

# Polyfused Nitrogen Heterocycles: XIX.\* Oxidative Imidazo-Fusion of 3-Benzoylquinoxalin-2-ones with Benzylamines in the Synthesis of Bis(imidazo[1,5-a]quinoxalin-1- and -5-yl) Derivatives

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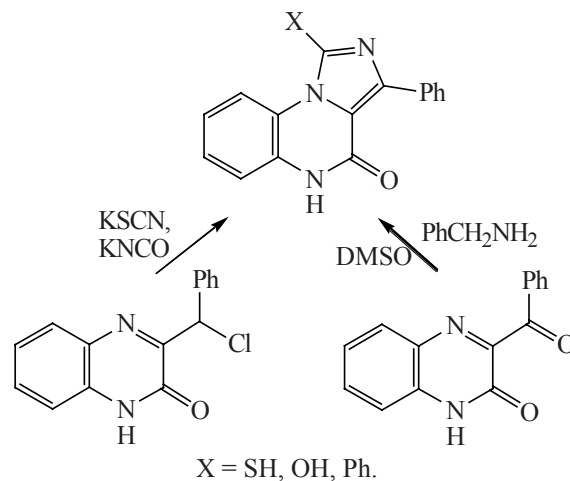
**Abstract**—Oxidative cyclocondensation of bis(3-benzoylquinoxalin-1-yl)alkanes and oxaalkanes with benzylamine and 3-benzoylquinoxalinones with *m*-xylylenediamine proceeded with the formation of bis-(imidazo[1,5-*a*]quinoxalinyl) derivatives where the hetaryl fragments were linked by a spacer both through the imidazole and quinoxaline fragments

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Derivatives of imidazo[1,5-*a*]quinoxalines are used in the synthesis of pharmacologically active compounds as agonists and antagonists of the receptor of GABA/diazepine, inhibitors of CAMP and cGMP phosphodiesterases, agonists of receptors of A<sub>1</sub>- and A<sub>2a</sub>-adenosines [2–8]. Proceeding from quinoxalines 4 types of building up this tricyclic system are possible: by intramolecular cyclization of functionalized quinoxalines [9–12], and by reacting quinoxalines derivatives with synthetic equivalents of one-carbon [13, 14], carbon-nitrogen-carbon [15–20], and nitrogen-carbon [13, 21, 22] synthons. Although the performance of the first two types of processes requires functionalized quinoxaline derivatives that as a rule are prepared by multistage syntheses, and the third type is experimentally difficult the designing of the imidazo[1,5-*a*]quinoxaline system by these routes is relatively well documented.

We formerly developed a new assembling procedure for imidazo[1,5-*a*]quinoxaline system by introducing a C–N fragment into the structure of a quinoxaline derivative [13, 21, 22]. The method is based either on a reaction of 3- $\alpha$ -chlorobenzylquinoxalines with potassium thiocyanate or isothiocyanate [13, 21], or on a reaction of 3-benzoylquinoxalines with benzylamines [22] (oxidative imidazofusion), and it utilizes available reagents. This

\* For communication XVIII, see [1].

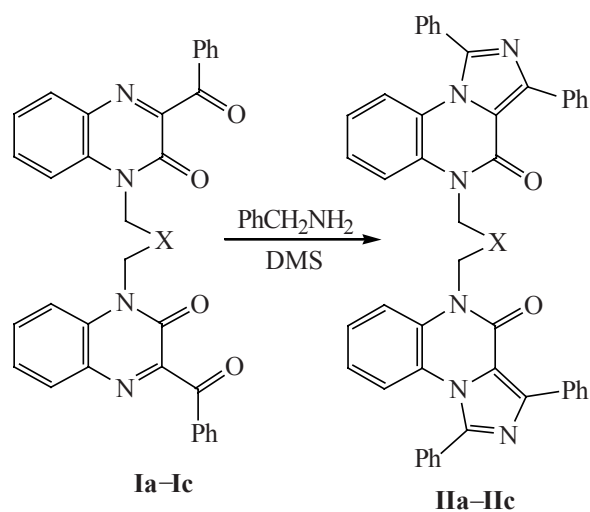


procedure is experimentally simple and provides the desired tricyclic compounds in high yields.

This study is dedicated to the application of this method to the synthesis of bisimidazoquinoxalinones, bisanalogs of fused quinoxalines that as a rule are of biological activity similar to their monoanalogs [23].

Based on the reaction under consideration compounds with two imidazoquinoxaline fragments can be synthesized using two bifunctional compounds with terminal benzoylquinoxaline and benzylamine fragments. A reaction of benzylamine at heating in DMSO solution with  $\alpha,\omega$ -bis(3-benzoyl-2-oxoquinoxalin-

1-yl)alkanes and -oxaalkanes (**I**) easily obtained by reacting 3-benzoylquinoxalin-2-ones with various  $\alpha,\omega$ -dibromoalkanes and oxaalkane [24] led to the formation of crystalline compounds whose IR spectrum contained a single absorption band of  $\nu_{C=O}$  in the region 1645–1655  $\text{cm}^{-1}$ . The presence in the electron ionization mass spectra of molecular ions  $[M]^+$  744 of compound **IIa**,  $[M]^+$  756 of compound **IIb**, and  $[M]^+$  788 of compound **IIc**, and in the  $^1\text{H}$  NMR spectra of proton signals from aromatic fragments alongside the proton signals of methylene groups indicates the formation of  $\alpha,\omega$ -bis-(4-oxo-1,3-diphenylimidazo[1,5-*a*]-quinoxalin-5-yl)alkanes and -oxaalkanes (**II**).



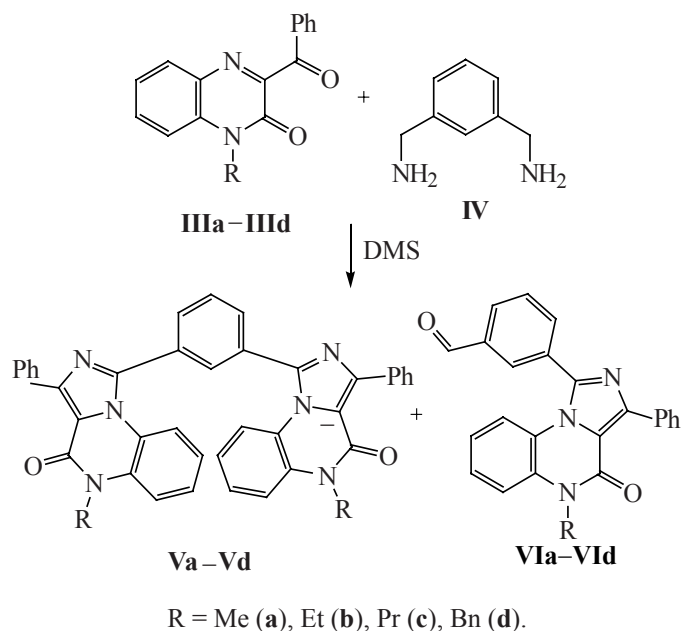
X =  $\text{CH}_2\text{OCH}_2$  (**a**),  $(\text{CH}_2)_4$  (**b**),  $\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2$  (**c**).

The alteration of the character of  $\text{N}^4$  atom in going into  $\text{N}^{10}$  atom from pyridine character in initial compounds **I** to pyrrole one in reaction products **II** is revealed in the  $^1\text{H}$  NMR spectra by the upfield shift of all protons from the quinoxaline system of compounds **II** (to the region 6.9–7.6 ppm) compared to the signals of the quinoxaline protons of initial compounds **I** observed in the region 7.4–8.0 ppm.

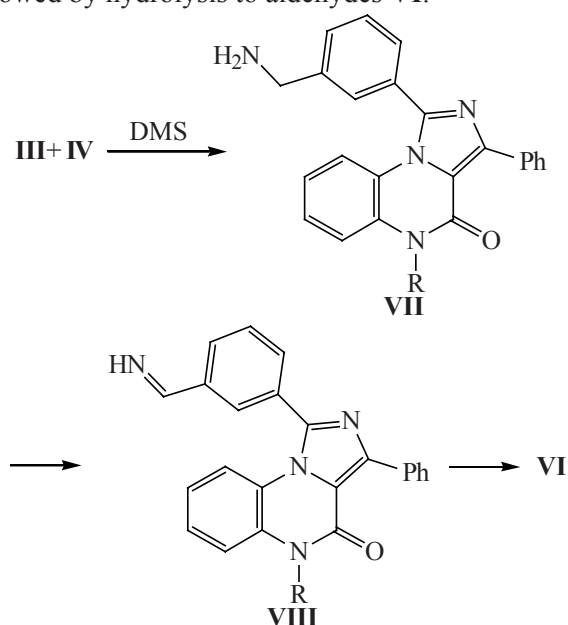
Unlike benzoylquinoxalinone [22] that treated with equimolar amount of benzylamine easily transformed into 1,3-diphenylimidazo[1,5-*a*]quinoxalin-4(1*H*)-one benzoylquinoxalinonopodands required a longer reaction time and benzylamine excess to obtain the corresponding bis(imidazo[1,5-*a*]-quinoxaliny) derivatives.

The second approach to the synthesis of bisimidazoquinoxalines is based on the method we have formerly developed involving a reaction of compounds containing two aminomethyl moieties in a benzene ring. The

procedure makes it possible to obtain bisimidazoquinoxalines linked by a spacer at the position 1. A reaction of *m*-xylylenediamine (**IV**) with various *N*-alkylbenzoylquinoxalinones **III** results in the fusion of imidazole rings and in the formation of *m*-bisheterylbenzenes **V** as the main products and formylphenylimidazo[1,5-*a*]quinoxalinones **VI** as the side reaction products.



The latter compounds form apparently from initially arising aminomethylphenylimidazoquinoxalines **VII** that under the reaction conditions are oxidized to imines **VIII** followed by hydrolysis to aldehydes **VI**.



The structure of compounds **V** was established from IR,  $^1\text{H}$  NMR, and mass spectra and from the data of elemental analysis. The IR spectra of compounds **V** lack absorption bands  $\nu(\text{CO}_{\text{ket}})$  in the region 1675–1690  $\text{cm}^{-1}$ . In the electron ionization mass spectra molecular ions are present  $[M]^+$  624, 680, 776 of compounds **Va**, **Vc**, and **Vd** respectively. In the  $^1\text{H}$  NMR spectrum 22 signals of aromatic protons are observed. The protons of the *m*-phenylene fragment appear separately from the other aromatic protons signals in weaker field (7.9–8.1 ppm) as a singlet of  $\text{H}^2$ , a doublet ( $\text{H}^4$  and  $\text{H}^6$ ,  $J$  7.8 Hz), and a doublet of doublets ( $\text{H}^5$ ,  $J$  7.6, 7.6 Hz). They have intensity corresponding to a half of that of the phenyl rings protons and of quinoxaline systems. In the upfield region similar to compounds **II** appears a signal of  $\text{H}^8$  proton of the quinoxaline system as a doublet of doublets ( $J \sim 8.0$ ,  $\sim 7.6$  Hz) at  $\sim 7.00$  ppm. The formation of compounds **Vla–Vld** was revealed by the electron ionization mass spectra, and compound **Vla** was isolated and characterized. The IR spectrum of imidazoquinoxaline **Vla** contained absorption bands of two carbonyl groups with  $\nu(\text{CO}_{\text{amide}})$  1648 and  $\nu(\text{CO}_{\text{ald}})$  1693  $\text{cm}^{-1}$ . In the  $^1\text{H}$  NMR spectrum the protons of 1,3-disubstituted benzene fragment appeared as four and not three signals characteristic of the  $^1\text{H}$  NMR spectrum of compound **Va**; two of the signals, the singlet from proton  $\text{H}^6$  at 8.29 ppm and the doublet ( $J$  7.56 Hz) from proton  $\text{H}^4$  at 8.18 ppm, are located more downfield due to the stronger electron-withdrawing effect of the aldehyde group. The aldehyde group signal appears at 10.14 ppm.

## EXPERIMENTAL

Melting points were measured on a Boëtius heating block. IR spectra of compounds synthesized were recorded on a Fourier spectrometer Bruker Vector-22 from mulls in mineral oil.  $^1\text{H}$  NMR spectra were registered on a spectrometer Avance-600 at operating frequency 600.00 MHz from solutions in  $\text{DMSO}-d_6$ . Mass spectra of electron ionization were taken on a quadrupole mass spectrometer TRACE MS, sample admission was performed directly through a system with water cooling.

**$\alpha,\omega$ -Bis(4-oxo-1,3-diphenylimidazo[1,5-*a*]-quinoxalin-5-yl)alkanes and -oxaalkanes II.** A solution of 0.34 mmol of compound **I** and 1.4 mmol of benzylamine in 6 ml of  $\text{DMSO}$  was stirred at 140–150°C for 8 h, then it was cooled and poured into water. The separated crystals were filtered off, washed with water, and dried.

**1,5-Bis(4-oxo-1,3-diphenylimidazo[1,5-*a*]-quinoxalin-5-yl)-3-oxapentane (IIa).** Yield 48%, mp 174–176°C ( $\text{DMSO}$ ). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 694, 750, 781, 1053, 1108, 1180, 1255, 1300, 1324, 1337, 1447, 1485, 1503, 1610, 1655.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.85 t (4H,  $\text{OCH}_2$ ,  $J$  5.46 Hz), 4.39 t (4H,  $\text{NCH}_2$ ,  $J$  5.46 Hz), 6.87 d.d (2H,  $\text{H}^8_{\text{quinoxaline}}$ ,  $J$  8.10, 7.56 Hz), 7.10 d (2H,  $\text{H}^9_{\text{quinoxaline}}$ ,  $J$  8.34 Hz), 7.15 d.d (2H,  $\text{H}^7_{\text{quinoxaline}}$ ,  $J$  7.86, 7.32 Hz), 7.37 d.d (2H,  $\text{H}^2_{\text{-Ph}}$ ,  $J$  7.32, 6.54 Hz), 7.41 d.d (4H,  $\text{H}^m_{1\text{-Ph}}$ ,  $J$  7.32, 7.08 Hz), 7.57 d (2H,  $\text{H}^6_{\text{quinoxaline}}$ ,  $J$  8.88 Hz), 7.60 d (4H,  $\text{H}^1_{\text{-Ph}}$ ,  $J$  7.08 Hz), 7.64 d.d (2H,  $\text{H}^2_{3\text{-Ph}}$ ,  $J$  7.62, 6.78 Hz), 7.65 d (4H,  $\text{H}^m_{3\text{-Ph}}$ ,  $J$  7.62 Hz), 8.12 d (4H,  $\text{H}^3_{\text{-Ph}}$ ,  $J$  7.56 Hz). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 746 (2), 745 (6), 744  $[M]^+$  (11), 757 (8), 407 (8), 381 (28), 363 (44), 337 (100), 260 (10), 234 (18), 219 (24), 205 (32), 102 (38). Found, %: C 77.32; H 4.95; N 11.36.  $\text{C}_{48}\text{H}_{36}\text{N}_6\text{O}_3$ . Calculated, %: C 77.40; H 4.87; N 11.28.

**1,6-Bis(4-oxo-1,3-diphenylimidazo[1,5-*a*]-quinoxalin-5-yl)hexane (IIb).** Yield 77%, mp 271–273°C ( $\text{DMSO}$ ). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 694, 704, 747, 781, 1050, 1121, 1250, 1300, 1335, 1395, 1447, 1485, 1503, 1611, 1655.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.45–1.55 m [4H,  $(\text{CH}_2)_2(\text{CH}_2)_2(\text{CH}_2)_2$ ], 1.65–1.75 m [4H,  $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_2\text{CH}_2$ ], 4.24 t (4H,  $\text{NCH}_2$ ,  $J$  7.47 Hz), 6.97 d.d (2H,  $\text{H}^8_{\text{quinoxaline}}$ ,  $J$  8.34, 8.10 Hz), 7.19 d.d (2H,  $\text{H}^9_{\text{quinoxaline}}$ ,  $J$  8.37, 1.29 Hz), 7.43–7.47 m (4H,  $\text{H}^7_{\text{quinoxaline}}$  and  $\text{H}^2_{3\text{-Ph}}$ ), 7.44 d.d (4H,  $\text{H}^m_{3\text{-Ph}}$ ,  $J$  7.56, 7.32 Hz), 7.57 d (2H,  $\text{H}^6_{\text{quinoxaline}}$ ,  $J$  8.10 Hz), 7.60–7.68 m (6H,  $\text{H}^m_{1\text{-Ph}}$ ), 7.72 d.d (4H,  $\text{H}^1_{\text{-Ph}}$ ,  $J$  7.56, 1.56 Hz), 8.14 d.d (4H,  $\text{H}^3_{\text{-Ph}}$ ,  $J$  7.68, 1.32 Hz). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 757 (7), 756  $[M]^+$  (11), 420 (32), 406 (44), 378 (50), 364 (57), 337 (70), 322 (16), 205 (16). Found, %: C 79.46; H 5.28; N 11.21.  $\text{C}_{50}\text{H}_{40}\text{N}_6\text{O}_2$ . Calculated, %: C 79.34; H 5.33; N 11.10.

**1,8-Bis(4-oxo-1,3-diphenylimidazo[1,5-*a*]-quinoxalin-5-yl)-3,5-dioxaoctane (IIc).** Yield 60%, mp 216–218°C ( $\text{DMSO}$ ). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 670, 695, 744, 777, 1005, 1033, 1101, 1124, 1178, 1246, 1257, 1300, 1326, 1352, 1393, 1445, 1485, 1504, 1591, 1609, 1645.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.59 C (4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 3.73 t (4H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $J$  6.04 Hz), 4.33 t (4H,  $\text{NCH}_2$ ,  $J$  6.04), 6.88 d.d (2H,  $\text{H}^8_{\text{quinoxaline}}$ ,  $J$  7.40, 7.36 Hz), 7.12 d (2H,  $\text{H}^9_{\text{quinoxaline}}$ ,  $J$  8.04 Hz), 7.28 d.d (2H,  $\text{H}^7_{\text{quinoxaline}}$ ,  $J$  8.04, 7.36 Hz), 7.32–7.70 m (18H,  $\text{H}^6_{\text{quinoxaline}}$ , 3- $\text{C}_6\text{H}_5$ ;  $\text{H}^m_{1\text{-Ph}}$ ), 8.11 d (4H,  $\text{H}^3_{\text{-Ph}}$ ,  $J$  6.68 Hz). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 788  $[M]^+$  (5), 452 (5), 425 (7), 394 (7), 364 (37), 337 (100), 322 (5), 234 (11), 219 (25), 205 (15). Found, %: C 76.27; H 5.23;

N 10.56. C<sub>50</sub>H<sub>40</sub>N<sub>6</sub>O<sub>4</sub>. Calculated, %: C 76.12; H 5.11; N 10.65.

**1,3-Bis(5-alkyl-4-oxo-3-phenylimidazo[1,5-*a*]-quinoxalin-1-yl)benzenes (V).** A solution of 0.9 mmol of compound III and 0.66 mmol of compound IV in 6 ml of DMSO was stirred at 140–150°C for 24 h, then it was cooled and poured into water, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 ml), washed with water, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel (eluent CH<sub>2</sub>Cl<sub>2</sub>–EtOH, 200:1).

**1,3-Bis(5-methyl-4-oxo-3-phenylimidazo[1,5-*a*]-quinoxalin-1-yl)benzene (Va).** Yield 31%, mp 321–323°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 695, 750, 1104, 1259, 1303, 1333, 1348, 1396, 1502, 1591, 1656. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.60 s (6H, CH<sub>3</sub>), 7.11 d.d.d (2H, H<sup>8</sup><sub>quinoxaline</sub>, *J* 8.16, 7.64 Hz), 7.35–7.50 m (10H, H<sup>7,9</sup><sub>quinoxaline</sub>, H<sup>*m,p*</sup><sub>Ph</sub>), 7.58 d (2H, H<sup>6</sup><sub>quinoxaline</sub>, *J* 7.80 Hz), 7.89 m.d (1H, H<sup>5</sup>, *J* 7.86, 7.56 Hz), 8.03 d (2H, H<sup>4,6</sup>, *J* 7.86 Hz), 8.12 s (1H, H<sup>2</sup>), 8.16 d (4H, H<sup>3</sup><sub>Ph</sub>, *J* 7.08 Hz). Mass spectrum, *m/z* (*I*<sub>rel.</sub> %): 625 (40), 624 [M]<sup>+</sup> (86), 521 (30), 381.1 (32), 337.0 (62), 312.2 (12), 273.0 (18), 233.1 (30), 218.8 (100), 205.0 (34), 150.8 (24), 106 (32), 97 (42), 94 (50), 54 (56). Found, %: C 76.85; H 4.61; N 13.32. C<sub>40</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub>. Calculated, %: C 76.91; H 4.52; N 13.45.

**1,3-Bis(5-ethyl-4-oxo-3-phenylimidazo[1,5-*a*]-quinoxalin-1-yl)benzene (Vb).** Yield 43%, mp 322–324°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 695, 715, 728, 823, 859, 926, 1111, 1184, 1253, 1301, 1400, 1446, 1500, 1588, 1609, 1653. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 1.28 t (3H, CH<sub>3</sub>, *J* 7.11 Hz), 4.29 q (2H, CH<sub>2</sub>, *J* 7.11 Hz), 7.09 d.d (2H, H<sup>8</sup><sub>quinoxaline</sub>, *J* 8.34, 7.56 Hz), 7.35–7.50 m (10H, H<sup>7,9</sup><sub>quinoxaline</sub>, H<sup>*m,p*</sup><sub>Ph</sub>), 7.62 d (2H, H<sup>6</sup><sub>quinoxaline</sub>, *J* 8.10 Hz), 7.88 d.d (1H, H<sup>5</sup>, *J* 7.56, 7.56 Hz), 8.03 d (2H, H<sup>4,6</sup>, *J* 7.80 Hz), 8.11 s (1H, H<sup>2</sup>), 8.17 d (4H, H<sup>3</sup><sub>Ph</sub>, *J* 7.08 Hz). Found, %: C 77.35; H 4.81; N 12.75. C<sub>42</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub>. Calculated, %: C 77.28; H 4.94; N 12.87.

**1,3-Bis(5-propyl-4-oxo-3-phenylimidazo[1,5-*a*]-quinoxalin-1-yl)benzene (Vc).** Yield 39%, mp 146–148°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 694, 750, 783, 1075, 1114, 1144, 1181, 1228, 1252, 1298, 1485, 1591, 1611, 1662. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.98 t (6H, CH<sub>3</sub>, *J* 7.36 Hz), 1.65–1.72 m (4H, CH<sub>2</sub>CH<sub>3</sub>), 4.18 t (4H, NCH<sub>2</sub>, *J* 7.36 Hz), 7.07 d.d (2H, H<sup>8</sup><sub>quinoxaline</sub>, *J* 8.16, 7.64 Hz), 7.30–7.50 m (10H, H<sup>7,9</sup><sub>quinoxaline</sub>, H<sup>*m,p*</sup><sub>Ph</sub>), 7.59 d (2H, H<sup>6</sup><sub>quinoxaline</sub>, *J* 8.72 Hz), 7.88 d.d (1H, H<sup>5</sup>, *J* 7.64, 7.64 Hz), 8.02 d (2H, H<sup>4,6</sup>, *J* 7.64 Hz), 8.11 s (1H, H<sup>2</sup>), 8.14 d (4H, H<sup>3</sup><sub>Ph</sub>, *J* 7.64 Hz). Mass spectrum, *m/z* (*I*<sub>rel.</sub> %): 682 (2), 681

(10), 680 [M]<sup>+</sup> (24), 638 (6), 596 (8), 375 (10), 304 (16), 298 (36), 246 (25), 233 (29), 219 (49), 205 (100), 190 (18). Found, %: C 77.48; H 5.27; N 12.46. C<sub>44</sub>H<sub>36</sub>N<sub>6</sub>O<sub>2</sub>. Calculated, %: C 77.63; H 5.33; N 12.34.

**1,3-Bis(5-benzyl-4-oxo-3-phenylimidazo[1,5-*a*]-quinoxalin-1-yl)benzene (Vd).** Yield 32%, mp 143–145°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 458, 670, 782, 960, 1028, 1076, 1128, 1257, 1300, 1401, 1485, 1495, 1592, 1612, 1656. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 5.40 c (4H, CH<sub>2</sub>), 7.02 d.d (2H, H<sup>8</sup><sub>quinoxaline</sub>, *J* 7.92, 7.86 Hz), 7.20–7.50 m (22H, H<sup>6,7,9</sup><sub>quinoxaline</sub>, H<sup>*m,p*</sup><sub>3-Ph</sub>, CH<sub>2</sub>Ph), 7.88 d.d (1H, H<sup>5</sup>, *J* 7.92, 7.44 Hz), 8.05 d (2H, H<sup>4,6</sup>, *J* 7.44 Hz), 8.15 c (1H, H<sup>2</sup>), 8.16 d (4H, H<sup>3</sup><sub>Ph</sub>, *J* 7.44 Hz). Mass spectrum, *m/z* (*I*<sub>rel.</sub> %): 776 [M]<sup>+</sup> (2), 685 (6), 233 (3), 205 (7). Found, %: C 80.47; H 4.71; N 10.75. C<sub>52</sub>H<sub>36</sub>N<sub>6</sub>O<sub>2</sub>. Calculated, %: C 80.39; H 4.67; N 10.82.

**5-Methyl-1-(3-formylphenyl)-3-phenylimidazo[1,5-*a*]quinoxalin-4-one (VIa).** Yield 8%, mp 237–239°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 672, 696, 755, 804, 979, 1055, 1105, 1192, 1301, 1332, 1400, 1483, 1613, 1648, 1693. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.63 s (3H, CH<sub>3</sub>), 7.03 d.d (1H, H<sup>8</sup>, *J* 8.10, 7.56 Hz), 7.21 d (1H, H<sup>9</sup>, *J* 8.34 Hz), 7.39–7.50 m (4H, H<sup>7</sup>, H<sup>*m,p*</sup><sub>Ph</sub>), 7.59 d (1H, H<sup>6</sup>, *J* 8.34 Hz), 7.86 d.d (1H, H<sup>5</sup><sub>phenylene</sub>, *J* 7.80, 7.62 Hz), 8.09 d (1H, H<sup>6</sup><sub>phenylene</sub>, *J* 7.86 Hz), 8.18 d (1H, H<sup>4</sup><sub>phenylene</sub>, *J* 7.56 Hz), 8.18 d (2H, H<sup>3</sup><sub>Ph</sub>, *J* 7.56 Hz), 8.29 c (1H, H<sup>2</sup><sub>phenylene</sub>), 10.14 c (1H, CHO). Mass spectrum, *m/z* (*I*<sub>rel.</sub> %): 380 (24), 379 [M]<sup>+</sup> (94), 276 (100), 219 (68), 218 (18), 152 (14), 124 (34). Found, %: C 75.79; H 4.61; N 11.25. C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>. Calculated, %: C 75.98; H 4.52; N 11.07.

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