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Full Paper

Substitutions of Fluorine Atoms and Phenoxy Groups in the Synthesis of Quinoxaline 1,4-di-*N*-oxide Derivatives†

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Abstract: The unexpected substitution of fluorine atoms and phenoxy groups attached to quinoxaline or benzofuroxan rings is described. The synthesis of 2-benzyl- and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives was based on the classical Beirut reaction. The tendency of fluorine atoms linked to quinoxaline or benzofuroxan rings to be replaced by a methoxy group when dissolved in an ammonia saturated solution of methanol was clearly demonstrated. In addition, 2-phenoxyquinoxaline 1,4-di-*N*-oxide derivatives became 2-aminoquinoxaline 1,4-di-*N*-oxide derivatives in the presence of gaseous ammonia.

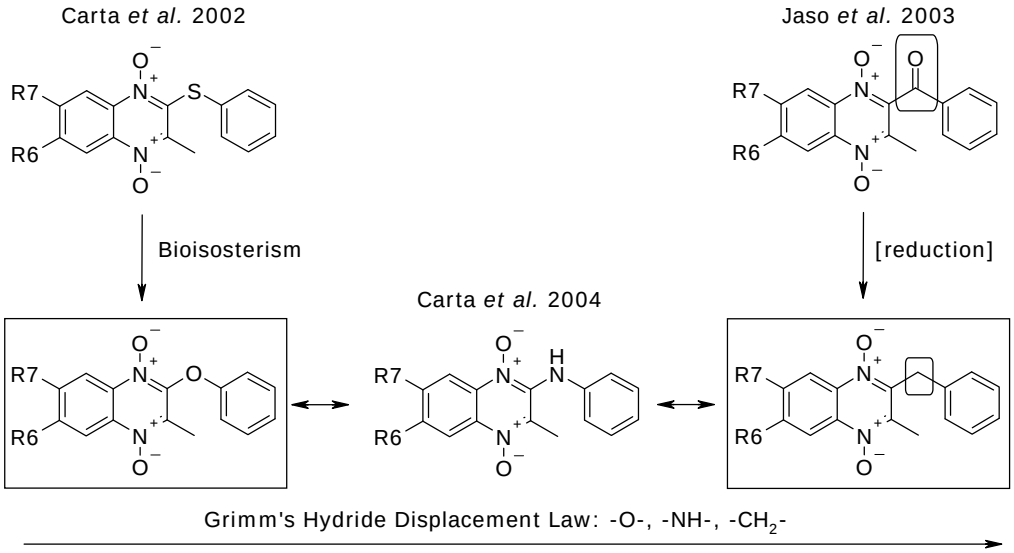
Keywords: Quinoxaline, *N*-oxides, Beirut reaction, gaseous ammonia.

Introduction

Quinoxaline and quinoxaline-1,4-di-*N*-oxide are heterocycles that are frequently used in the synthesis of biologically active compounds [1-4]. The quinoxaline moiety is described as a bioisoster

of the quinoline, naphthyl, benzothienyl and other aromatic rings [5], and the widespread activity of quinoxaline-1,4-di-*N*-oxide derivatives can be associated with the generation of free radicals [6]. In our continuing efforts to find quinoxaline-1,4-di-*N*-oxide derivatives with antimycobacterial [7-9] antiprotozoal [10-16] and anti-cancer activity [17, 18], a series of 2-benzyl-3-methylquinoxaline 1,4-di-*N*-oxide derivatives was proposed. With regards to work carried out by our research team, this series involves the analogues of 2-benzoyl-3-methylquinoxaline 1,4-di-*N*-oxide derivatives in which the carbonyl group has been reduced [7]. In addition, with regards to Carta's paper [19], this series, together with a series of 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives, could complete the bioisosterism replacements based on Grimm's Hydride Displacement Law (Scheme 1). This law states that the addition of a hydrogen atom with a pair of electrons (i.e. hydride) to an atom belonging to groups 4A, 5A, 6A, 7A on the Periodic Table, produces an isoelectronic pseudoatom, showing the same physical properties as those present in the column immediately behind the initial atom on the Periodic Table of the Elements [5]. The aim of this work was to obtain 2-benzyl- and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives as potential antitubercular drug candidates.

Scheme 1. Design of new quinoxaline-1,4-di-*N*-oxide derivatives with antimycobacterial activity.



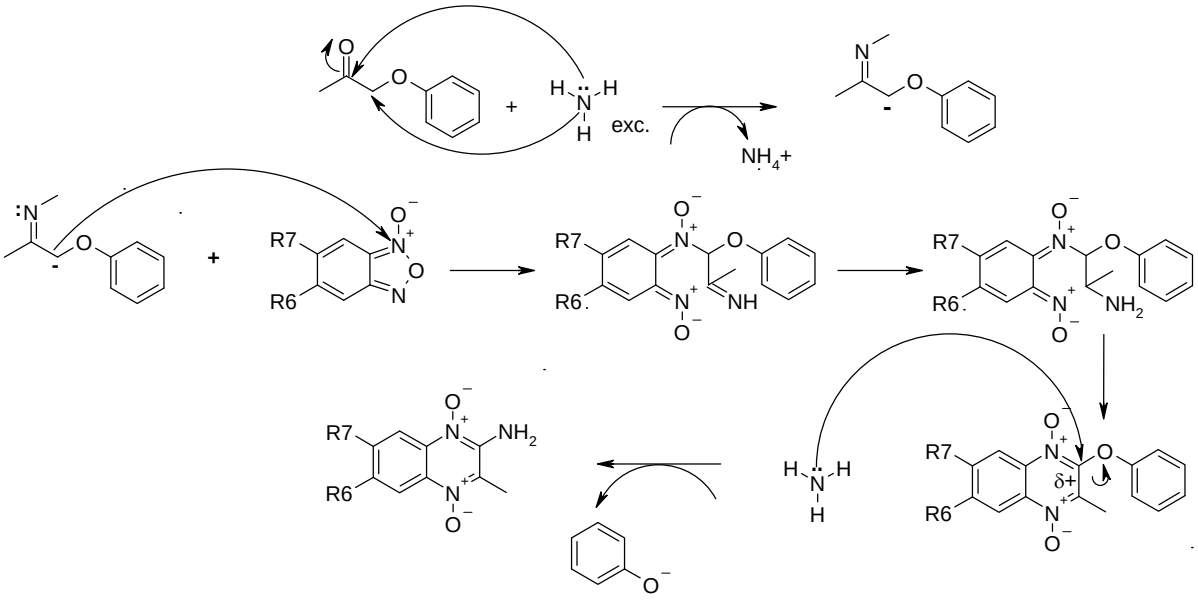
Results and Discussion

In a continuing effort to obtain new antitubercular drug candidates, the synthesis of 2-benzyl- and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives was proposed. The synthesis of each of these compounds was based on the classical Beirut reaction and, in this case, methanol and gaseous ammonia were chosen as reaction solvent and catalyst, respectively.

After workup, all the compounds obtained were chemically characterized by thin layer chromatography (TLC), infrared (IR) and nuclear magnetic resonance (^{1}H-NMR) spectra, as well as by elemental microanalysis. From these analyses, it was realised that the reaction with phenoxyacetone had failed to give the functionalized 2-phenoxy derivatives; surprisingly, this reaction gave other quinoxaline 1,4-di-*N*-oxide derivatives **10-12**, with an amino group, instead of the phenoxy moiety, linked to C2 of the quinoxaline ring (analytical data in the Experimental section). It is well known that

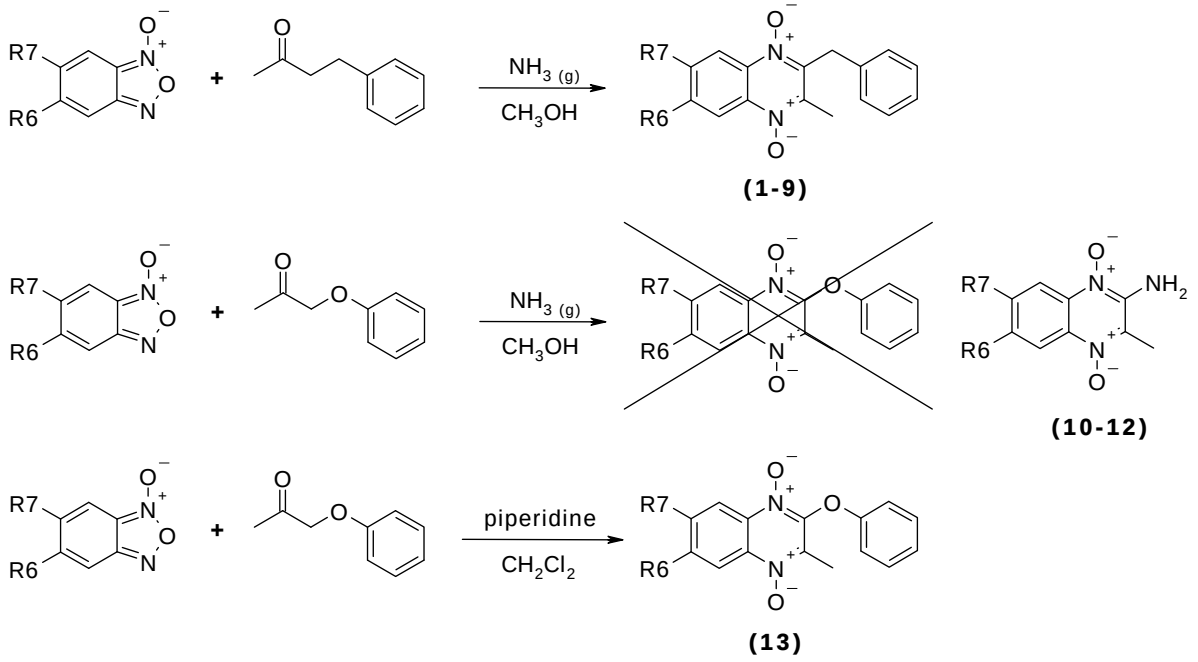
the phenoxy scaffold is a good leaving group and that the ammonia gas is a potent base; the curious part is that first the quinoxaline is formed and later, the substitution occurs (the events could not have occurred in any other way due to the products obtained) (Scheme 2).

Scheme 2. Possible mechanism of reaction for 2-amino-3-methylquinoxaline 1,4-di-*N*-oxide derivatives.



The experimental conditions (reaction solvent and catalyst) were explored with the aim of obtaining the target compounds. In an attempt to synthesize the 2-phenoxy derivatives, the catalyst and the solvent were substituted by piperidine and dichloromethane, respectively. In this case, the 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide (**13**) was obtained (Scheme 3).

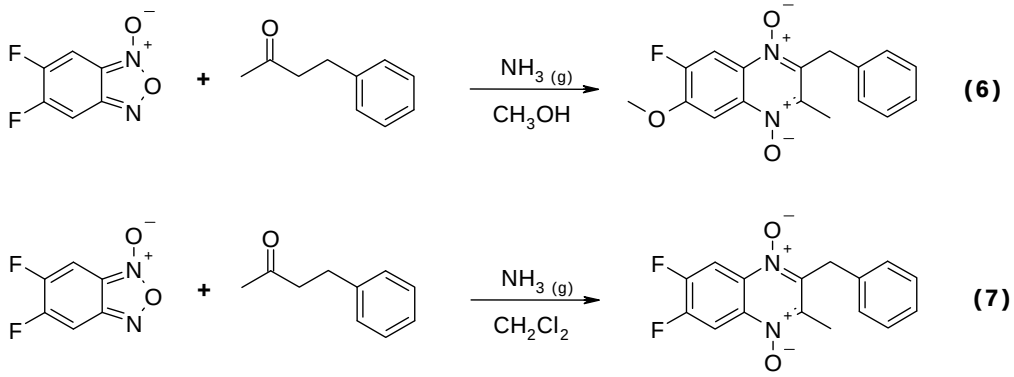
Scheme 3. Synthesis of 2-benzyl- and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives.



The formation of isomeric quinoxaline 1,4-di-*N*-oxide was observed in the case of monosubstituted benzofuroxans. According to previous reports [20], we have observed that 7-substituted quinoxaline 1,4-di-*N*-oxide derivatives prevailed over the 6-isomer, or in the case of the methoxy substituent, only the 7-isomer was formed (NOESY data, not shown). In practice, the workup and purification permitted isolation of the 7-isomer [21].

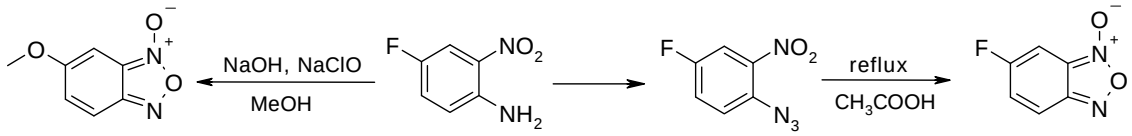
On the other hand, it was also observed that the reaction of difluorobenzofuroxan with benzylacetone in methanol failed to give 2-benzyl-6,7-difluoro-3-methylquinoxaline 1,4-di-*N*-oxide (**7**); the ^{1}H-NMR spectra of the obtained compound showed the presence of a methoxy group in the structure and that it corresponded to a 6,7-disubstituted quinoxaline; we consequently thought that, under these conditions, the fluorine atom in position 6 was being substituted by a methoxy group from the solvent (compound **6**). Such a displacement of the fluorine atom in position 6 has been observed on other occasions [22]. In an attempt to obtain the 6,7-difluoro derivative, the solvent was changed but keeping the remainder of the reaction conditions constant. In this case, using dichloromethane as reaction solvent, 2-benzyl-6,7-difluoro-3-methyl-quinoxaline 1,4-di-*N*-oxide (**7**) was obtained (Scheme 4).

Scheme 4. Synthesis of 2-benzyl-7-fluoro-6-methoxy- and 2-benzyl-6,7-difluoro-3-methylquinoxaline 1,4-dioxides.



Finally, we observed another curiosity arising from the use of fluorinated compounds. When we attempted to prepare R7(R6)-fluorobenzofuroxan by oxidation of the corresponding fluoronitroaniline, as previously described [23], the compound obtained was actually R7(R6)-methoxybenzofuroxan. Once again, methanol was present in the reaction as solvent. Therefore R7(R6)-fluorobenzofuroxan was prepared by thermal decomposition as reported [22, 23, 24].

Scheme 5. Synthesis of 5(6)-fluorobenzofuroxan from the corresponding o-nitroaniline.



Conclusions

Summarizing, this work clearly demonstrates the tendency of fluorine atoms linked to quinoxaline or benzofuroxan rings to leave their positions and be replaced by a methoxy group when dissolving in an ammonia saturated solution of methanol. In addition, the 2-phenoxyquinoxaline 1,4-di-*N*-oxide

derivatives, in the presence of gaseous ammonia, become 2-aminoquinoxaline 1,4-di-*N*-oxide derivatives.

Experimental

General

All the synthesized compounds were chemically characterized by thin layer chromatography (TLC), infrared (IR), nuclear magnetic resonance (^{1}H-NMR), mass spectra (MS) and elemental microanalysis (CHN). Alugram SIL G/UV254 (Layer: 0.2 mm) (Macherey-Nagel GmbH & Co. KG., Düren, Germany) was used for TLC and Silica gel 60 (0.040-0.063 mm, Merck) for Flash Column Chromatography. The ^{1}H-NMR spectra were recorded on a Bruker 400 Ultrashield instrument (400 MHz), using TMS as the internal standard and with DMSO-d_6 or $CDCl_3$ as the solvents; the chemical shifts are reported in ppm (δ) and coupling constants (*J*) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (double doublet) and m (multiplet). The IR spectra were recorded on a Nicolet Nexus FTIR (Thermo, Madison, USA) in KBr pellets. Mass spectra were measured on a MSD/DS 5973N mod. G2577A mass spectrometer (Agilent Technologies, Waldbronn, Germany) equipped with a direct insertion probe (DIP) and the ionization method was electron impact (EI, 70 eV). Elemental microanalyses were obtained on an CHN-900 Elemental Analyzer (Leco, Tres Cantos, Spain) from vacuum-dried samples. The analytical results for C, H, and N, were within ± 0.4 of the theoretical values. Chemicals were purchased from Panreac Química S.A. (Barcelona, Spain), Sigma-Aldrich Química, S.A. (Alcobendas, Spain), Acros Organics (Janssen Pharmaceuticalaan, Geel, Belgium) and Lancaster (Bischheim-Strasbourg, France).

General synthesis of 2-benzyl-3-methylquinoxaline 1,4-di-N-oxide derivatives **1-9** [11, 19]

Equimolar amounts (3.0–10.0 mmol) of the appropriate benzofuroxan and benzylacetone were added to methanol (20 mL) [or dichloromethane (20 mL) for the 6,7-difluoro derivative]. Gaseous ammonia gas was bubbled for 10 minutes through the mixture, which was then stirred at room temperature for 4 hours. After evaporating to dryness under reduced pressure, a crude solid was obtained, which was then washed by adding diethyl ether and purified by recrystallization from a mixture of methanol/dichloromethane.

2-Benzyl-3-methylquinoxaline 1,4-di-N-oxide (**1**). IR ν/cm^{-1}: 1320, 1074, 713; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.76 (s, 3H, C3-C**H$_3$**), 4.62 (s, 2H, C2-C**H$_2$**-Ph), 7.29 (m, 5H, CH_2-C_6**H$_5$**), 7.85 (m, 2H, H_6+H_7), 8.67 (m, 2H, H_5+H_8).

2-Benzyl-7-fluoro-3-methylquinoxaline 1,4-di-N-oxide (**2**). IR ν/cm^{-1}: 1321, 1077, 712; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.75 (s, 3H, C3-C**H$_3$**), 4.60 (s, 2H, C2-C**H$_2$**-Ph), 7.30 (m, 5H, CH_2-C_6**H$_5$**), 7.58 (ddd, *J*=2.74, 7.39, 9.52 Hz, 1H, H_6), 8.33 (dd, *J*= 2.69, 8.75 Hz, 1H, H_8), 8.68 (dd, *J*=5.10, 9.48 Hz, 1H, H_5).

2-Benzyl-7-chloro-3-methylquinoxaline 1,4-di-N-oxide (**3**). IR ν/cm^{-1}: 1323, 1076, 713; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.74 (s, 3H, C3-C**H$_3$**), 4.59 (s, 2H, C2-C**H$_2$**-Ph), 7.30 (m, 5H, CH_2-C_6**H$_5$**), 7.77 (dd, *J*=2.21, 9.17 Hz, 1H, H_6), 8.60 (d, *J*=9.16 Hz, 1H, H_5), 8.69 (d, *J*=2.20 Hz, 1H, H_8).
2-Benzyl-3,7-dimethylquinoxaline 1,4-di-N-oxide (**4**). IR ν/cm^{-1}: 1322, 1080, 704; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.63 (s, 3H, C7-C**H$_3$**), 2.77 (s, 3H, C3-C**H$_3$**), 4.62 (s, 2H, C2-C**H$_2$**-Ph), 7.30 (m, 5H, CH_2-C_6**H$_5$**), 7.85 (m, 2H, H_6+H_7), 8.67 (m, 2H, H_5+H_8), 7.68 (d, *J*=8.91 Hz, 1H, H_6), 8.47 (s, 1H, H_8), 8.54 (d, *J*=8.78 Hz, 1H, H_5).

2-Benzyl-7-methoxy-3-methylquinoxaline 1,4-di-N-oxide (**5**). IR ν/cm^{-1}: 1322, 1071, 707; ^{1}H-NMR ($CDCl_3$). δ/ppm: 2.74 (s, 3H, C3-C**H$_3$**), 4.02 (s, 3H, C7-OC**H$_3$**), 4.61 (s, 2H, C2-C**H$_2$**-Ph), 7.25 (m, 5H, CH_2-C_6**H$_5$**), 7.43 (dd, *J*=2.72, 9.49 Hz, 1H, H_6), 7.98 (d, *J*=2.71 Hz, 1H, H_8), 8.54 (d, *J*=9.46 Hz, 1H, H_5).

2-Benzyl-7-fluoro-6-methoxy-3-methylquinoxaline 1,4-di-N-oxide (**6**). IR ν/cm^{-1}: 1321, 1078, 703; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.75 (s, 3H, C3-C**H$_3$**), 4.11 (s, 3H, C6-OC**H$_3$**), 4.58 (s, 2H, C2-C**H$_2$**-Ph), 7.29 (m, 5H, CH_2-C_6**H$_5$**), 8.07 (d, *J*=7.85 Hz, 1H, H_5), 8.33 (d, *J*=10.72 Hz, 1H, H_8).

2-Benzyl-6,7-difluoro-3-methylquinoxaline 1,4-di-N-oxide (**7**). IR ν/cm^{-1}: 1322, 1080; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.75 (s, 3H, C3-C**H$_3$**), 4.58 (s, 2H, C2-C**H$_2$**-Ph), 7.30 (m, 5H, CH_2-C_6**H$_5$**), 8.47 (dd, *J*=9.28, 16.80 Hz, 2H, H_5+H_8).

2-Benzyl-6,7-dichloro-3-methylquinoxaline 1,4-di-N-oxide (**8**). IR ν/cm^{-1}: 1320, 1074, 713; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.74 (s, 3H, C3-C**H$_3$**), 4.56 (s, 2H, C2-C**H$_2$**-Ph), 7.33 (m, 5H, CH_2-C_6**H$_5$**), 8.75 (s, 1H, H_5); 8.78 (s, 1H, H_8).

2-Benzyl-3,6,7-trimethylquinoxaline 1,4-di-N-oxide (**9**). IR ν/cm^{-1}: 1327, 1082, 706; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.52 (s, 6H, C6-C**H$_3$**+C7-C**H$_3$**), 2.73 (s, 3H, C3-C**H$_3$**), 4.59 (s, 2H, C2-C**H$_2$**-Ph), 7.27 (m, 5H, CH_2-C_6**H$_5$**), 8.39 (s, 1H, H_8), 8.42 (s, 1H, H_5).

General synthesis of 2-amino-3-methylquinoxaline 1,4-di-N-oxide derivatives **10**-**12**.

Equimolar amounts (3.0–10.0 mmol) of the appropriate benzofuroxan and phenoxyacetone were added to methanol (20 mL). Gaseous ammonia was bubbled through the mixture for 10 minutes and then it was stirred at room temperature for 4 hours. After evaporating to dryness under reduced pressure, a crude solid was obtained. This was then washed by adding diethyl ether and purified by recrystallization from a mixture of methanol/dichloromethane.

2-Amino-3-methylquinoxaline 1,4-di-N-oxide (**10**). IR ν/cm^{-1}: 3400, 3290, 1616, 1329; ^{1}H-NMR (DMSO-d_6) δ/ppm: 2.57 (s, 3H, C3-C**H$_3$**), 7.61 (m, 3H, N**H$_2$**+H_6), 7.81 (t, *J*=7.78 Hz, 1H, H_7), 8.31 (dd, *J*=0.72, 8.53 Hz, 1H, H_5), 8.37 (dd, *J*=0.73, 8.53 Hz, 1H, H_8).

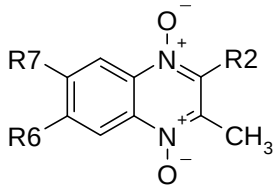
2-Amino-7-chloro-3-methylquinoxaline 1,4-di-N-oxide (**11**). IR ν/cm^{-1}: 3385, 3262, 1623, 1327; ^{1}H-NMR (DMSO-d_6). δ/ppm: 2.55 (s, 3H, C3-C**H$_3$**), 7.61 (dd, *J*=1.58, 9.07 Hz, 1H, H_6), 7.77 (s, 2H, N**H$_2$**), 8.26 (d, *J*=2.23 Hz, 1H, H_8), 8.36 (d, *J*=9.12 Hz, 1H, H_5).

2-Amino-6,7-dichloro-3-methylquinoxaline 1,4-di-N-oxide (**12**). IR ν/cm^{-1}: 3416, 3299, 1617, 1325; ^{1}H-NMR (DMSO-d_6). δ/ppm: 2.55 (s, 3H, C3-C**H$_3$**), 7.86 (s, 2H, N**H$_2$**), 8.42 (s, 1H, H_5), 8.50 (s, 1H, H_8)

Synthesis of 3-methyl-2-phenoxyquinoxaline 1,4-di-N-*oxide* (**13**).

An equimolar amount of phenoxyacetone was added to a solution of the appropriate benzofuroxan (3.0-10.0 mmol) in dry dichloromethane (35 mL). The mixture was allowed to stand at 0 ºC. Piperidine (1 mL) was added dropwise and the reaction mixture was stirred at room temperature in darkness for 4 hours. After evaporating to dryness under reduced pressure, a crude solid was obtained, which was then washed by adding diethyl ether (or *n*-hexane), affording the target compound. The precipitate obtained was purified by recrystallization from a mixture of methanol/dichloromethane. IR ν/cm^{-1}: 1326, 1093, 760; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.72 (s, 3H, C3-C**H$_3$**), 6.98 (d, *J*=7.72 Hz, 2H, $H_{2'}$+$H_{6'}$), 7.19 (t, *J*= 7.42 Hz, 1H, $H_{4'}$), 7.39 (dd, *J*=7.57 Hz, 2H, $H_{3'}$+$H_{5'}$); 7.87 (m, 2H, H_6+H_7); 8.63 (m, 1H, H_5); 8.69 (m, 1H, H_8).

Table 1. Structure, analytical data (C, H, N) and MS of the synthesized compounds



ID	R2	R6	R7	Formula	MW	Calc. C (found)	Calc. H (found)	Calc. N (found)	MS (EI, 70 eV): m/z
1	CH_2-Ph	H	H	$C_{16}H_{14}N_2O_2$	266.30	72.17 (71.78)	5.30 (5.27)	10.52 (10.24)	266 ([M$^-$]$^+$), 249, 232
2	CH_2-Ph	H	F	$C_{16}H_{13}FN_2O_2$	284.29	67.60 (67.34)	4.61 (4.52)	9.85 (10.19)	284 ([M$^-$]$^+$), 267, 250
3	CH_2-Ph	H	Cl	$C_{16}H_{13}ClN_2O_2$	300.75	63.90 (64.01)	4.36 (4.30)	9.31 (9.42)	300 ([M$^-$]$^+$), 283, 266
4	CH_2-Ph	H	CH_3	$C_{17}H_{16}N_2O_2$	280.33	72.84 (72.45)	5.75 (5.66)	9.99 (10.30)	280 ([M$^-$]$^+$), 263, 246, 230
5	CH_2-Ph	H	OCH_3	$C_{17}H_{16}N_2O_3$	296.33	68.91 (68.59)	5.44 (5.34)	9.45 (9.58)	296 ([M$^-$]$^+$), 279, 262, 247, 219
6	CH_2-Ph	F	OCH_3	$C_{17}H_{15}FN_2O_3$	314.32	64.96 (65.01)	4.81 (4.83)	8.91 (8.69)	314 ([M$^-$]$^+$), 297, 280, 265, 237
7	CH_2-Ph	F	F	$C_{16}H_{12}F_2N_2O_2$	302.28	63.58 (63.61)	4.00 (3.70)	9.27 (9.00)	302 ([M$^-$]$^+$), 285, 268

Table 1. Cont.

8	CH_2-Ph	Cl	Cl	$C_{16}H_{12}Cl_2N_2O_4$	335.19	57.33 (57.04)	3.61 (3.52)	8.36 (7.99)	334 ($[M^-]^+$), 317, 300, 285
9	CH_2-Ph	CH_3	CH_3	$C_{18}H_{18}N_2O_2$	294.36	73.45 (73.16)	6.16 (6.16)	9.52 (9.41)	294 ($[M^-]^+$), 277, 260, 245
10	NH_2	H	H	$C_9H_9N_3O_2 \cdot H_2O$	191.19+18.02	51.67 (51.61)	5.30 (5.52)	20.09 (19.77)	191 ($[M^-]^+$), 173, 145
11	NH_2	H	Cl	$C_9H_8ClN_3O_2 \cdot ½H_2O$	225.64+9.01	46.03 (46.40)	3.83 (3.63)	17.90 (17.51)	225 ($[M^-]^+$), 208, 191
12	NH_2	Cl	Cl	$C_9H_7Cl_2N_3O_2$	260.08	41.56 (41.90)	2.71 (2.72)	16.16 (15.78)	259 ($[M^-]^+$), 243, 226
13	O-Ph	H	H	$C_{15}H_{12}N_2O_3$	268.27	67.16 (66.81)	4.51 (4.52)	10.44 (10.05)	268 ($[M^-]^+$), 251, 234, 175

Acknowledgements

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