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SYNTHESIS AND ANTI-HIV ACTIVITY OF NEW HOMO ACYCLIC NUCLEOSIDES, 1-(PENT-4-ENYL)QUINOXALIN-2-ONES AND 2-(PENT-4-ENYLOXY)QUINOXALINES

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A series of acyclonucleosides 6,7-disubstituted 1-(pent-4-enyl)quinoxalin-2-one derivatives and the O-analogs were synthesized by a one-step condensation of the corresponding quinoxaline bases with 5-bromo-1-pentene.The acyclonucleosides prepared were assayed against HIV-1 and HIV-2 in MT-4 cells. 6,7-Dimethyl-2-(pent-4-enyloxy)quinoxaline showed inhibition of HIV-1 with EC_{50} value of 0.22 ± 0.08 μg/ml and a therapeutic index of 13. This means that it was cytotoxic to MT-4 cells at CC_{50} of 2.6 ± 0.1 μg/ml.

Keywords: acyclonucleosides, glycosides, quinoxalines, alkylation, antiviral activity.

The use of acyclonucleoside analogs as antiviral chemotherapeutic agents has stimulated extensive research in the synthesis of this class of compounds [1-4]. The discovery of *acyclovir* (Zovirax®) [5, 6] as a potent antiherpetic drug [7-9] was followed by a great number of chemical analogs of *acyclovir* such as (*RS*)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (HBG) (**1**), 9-[(1,3-dihydroxy- 2-propoxy)methyl]guanine (DHPG) **2** [10, 11], 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and (*S*)-1-(3-hydroxy-2-phosphonylmethoxy-propyl)adenine (HPMPA) [12] derivatives. Structure–activity relationship studies have shown that the side chains of acyclonucleosides play a crucial role in the interaction of the acyclonucleosides with their antiviral target enzymes [13] (phosphorylation). The orientation of the heterocyclic base about the glycosidic bond in nucleosides is an important conformational parameter, and has been clearly delineated in a variety of enzymatic reactions [14]. These studies prompted us to use the 1,2-dihydroquinoxalone as nucleobase carrying alkyl side chains at N and O atoms, since some quinoxaline derivatives showed a remarkable biological activity [15, 16]. The pharmacological applications of quinoxalines include their use as angiotension II receptor antagonists [17], N-methyl-D-aspartate (NMDA) antagonists [18], anti-inflammatory [19], antidepressant-tranquilizing [20, 21], antitumor agents [22, 23], as well as the agents against hepatitis B virus (HBV) [24].

Recently, Ali and Fathalla [25] have reported the regioselective alkylation of quinoxalines with allyl bromide in the presence of NaH to give a mixture of O- and N-allyl-substituted quinoxalines **3** (27-33%) and

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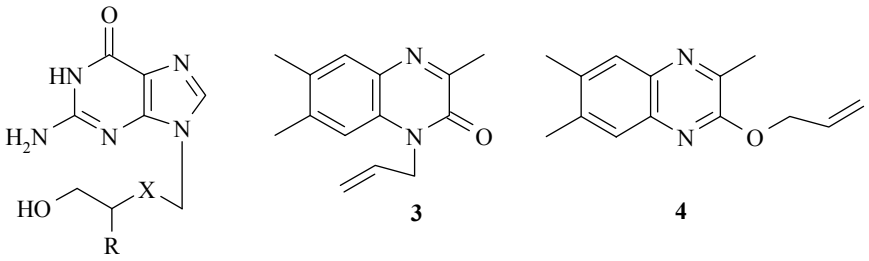
4 (56-72%), respectively, as promising antiviral acyclic N-nucleosides. As an on-going program for the synthesis of acyclonucleosides [26-28] we report here the synthesis of new analogs of 1,2-dihydro-2-quinoxalinone acyclonucleosides with evaluation of their anti-HIV activity.



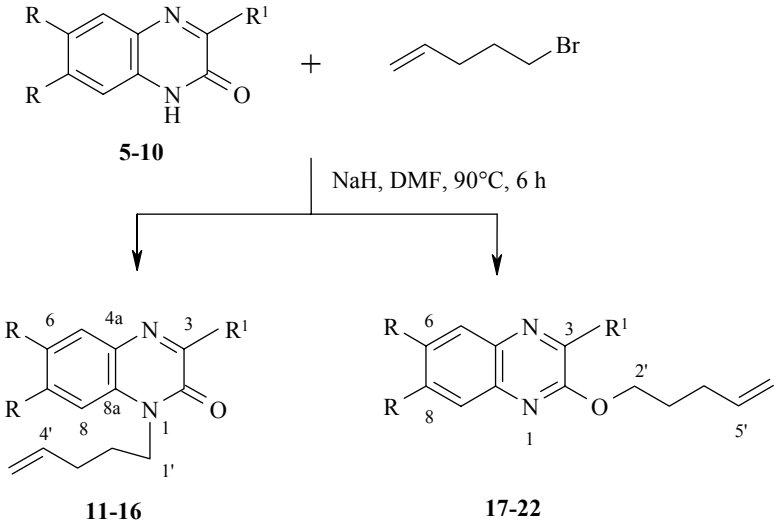
1, **2** **3** **4**

1 R = H, X = $CHCH_2OH$; **2** R = CH_2OH, X = O

The reaction of the quinoxalines **5-10** with 5-bromo-1-pentene in the presence of NaH in DMF at 90°C afforded a mixture of N- (**11-16**) and O-alkyl-substituted quinoxalines **17-22** (Scheme 1). The two alkylated isomers were separated by silica gel column chromatography to give **11-16** in 54-62% yield and **17-22** in 22-32% yield.

The structures of the newly synthesized quinoxaline derivatives were confirmed by NOE experiments and ^{13}C NMR and mass spectra. The site of alkylation of **11-16** at N-1 was visible in the ROESY spectra, where the 1'-CH_2 protons at δ_H 4.16-4.25 showed cross signals to the aromatic H-8 at δ_H 7.98-7.46, but not to H-5 of the quinoxaline ring. The proton spin system of compounds **11-16** was further identified from DFQ-COSY [29] spectra, where the multiplets of the olefinic protons H-4' at the region δ_H 5.78-5.89 were found to correlate with the singlets at δ_C 136.8-132.8 for C-4'. From the gradient selected HMBC [30] spectra of compounds **11-16**, C-1' at δ_C 41.0-41.9 showed heteronuclear long correlations to the H-4' at δ_H 5.78-5.89. Furthermore, 1'-CH_2 proton at δ_H 4.16-4.25 showed $^3J_{C,H}$ couplings with C=O at δ_C 158.2-154.1, and $^2J_{C,H}$ couplings with C-2' at δ_C 26.0. The quinoxaline carbon atoms were fully analyzed and are in agreement with those of the known derivatives prepared previously [25].

Scheme 1



5-10 NaH, DMF, 90°C, 6 h

11-16 **17-22**

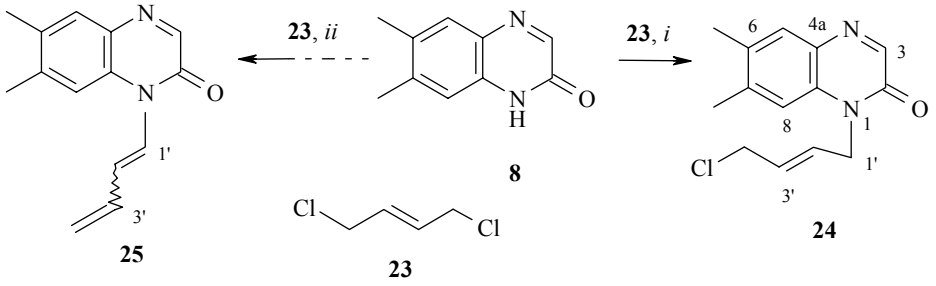
5, **11**, **17** R = R^1 = H; **6**, **12**, **18** R = H, R^1 = Me; **7**, **13**, **19** R = H, R^1 = Ph;
8, **14, 20** R = Me, R^1 = H; **9**, **15**, **21** R = R^1 = Me; **10**, **16**, **22** R = Me, R^1 = Ph

The structures of the O-alkyl analogs **17-22** were confirmed from the NMR and mass spectra. In the ^{13}C NMR spectra, the C-2' resonated at relatively lower field (δ_C 65.9-65.1) in comparison to C-1' of the N-analogs (δ_C 41.0-41.9 ppm) due to the difference in the deshielding nature between N and O atoms. Furthermore, the multiplet of the 2'-CH_2 protons at δ_H 4.48-4.38 showed $^2J_{C,H}$ couplings with C-2 at δ_C 157.2–155.2. The 3'-CH_2 – 5'-CH_2 were assigned by the HMBC correlation, whereas the protons and carbons of the quinoxaline ring were analyzed from the NMR spectra as well as by comparison with the spectral date of compounds **11-16**.

Alkylation of the base compound **8** with an excess of (*E*)-1,4-dichlorobut-2-ene (**23**) in the presence of K_2CO_3 at 80°C led to the open-chain analog and gave compound **24** in 36% yield after chromatographic purification (Scheme 2). The site of alkylation was confirmed by an NOE experiment as well as mass spectrum. The ROESY spectrum of **24** revealed a cross signal between 1'-CH_2 protons at δ_H 4.01 and the aromatic H-8 at δ_H 7.45 ppm, but not to H-5, indicating the N- and not O-alkylation of the quinoxaline ring. In the ^1H NMR (HMQC) [31] spectrum of compound **24**, two doublets of triplets appeared at δ_H 6.00 and 5.92 ppm (δ_C 128.1 and 130.4 ppm). They could be assigned to H-2' and H-3' (C-2' and C-3') by a spin decoupling experiment. These NMR data are in agreement with those of 9-[(*E*)-4-chloro-2-butene-1-yl]adenine [32].

When the quinoxaline base **8** was treated with compound **23** in the presence of NaH, the N-butadienyl derivative **25** (37%) was obtained as the result of dehydrochlorination of the intermediate **24**. The structural assignment follows from mass spectrum and a 2D NMR spectrum showing overlapping signals for the H-1' and H-2' at δ_H 6.54 and δ_H 6.55 correlated with δ_C 128.1 and 109.2 ppm (C-1' and C-2'), respectively. Irradiation at δ_H 6.54 produced a 16% NOE effect on the signal at δ_H 7.44 ppm assigned to H-8, indicating that the conjugated diene side-chain is attached to N-1. It proved to be difficult to assign the configuration of the N-vinyl group on the basis of the NMR spectra (Scheme 2).

Scheme 2



i K_2CO_3, DMF, 80°C; *ii* NaH, DMF

Compounds **11-22** were evaluated for their *in vitro* anti-HIV activity using the MT-4/MTT assay [33]. The results are summarized Table 1, in which the data for *efavirenz* [34] and *capravirine* [35] were included for comparison. All the tested compounds are inactive, except **20,** which was found to be the only compound from the series inhibiting HIV-1 replication in cell culture. Compound **20** showed an EC_{50} of 0.22 ± 0.08 μg/ml and a CC_{50} of 2.6 ± 0.1 μg/ml, resulting in a selectivity index of 13.

Based on the chemical structure and the fact that compound **20** inhibits HIV-1, but not HIV-2, replication, this molecule can be proposed to act as a non-nucleoside reverse transcriptase inhibitor (NNRTI). This hypothesis was further confirmed by assaying the compound against a typical NNRTI-resistant HIV-1 strain (double mutation in RT: K103N and Y181C). Compound **20** completely lost its inhibitory activity against this resistant strain.

TABLE 1. *In vitro anti*-HIV-1 and HIV-2 of Some New Alkylated Quinoxalines*

Compound	Virus strain	EC_{50}, μg/ml	CC_{50}, μg/ml	SI
11	III_B	>2.5	2.5 ± 0.1	<1
	ROD	>2.5	2.5 ± 0.1	<1
12	III_B	>97.7	97.7 ± 12.9	<1
	ROD	>97.7	97.7 ± 12.9	<1
13	III_B	>48.0	48.0 ± 6.1	<1
	ROD	>48.0	48.0 ± 6.1	<1
14	III_B	>102.0	102.0 ± 12.5	<1
	ROD	>102.0	102.0 ± 12.5	<1
15	III_B	>117.0	117.0 ± 4.2	<1
	ROD	>117.0	117.0 ± 4.2	<1
16	III_B	>16.9	16.9 ± 3.2	<1
	ROD	>16.9	16.9 ± 3.2	<1
17	III_B	>96.2	96.2 ± 9.7	<1
	ROD	>96.2	96.2 ± 9.7	<1
18	III_B	>121.0	121.0 ± 0.7	<1
	ROD	>121.0	121.0 ± 0.7	<1
19	III_B	>101.0	101.0 ± 19.6	<1
	ROD	>101.0	101.0 ± 19.6	<1
20	III_B	0.22 ± 0.08	2.6 ± 0.1	13
	ROD	>2.6	2.6 ± 0.1	<1
21	III_B	>2.2	2.2 ± 0.1	<1
	ROD	>2.2	2.2 ± 0.1	<1
22	III_B	>2.0	2.0 ± 0.3	<1
	ROD	>2.0	2.0 ± 0.3	<1
Efavirenz [32]	III_B	0.003	40	13 333
Capravirine [33]	III_B	0.0014	11	7 857

* *Anti*-HIV-1 activity measured with strain III_B; *anti*-HIV-2 activity measured with strain ROD. EC_{50} – compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect. CC_{50} – compound concentration that reduces the viability of mock-infected MT-4 cells by 50%. SI – selectivity index (CC_{50}/EC_{50}).

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and the values are uncorrected. NMR spectra were measured with Bruker AC 250 (250 MHz) in $CDCl_3$ (Compounds **11-22**) and DMSO-d_6 (Compounds **24**, **25**) using TMS as an internal standard. Mass spectra were determined with FAB-MS modified Finningan MAT 312/ AMD 5000 spectrometer at 790 eV and T = 70 MALDI-MS using Na^+ as dropping ion.

Alkylation Reaction (General Method). A mixture of compounds **5-11** (10.0 mmol) and NaH (10.0 mmol) in dry DMF (15 ml) was stirred at 90°C for 1 h. After cooling, 5-bromo-2-pentene (1.79 g, 12.0 mmol) was added and the mixture was stirred at 90°C for 5 h. After cooling the solution was evaporated to dryness and the residue was partitioned between $CHCl_3$ (3×30 ml) and water (30 ml). The combined organic extract was dried, filtered and evaporated to dryness and the residue was poured on silica gel column (20 g). Elution with petroleum ether–ethyl acetate (50:1) afforded first the 2-(pent-4-enyloxy)quinoxaline derivatives (**17-22**) followed by the N-analogs, 1-(pent-4-enyl)quinoxalin-2-one derivatives (**11-16**).

1-(Pent-4-enyl)quinoxalin-2-one (11) and 2-(Pent-4-enyloxy)quinoxaline (17). From **5** (1.47 g).

Compound 11. Yield 1.2 g (56%); yellow oil. ^{1}H NMR, δ, ppm (*J*, Hz): 8.20 (1H, s, H-3); 7.80 (1H, dd, *J* = 1.5, *J* = 8.5, H-8); 7.51 (1H, m, H-6); 7.29-7.47 (2H, m, H-5,7); 5.78 (1H, m, H-4'); 5.06 (1H, dd, $J_{4',5'}$ = 1.6, $J_{5',5''}$ = 14.5, H-5'); 4.99 (1H, dd, $J_{4',5''}$ = 10.5, H-5''); 4.16 (2H, dd, *J* = 1.9, *J* = 9.7, 1'-CH_2); 2.57 (3H, s, CH_3); 2.18 (2H, dd, *J* = 7.0, *J* = 14.0, 3'-CH_2); 1.84 (2H, m, 2'-CH_2). ^{13}C NMR, δ, ppm: 154.5 (C=O); 149.9 (C-3); 136.7 (C-4a); 133.4 (C-4'); 132.1 (C-8a); 130.8 (C-7); 130.4 (C-6); 123.3 (C-8); 115.6 (C-5); 113.5 (C-5'); 41.2 (C-1'); 30.7 (C-3'); 26.0 (C-2'). Mass spectrum, *m/z* (I_{rel}, %): 237 $[M+Na]^+$ (85). Found, %: C 72.59; H 6.44; N 12.76. $C_{13}H_{14}N_2O$. Calculated, %: C 72.87; H 6.59; N 13.07.

Compound 17. Yield 0.49 g (23%); colorless oil. ^{1}H NMR, δ, ppm (*J*, Hz): 8.42 (1H, s, H-3); 7.98 (1H, dd, *J* = 1.3, *J* = 8.0, H-8); 7.79 (1H, dd, *J* = 1.4, *J* = 8.0, H-6); 7.76-7.44 (2H, m, H-6,7); 5.93-5.76 (1H, m, H-5'); 5.10 (1H, dd, $J_{5',6'}$ = 1.6, $J_{6',6''}$ = 14.3, H-6'); 5.02 (1H, dd, $J_{5',6''}$ = 9.0, H-6''); 4.44 (2H, m, 2'-CH_2); 2.23 (2H, m, 4'-CH_2); 1.94 (2H, m, 3'-CH_2). ^{13}C NMR, δ, ppm: 157.2 (C-2); 140.2 (C-8a); 139.7 (C-4a); 138.7 (C-3); 137.4 (C-4a); 129.7 (C-7); 128.8 (C-5); 127.0 (C-8); 126.1 (C-6); 115.1 (C-5'); 65.6 (C-2'); 30.0 (C-4'); 27.8 (C-3'). Mass spectrum, *m/z* (I_{rel}, %): 237 $[M+Na]^+$ (90). Found, %: C 72.55; H 6.49; N 12.83. $C_{13}H_{14}N_2O$. Calculated, %: C 72.87; H 6.59; N 13.07.

3-Methyl-1-(pent-4-enyl)quinoxalin-2-one (12) and 3-Methyl-3-(pent-4-enyloxy)quinoxaline (18). From **6** (1.61 g).

Compound 12. Yield 1.41 g (62%); brown oil. ^{1}H NMR, δ, ppm (*J*, Hz): 7.79 (1H, dd, *J* = 1.0, *J* = 8.5, H-8); 7.48 (1H, m, H-6); 7.31-7.24 (2H, m, H-5,7); 5.85 (1H, m, H-4'); 5.06 (1H, dd, $J_{4',5'}$ = 1.5, $J_{5',5''}$ = 15.0, H-5'); 5.03 (1H, dd, $J_{4',5''}$ = 9.0, H-5''); 4.20 (2H, d, *J* = 1.5, *J* = 10.0, 1'-CH_2); 2.15 (2H, dd, *J* = 7.0, *J* = 14.4, 3'-CH_2); 1.77 (2H, m, 2'-CH_2). ^{13}C NMR, δ, ppm: 158.2 (C=O); 154.8 (C-3); 136.7 (C-4a); 132.8 (C-4'); 132.2 (C-8a); 129.6 (C-7); 129.4 (C-6); 123.3 (C-8); 115.6 (C-5); 113.5 (C-5'); 41.7 (C-1'); 30.9 (C-3'); 26.0 (C-2'), 21.3 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 251 $[M+Na]^+$ (87). Found, %: C 73.41; H 6.94; N 11.97. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06; N 12.27.

Compound 18. Yield 0.71 g (32%); yellow oil. ^{1}H NMR, δ, ppm (*J*, Hz): 7.92 (1H, dd, *J* = 1.0, *J* = 7.9, H-7); 7.88 (1H, dd, *J* = 1.0, *J* = 7.9, H-6); 7.78-7.46 (2H, m, H-5,8); 5.95 (1H, m, H-5'); 5.11 (1H, dd, $J_{5',6'}$ = 1.3, $J_{6',6''}$ = 17.3, H-6'); 5.04 (1H, dd, $J_{5',6''}$ = 10.3, H-6''); 4.46 (2H, t, *J* = 6.5, 2'-CH_2); 2.61 (3H, s, CH_3); 2.25 (m, 4'-CH_2); 1.94 (2H, m, 3'-CH_2). ^{13}C NMR, δ, ppm: 156.0 (C-2); 147.8 (C-3); 139.7 (C-8a); 138.2 (C-4a); 137.4 (C-5'); 128.4 (C-7); 127.8 (C-5); 126.5 (C-8); 125.9 (C-6); 115.0 (C-6'); 65.5 (C-2'); 30.1 (C-4'); 27.8 (C-3'), 20.1 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 251 $[M+Na]^+$ (80). Found, %: C 73.37; H 6.91; N 11.89. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06; N 12.27.

1-(Pent-4-enyl)-3-phenylquinoxalin-2-one (13) and 2-(Pent-4-enyloxy)-3-phenylquinoxaline (19). From **7** (2.22 g).

Compound 13. Yield 1.60 g (55%); mp 40-43°C. ^{1}H NMR), δ, ppm (*J*, Hz): 8.35–8.30 (2H, m, Ph-H); 7.92 (1H, dd, *J* = 1.4, *J* = 7.7, H-8); 7.57-7.24 (6H, m, H-5,6,7, Ph-H); 5.89 (1H, m, H-4'); 5.13 (1H, dd, $J_{4',5'}$ = 1.5, $J_{5',5''}$ = 14.5, H-5'); 5.02 (1H, dd, $J_{4',5''}$ = 10.2, H-5''); 4.25 (2H, m, 1'-CH_2); 2.20 (2H, dd, *J* = 8.0, *J* = 14.0, 3'-CH_2); 1.84 (2H, m, 2'-CH_2). ^{13}C NMR, δ, ppm: 154.2 (C-2); 153.7 (C-3); 136.9 (C-4a); 135.9 (C-4'); 133.2 (Ar-C); 132.3 (C-8a); 130.5, 130.1, 129.4 (Ar-C); 127.9 (C-7); 123.3 (C-6); 115.7 (C-5); 113.5 (C-5'); 41.9 (C-1'); 30.9 (C-3'); 26.0 (C-2'). Mass spectrum, *m/z* (I_{rel}, %): 291 $[M+H]^+$ (92). Found, %: C 78.37; H 6.15; N 9.40. $C_{19}H_{18}N_2O$. Calculated, %: C 78.59; H 6.25; N 9.65.

Compound 19. 0.81 g (28%); colorless oil. ^{1}H NMR, δ, ppm (*J*, Hz): 8.02-7.93 (2H, m, Ph-H); 7.89 (1H, dd, *J* = 1.4, *J* = 8.0, H-8); 7.65 (1H, dd, *J* = 1.4, *J* = 8.0, H-5); 7.45-7.26 (5H, m, H-6,7, Ph-H); 5.70 (1H, m, H-5'); 4.93 (1H, dd, $J_{5',6'}$ = 1.6, $J_{6',6''}$ = 15.7, H-6'); 4.88 (1H, dd, $J_{5',6''}$ = 15.2, H-6''); 4.38 (2H, t, *J* = 6.5, 2'-CH_2); 2.08 (2H, m, 4'-CH_2); 1.80 (2H, m, 3'-CH_2). ^{13}C NMR, δ, ppm: 155.3 (C-2); 146.2 (C-3); 139.8 (C-8a); 138.7 (C-4a); 137.5 (C-5'); 136.0 (Ar-C); 129.6 (C-7); 129.4, 129.3, 129.0, 126.5, 126.4 (C-5,6,8, Ar-C); 115.1 (C-6'); 65.9 (C-2'); 30.2 (C-4'); 27.8 (C-3'). Mass spectrum, *m/z* (I_{rel}, %): 313 $[M+Na]^+$ (80). Found, %: C 78.30; H 6.12; N 9.37. $C_{19}H_{18}N_2O$. Calculated, %: C 78.59; H 6.25; N 9.65.

6,7-Dimethyl-1-(pent-4-enyl)quinoxalin-2-one (**14**) **and 6,7-Dimethyl-2-(pent-4-enyloxy)quinoxaline** (**20**). From **8** (1.75 g).

Compound 14. Yield 1.31 g (54%); mp 71-73°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.15 (1H, s, H-3); 7.56 (1H, bs, H-8); 7.06 (1H, bs, H-5); 5.86 (1H, m, H-4'); 5.14 (1H, dd, $J_{4',5'}$ = 1.4, $J_{5',5''}$ = 12.7, H-5'); 5.07 (1H, dd, $J_{4',5''}$ = 10.7, H-5''); 4.16 (2H, m, 1'-CH_2); 2.41, 2.32 (6H, 2 s, 2 CH_3); 2.21 (2H, dd, *J* = 7.1, *J* = 14.6, 3'-CH_2); 1.80 (2H, m, 2'-CH_2). ^{13}C NMR, δ, ppm: 154.6 (C=O); 148.7 (C-3); 140.6 (C-4a); 136.8 (C-7,4'); 132.2 (C-6); 130.4 (C-8a); 130.1 (C-5); 115.5 (C-8); 113.5 (C-5'); 41.0 (C-1'); 30.7 (C-3'); 26.0 (C-2'), 20.4, 18.8 (2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 243 $[M+H]^+$ (82). Found, %: C 74.12; H 7.35; N 11.32. $C_{15}H_{18}N_2O$. Calculated, %: C 74.35; H 7.49; N 11.56.

Compound 20. Yield 0.70 g (29%); mp 56-58°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.35 (1H, s, H-3); 7.73 (1H, bs, H-8); 7.58 (1H, bs, H-6); 5.85 (1H, m, H-5'); 5.11 (1H, dd, $J_{5',6'}$ = 1.5, $J_{6',6''}$ = 13.3, H-6'); 5.03 (1H, dd, $J_{5',6''}$ = 13.1, H-6''); 4.45 (2H, t, $J_{5',6'}$ = 6.6, 2'-CH_2); 2.42 (6H, s, 2 CH_3); 2.25 (2H, m, H_2-4'); 1.94 (2H, m, $J_{5',6'}$ = 1.5, 3'-CH_2). ^{13}C NMR, δ, ppm: 156.2 (C-2); 148.2 (C-7); 143.6 (C-6); 139.1 (C-4a); 138.9 (C-3); 135.7 (C-4a); 134.3 (C-5'); 128.0 (C-5); 127.2 (C-8); 115.1 (C-6'); 65.1 (C-2'); 30.3 (C-3'); 26.2 (C-2'), 20.2, 18.9 (2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 243 $[M+H]^+$ (80). Found, %: C 74.06; H 7.40; N 11.33. $C_{15}H_{18}N_2O$. Calculated, %: C 74.35; H 7.49; N 11.56.

3,6,7-Trimethyl-1-(pent-4-enyl)quinoxalin-2-one (**15**) **and 3,6,7-Trimethyl-3-(pent-4-enyloxy)-quinoxaline** (**21**). From **9** (1.89 g).

Compound 15. Yield 1.48 g (58%); mp 43-46°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.53 (1H, s, H-8); 7.02 (1H, s, H-5); 5.87 (1H, m, H-4'); 5.16 (1H, dd, $J_{4',5'}$ = 1.6, $J_{5',5''}$ = 13.2, H-5'); 5.08 (1H, dd, $J_{4',5''}$ = 10.1, H-5''); 4.20 (2H, m, 1'-CH_2); 2.56, 2.40, 2.18 (9H, 3 s, 2CH_3); 2.20 (2H, dd, *J* = 6.8, *J* = 14.0, 3'-CH_2); 1.85 (2H, m, 2'-CH_2). ^{13}C NMR, δ, ppm: 156.5 (C=O); 154.5 (C-3); 138.7 (C-4a); 136.9 (C-7, C-4'); 131.8 (C-6); 131.0 (C-8a); 129.9 (C-5); 115.4 (C-8); 113.7 (C-5'); 41.2 (C-1'); 30.7 (C-3'); 25.9 (C-2'), 20.1, 20.2, 18.8 (3 CH_3). Mass spectrum, *m/z* (I_{rel}, %): 257 $[M+H]^+$ (72). Found, %: C 74.75; H 7.77; N 10.73. $C_{16}H_{20}N_2O$. Calculated, %: C 74.97; H 7.86; N 10.93.

Compound 21. Yield 0.56 g (22%); mp 35–38°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.61 (1H, s, H-8); 7.46 (1H, s, H-5); 5.85 (1H, m, H-5'); 5.07 (1H, dd, $J_{5',6'}$ = 1.7, $J_{6',6''}$ = 17.1, H-6'); 4.99 (1H, dd, $J_{5',6''}$ = 11.1, H-5''); 4.42 (2H, t, *J* = 6.5, CH_2-2'); 2.56, 2.34 (9H, 2 s, 3 CH_3); 2.23 (2H, m, 4'-CH_2); 1.91 (2H, m, 3'-CH_2). ^{13}C NMR, δ, ppm: 156.1 (C-2); 146.8 (C-3); 138.6 (C-7); 138.4 (C-6); 137.8 (C-8a); 137.2 (C-4a); 135.8 (C-5'); 127.5, (C-5); 126.3 (C-8); 115.1 (C-6'); 65.6 (C-2'); 30.3 (C-4'); 28.1 (C-3'), 20.2, 20.1, 19.9 (3 CH_3). Mass spectrum, *m/z* (I_{rel}, %): 257 $[M+H]^+$ (79). Found, %: C 74.78; H 7.76; N 10.72. $C_{16}H_{20}N_2O$. Calculated, %: C 74.97; H 7.86; N 10.93.

6,7-Dimethyl-1-(pent-4-enyl)-3-phenylquinoxalin-2-one (**16**) **and 6,7-Dimethyl-2-(pent-4-enyloxy)-3-phenylquinoxaline** (**22**). From **10** (2.52 g).

Compound 16. Yield 1.94 g (61%); mp 98-100°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.32 (2H, m, Ph-H); 7.60 (1H, s, H-8); 7.47-7.41 (3H, m, Ph-H); 6.96 (1H, s, H-5); 5.85 (1H, m, H-4'); 5.06 (1H, dd, $J_{4',5'}$ = 1.2, $J_{5',5''}$ = 13.5, H-5'); 5.01 (1H, dd, $J_{4',5''}$ = 10.5, H-5''); 4.18 (2H, m, 1'-CH_2); 2.32, 2.26 (6H, 2 s, 2 CH_3); 2.20 (2H, dd, *J* = 6.9, *J* = 14.2, 3'-CH_2); 1.84 (2H, m, 2'-CH_2). ^{13}C NMR, δ, ppm: 154.1 (C=O); 152.2 (C-3); 139.9 (C-4a); 137.0 (C-7); 136.1 (C-4'); 132.2 (C-6); 131.6 (C-6); 130.4 (C-8a); 129.6, 129.3 (Ar-C); 127.7 (C-5); 115.5 (C-8); 113.7 (C-5'); 41.6 (C-1'); 30.8 (C-3'); 26.0 (C-2'), 20.4, 18.9 (2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 319 $[M+H]^+$ (69). Found, %: C 78.93; H 6.78; N 8.61. $C_{21}H_{22}N_2O$. Calculated, %: C 79.21; H 6.96; N 8.80.

Compound 22. Yield 0.73 g (23%); mp 45-47°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.11 (2H, m, Ph-H); 7.64 (1H, s, H-8); 7.53 (1H, s, H-5); 7.49-7.38 (3H, m, Ph-H); 5.82 (1H, m, H-5'); 5.02 (1H, dd, $J_{5',6'}$ = 1.2, $J_{6',6''}$ = 18.2, H-6'); 4.96 (1H, dd, $J_{5',6''}$ = 10.2, H-6''); 4.48 (2H, t, *J* = 6.5, 2'-CH_2); 2.36 (6H, s, 2CH_3); 2.21 (2H, m, 4'-CH_2); 1.94 (2H, m, 3'-CH_2). ^{13}C NMR, δ, ppm: 155.2 (C-2); 145.1 (C-3); 139.6 (C-7); 138.5 (C-6); 137.7 (C-8a); 137.6 (C-4a); 136.4 (C-5'); 129.6, 129.2, 128.8, 128.3 (Ar-C); 127.9 (C-5); 126.0 (C-8); 115.1 (C-6'); 65.8 (C-2'); 30.3 (C-4'); 28.0 (C-3'), 20.1, 19.8 (2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 319 $[M+H]^+$ (81). Found, %: C 78.96; H 6.89; N 8.65. $C_{21}H_{22}N_2O$. Calculated, %: C 79.21; H 6.96; N 8.80.

1-(*E*)-4-Chlorobut-2-enyl)-6,7-dimethylquinoxalin-2-one (**24**). A mixture of **8** (0.50 g, 2.86 mmol), K_2CO_3 (1.0 g, 7.23 mmol), and 1,4-dichlorobut-2-ene (**23**) (1.77 g, 14.3 mmol) in abs. DMF (5 ml) was stirred under N_2 at 80°C for 10 h. After cooling, the mixture was acidified with 1 M HCl to pH 1, then diluted with water (50 ml) and extracted with ethyl acetate (4×20 ml). The combined organic extract was dried (Na_2SO_4), filtered off, and evaporated to dryness. The residue was purified by column chromatography on silica gel column (50 g) using, in gradient, MeOH (0-10%) in $CHCl_3$ as an eluent to give compound **24** (0.27 g, 36%); mp 65-68°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.10 (1H, s, H-3); 7.45 (1H, bs, H-8); 7.02 (1H, bs, H-5); 6.00 (dt, $J_{2',3'}$ = 15.2, H-2'); 5.92 (1H, dt, $J_{3',4'}$ = 7.2, H-3'); 4.10 (2H, d, $J_{4',3'}$ = 7.2, 4'-CH_2); 4.01 (2H, d, $J_{1',2'}$ = 5.5, 1'-CH_2); 2.38, 2.30 (6H, 2s, 2CH_3). ^{13}C NMR, δ, ppm: 158.2 (C=O); 148.9 (C-3); 140.8 (C-4a); 136.5 (C-7); 132.8 (C-6); 130.4 (C-3'); 130.2 (C-8a); 130.0 (C-5); 128.1 (C-2'); 115.2 (C-8); 54.2 (C-4'); 44.2 (C-1'); 20.1, 18.5 (2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 262/264 $[M+H]^+$ (62). Found, %: C 63.80; H 5.66; N 10.42. $C_{14}H_{15}ClN_2O$. Calculated, %: C 64.00; H 5.75; N 10.66.

1-Butadienyl-6,7-dimethylquinoxalin-2-one (**25**). To a stirred solution of compound **8** (0.60 g, 3.44 mmol), in abs. DMF (15 ml) was added dry NaH (0.18 g, 7.50 mmol). When the evolution of H_2 has ceased, the mixture was stirred at 23°C for 1 h. After addition of compound **23** (1.71 g, 13.68 mmol), the mixture was stirred under N_2 at 60°C for 2 h. Work up in the manner described for **24** furnished compound **25** (0.28 g, 37%); mp 85-88°C (dec.). ^{1}H NMR, δ, ppm (*J*, Hz): 8.13 (1H, s, H-3); 7.44 (1H, bs, H-8); 7.10 (1H, bs, H-5); 6.54 (2H, m, H-1',2'); 6.20 (1H, dt, $J_{3',4'}$ = 1.1, H-3'); 5.63 (1H, dt, $J_{4',4''}$ = 14.1, H-4'); 5.45 (1H, dd, $J_{3',4''}$ = 5.2, H-4''); 2.37, 2.32 (6H, 2s, 2CH_3). ^{13}C NMR, δ, ppm: 158.7 (C=O); 149.1 (C-3); 140.3 (C-4a); 136.7 (C-7); 132.8 (C-6); 132.3 (C-3'); 130.2 (C-8a); 130.0 (C-5); 128.1 (C-1'); 125.6 (C-4'); 115.2 (C-8); 109.2 (C-2'); 20.4, 18.8 (2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 227 $[M+H]^+$ (89). Found, %: C 73.89; H 6.19; N 12.11. $C_{14}H_{14}N_2O$. Calculated %: C 74.31; H 6.24; N 12.38.

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