C-7 BI); 112.3 (C-7 Ind); 107.7 (C-3 Ind); 21.1 (CH_3). ^{15}N NMR spectrum (51 MHz), δ, ppm: 134.5 (N-1 Ind). Found, *m*/*z*: 248.1175 $[M+H]^+$. $C_{16}H_{13}N_3$. Calculated, *m*/*z*: 248.1182.



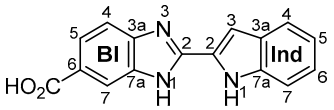
2-(1*H*-Indol-2-yl)-7-methyl-1*H*-benzimidazole (4e). Yield 0.83 g (68%), black powder, mp 242–244°C. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.68 (3H, s, CH_3); 7.17 (1H, dd, *J* = 7.7, *J* = 7.2, H-5 Ind); 7.32 (1H, d, *J* = 7.7, H-6 BI); 7.35 (1H, dd, *J* = 7.7, *J* = 7.3, H-6 Ind); 7.42 (1H, dd, *J* = 7.9, *J* = 7.8, H-5 BI); 7.58 (1H, d, *J* = 8.0, H-7 Ind); 7.61 (1H, d, *J* = 8.0, H-4 BI); 7.75 (1H, s, H-3 Ind); 7.78 (1H, d, *J* = 7.8, H-4 Ind); 12.56 (1H, s, NH Ind); 14.93 (1H, s, NH BI). ^{13}C NMR spectrum, δ, ppm: 142.8 (C-2 BI); 137.8 (C-7a Ind); 131.8 (C-3a BI); 131.6 (C-7a BI); 127.1 (C-3a Ind); 126.0 (C-6 BI); 125.7 (C-5 BI); 125.5 (C-6 Ind); 124.2 (C-7 BI); 122.0 (C-4 Ind); 121.6 (C-2 Ind); 121.0 (C-5 Ind); 112.3 (C-7 Ind); 110.9 (C-4 BI); 108.0 (C-3 Ind); 16.8 (CH_3). ^{15}N NMR spectrum (51 MHz), δ, ppm: 132.8 (N-1 Ind). Found, *m*/*z*: 248.1186 $[M+H]^+$. $C_{16}H_{13}N_3$. Calculated, *m*/*z*: 248.1182.



6-Chloro-2-(1*H*-indol-2-yl)-1*H*-benzimidazole (4f). Yield 0.41 g (76%), brownish-green powder, mp 290–292 C (mp 198–200°C[35b]). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.14 (1H, ddd, *J* = 7.3, *J* = 7.2, *J* = 1.0, H-5 Ind); 7.31 (1H, ddd, *J* = 7.9, *J* = 7.2, *J* = 1.0, H-6 Ind); 7.46 (1H, dd, *J* = 8.6, *J* = 1.9, H-5 BI); 7.55 (1H, dd, *J* = 8.2, *J* = 1.0, H-7 Ind); 7.66 (1H, s, H-3 Ind); 7.74 (1H, d, *J* = 7.8, H-4 Ind); 7.76 (1H, d, *J* = 8.4, H-4 BI); 7.81 (1H, d, *J* = 1.9, H-7 BI); 12.37 (1H, s, NH Ind). ^{13}C NMR spectrum, δ, ppm: 144.9 (C-2 BI); 137.8 (C-7a Ind); 134.7 (C-6 BI); 132.5 (C-7a BI); 129.0 (C-3a BI); 127.2 (C-3a Ind); 125.1 (C-6 Ind); 125.0 (C-5 BI); 122.0 (C-2 Ind); 121.8 (C-4 Ind); 120.8 (C-5 Ind); 115.0 (C-4 BI); 113.7 (C-7 BI); 112.3 (C-7 Ind); 107.2 (C-3 Ind). ^{15}N NMR spectrum (51 MHz), δ, ppm: 133.9 (N-1 Ind). Found, *m*/*z*: 268.0631 $[M(^{35}Cl)+H]^+$. $C_{15}H_{10}ClN_3$. Calculated, *m*/*z*: 268.0636.



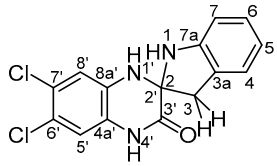
6-Amino-2-(1*H*-indol-2-yl)-1*H*-benzimidazole (4g). Yield 0.36 g (72%), dark-brown powder, 224–228°C. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 7.15 (1H, ddd, *J* = 7.3, *J* = 6.9, *J* = 0.9, H-5 Ind); 7.32 (1H, ddd, *J* = 7.1, *J* = 6.9, *J* = 0.9, H-6 Ind); 7.41 (1H, d, *J* = 8.4, H-4 BI); 7.54 (1H, dd, *J* = 7.8, *J* = 0.9, H-7 Ind); 7.70 (1H, s, H-3 Ind); 7.75 (1H, dd, *J* = 7.5, *J* = 0.9, H-4 Ind); 7.76 (1H, s, H-7 BI); 7.82 (1H, d, *J* = 8.6, H-5 BI); 12.43 (1H, s, NH Ind). ^{13}C NMR spectrum, δ, ppm: 144.5 (C-2 BI); 137.8 (C-7a Ind); 133.6 (C-6 BI); 133.6 (C-7a BI); 130.8 (C-3a BI); 127.2 (C-3a Ind); 125.2 (C-6 Ind); 122.5 (C-2 Ind); 121.8 (C-4 Ind); 120.9 (C-5 Ind); 119.6 (C-4 BI); 114.9 (C-5 BI); 112.3 (C-7 Ind); 107.5 (C-3 Ind); 107.4 (C-7 BI). ^{15}N NMR spectrum (51 MHz), δ, ppm: 55.3 (N-1 BI); 133.9 (N-1 Ind). Found, *m*/*z*: 249.1134 $[M+H]^+$. $C_{15}H_{12}N_4$. Calculated, *m*/*z*: 249.1135.



2-(1*H*-Indol-2-yl)-1*H*-benzimidazole-6-carboxylic acid (4h). Yield 0.40 g (72%), orange powder, mp 299–301°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.14 (1H, ddd, *J* = 7.3, *J* = 7.2, *J* = 0.9, H-5 Ind); 7.31 (1H, ddd, *J* = 7.8, *J* = 7.0, *J* = 0.9, H-6 Ind); 7.56 (1H, dd, *J* = 7.8, *J* = 0.9, H-7 Ind); 7.62 (1H, s, H-3 Ind); 7.75 (1H, dd, *J* = 7.6, *J* = 0.9, H-4 Ind); 7.81 (1H, d, *J* = 8.4, H-4 BI); 8.03 (1H, dd, *J* = 8.6, *J* = 1.5, H-5 BI); 8.26 (1H, d, *J* = 8.5, H-7 BI); 12.31 (1H, s, NH Ind). ^{13}C NMR spectrum, δ, ppm: 167.0 (CO_2H BI); 146.1 (C-2 BI); 137.9 (C-7a Ind); 137.3 (C-3a BI); 134.4 (C-7a BI); 127.3 (C-3a Ind); 126.8 (C-6 BI); 125.6 (C-5 BI); 124.9 (C-6 Ind); 123.5 (C-2 Ind); 121.7 (C-4 Ind); 120.7 (C-5 Ind); 115.6 (C-7 BI); 113.9 (C-4 BI); 112.3 (C-7 Ind); 106.9 (C-3 Ind). ^{15}N NMR spectrum (51 MHz), δ, ppm: 132.9 (N-1 Ind). Found, *m*/*z*: 278.0915 $[M+H]^+$. $C_{16}H_{11}N_3O_2$. Calculated, *m*/*z*: 278.0924.

Synthesis of compounds 2c and 3c. A solution of compound **1c** (2 mmol) in a mixture of EtOH (5 ml) and H_2O (5 ml) was stirred and treated by the addition of $Na_2S_2O_4$ (12 mmol) in tree portions at 3 h intervals. The reaction mixture was filtered, the filtrate was evaporated under water aspirator vacuum, washed with a saturated aqueous NaCl solution, and extracted with EtOAc. The organic layer was collected, dried over Na_2SO_4, and evaporated, providing compound **2c**. The collected precipitate was washed with a large amount (5×50 ml) of aqueous sodium carbonate solution (pH 9). The crystals that precipitated in the filtrate were filtered off, giving a mixture of compounds **2c** and **3c** in the ratio of 64:36 according to the data of ^{1}H NMR spectroscopy. The overall yield 0.23 g (36%), light-yellow powder, mp 216–219°C. IR spectrum of the mixture, ν, cm^{-1}: 3403, 3330, 3037, 2987, 2894, 2818, 1667 (sh), 1608, 1563. 1527, 1464, 1385, 1345, 1123, 909, 753.

3-(2-Aminobenzyl)-6,7-dichloroquinoxalin-2(1*H*)-one (2c). Yield 0.29 g (45%), light-yellow powder, mp 247–248°C. IR spectrum, ν, cm^{-1}: 3443, 3331, 3024, 2900, 2830, 1665, 1611, 1560, 1457, 1374, 1351, 1210, 1157, 1025, 857, 751. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 3.97 (2H, s, CH_2); 6.72 (1H, dd, *J* = 7.4, *J* = 7.4); 7.05 (1H, dd, *J* = 8.4, *J* = 7.4); 7.16 (1H, d, *J* = 7.7); 7.44 (1H, c); 7.48 (1H, d, *J* = 8.4); 7.90 (1H, c); 12.57 (1H, s, NH).



1',4'-Dihydro-6',7'-dichloro-3'*H*-spiro(indolin-2,2'-quinoxalin)-3'-one (3c). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.92 (1H, d, *J* = 16.8, 3-CH_2); 3.89 (1H, d, *J* = 16.8, 3-CH_2); 6.37 (1H, d, *J* = 7.3, H-7); 6.59 (1H, ddd, *J* = 7.4, *J* = 7.4, *J* = 1.0, H-5); 6.93 (1H, s, H-8'); 6.94 (1H, dd, *J* = 7.3, *J* = 7.4, H-6); 6.99 (1H, s, H-5'); 7.07 (1H, d, *J* = 7.3, H-4); 7.52 (1H, s, 1'-NH); 10.76 (1H, s, 4'-NH). ^{13}C NMR spectrum, δ, ppm: 164.4 (3'-C); 148.0 (C-7a); 132.5 (C-8a'); 127.4 (C-6); 126.0 (C-4a'); 125.1 (C-3a); 123.9 (C-4); 120.0 (C-7'); 119.2 (C-6'); 117.5 (C-5); 115.4 (C-5'); 115.0 (C-8'); 107.4 (C-7); 75.7 (2-C/2'-C); 38.9 (3-C). ^{15}N NMR spectrum (51 MHz), δ, ppm: 88.9 (N-1'); 129.3 (N-4').

5,6-Dichloro-2-(-1*H*-indol-2-yl)-1*H*-benzimidazole (4c). A solution of compound **2c** (0.1 g, 0.3 mmol) or a mixture of compounds **2c** and **3c** (obtained according to the procedure described above) in *n*-BuOH (5 ml) was stirred and treated with 2 drops of concentrated H_2SO_4 and then refluxed for 5 h. The solvent was then evaporated under water aspirator vacuum; the resulting viscous, partially crystalline residue was washed with aqueous 5% $NaHCO_3$ solution (50 ml). The crystals that precipitated were filtered off, washed with water (3×10 ml), and air-dried, providing compound **4c** (0.09 g, 96%). The spectral data were identical to those of sample obtained from 6,7-dichloro-3-(2-nitrobenzyl)quinoxalin-2(1*H*)-one (**1c**). In the case when a mixture of compounds **2c** and **3c** was used, the yield of product **4c** was 98%.

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