Comparative Use of Solvent-free KF-Al_2O_3 and K_2CO_3 in Acetone in the Synthesis of Quinoxaline 1,4-Dioxide Derivatives Designed as Antimalarial Drug Candidates

L. M. Lima[1,2], B. Zarranz[1], A. Marin[1], B. Solano[1], E. Vicente[1], S. Pérez Silanes[1], I. Aldana[1*] and A. Monge[1]

[1*]Unidad en Investigación y Desarrollo de Medicamentos,
Centro de Investigación en Farmacobiología Aplicada (CIFA),
University of Navarra, 31080 Pamplona, Spain

[2]Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio),
Faculdade de Farmácia, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro,
PO Box 68024, RJ 21944-970, Brazil

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In this paper we describe two new basic conditions for the synthesis of quinoxaline 1,4-dioxide derivatives in moderate to good yields. These conditions, exemplified by the use of K_2CO_3 in acetone or KF/Al_2O_3 in the absence of an organic solvent, were reproducible and applicable to the synthesis of 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide derivatives substituted in position 4 with electron-donating or electron-withdrawing groups.

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Introduction.

Interest in the preparation and reactions of quinoxaline 1,4-dioxides remains high partly due to the diverse biological activity observed in this type of heterocyclic compounds [1-3]. Our research group has recently described the preparation and pharmacological evaluation of various quinoxaline 1,4-dioxides derivatives with antichagas, antimalarial, anticancer and antituberculosis activities [4-10]. For example, we reported that compound, 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide (**1**), displays a hypoxia-selective cytotoxicity in cell culture which is similar to that observed for tirapazamine (TZP, **2**), a clinically promising anticancer agent that selectively kills the hypoxic cells [4-5].

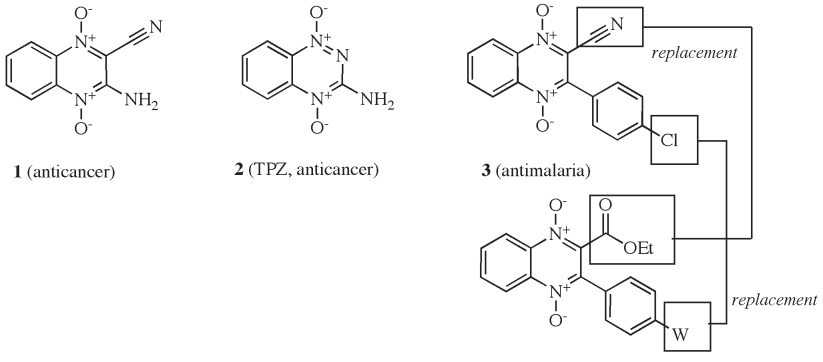
In an attempt to optimize the pharmacological activity of compound (**3**), a prototype of an antimalarial drug candidate [11], the synthesis of 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide funcionalized derivatives (**4-11**) was carried out in order to evaluate their antimalarial profile (Chart 1). This paper describes the systematic study of base and acid catalyst condensation of benzofurazan oxide (**12**) with ethyl benzoylacetate, as well as the comparative use of solvent free KF-Al_2O_3 and K_2CO_3 in acetone in the synthesis of the target esters (**4-11**) (Tables 1 and 2).

Results and Discussion.

Benzofurazan oxide (**12**) reacts with enamines that are generated *in situ* and also with enolates in order to form quinoxaline di-*N*-oxide in good yield [12-13]. This reaction, which has been given the name of Beirut reaction, is an excellent method for preparing a variety of heterocyclic compounds.

However, contrary to the condensation of benzofurazan oxide (**12**) with enamines, the use of β-keto-esters in a basic medium give quinoxaline di-*N*-oxide in low yields. For instance, the preparation of 2-methyl-3-car-

Chart 1



(**4-11**) W= H, F, Cl, Br, CH_3, CF_3, NO_2, OCH_3

boethoxyquinoxaline di-*N*-oxide, using triethylamine as the base and solvent, resulted in the formation of the desired product in 22% yield [13]. Nevertheless, some exceptions were found, as exemplified by the work of Kluge and coworkers, which describes the synthesis of 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide (**4**) in 47% of yield, using calcium hydroxide as base and 2-propanol as solvent [14].

In a continuing effort to synthesize new antimalarial drug candidates, a proposal was made to substitute the nitrile group, present in lead-compound **3**, with a carboethoxy moiety (Chart 1). A decision was made to vary the electronic profile of phenyl moiety and to correlate these modifications with the antimalarial profile of targets esters (**4-11**) (Chart 1).

The synthetic strategy was initiated by a systematic study carried out on the condensation of benzofurazan oxide (**12**) with ethyl benzoylacetate in order to identify a new methodology for the synthesis of 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide (**4**), previously described by Kluge and coworkers [14], followed by subsequent use of the selected methodology in the preparation of the target esters (**5-11**). Thus, **12** was condensed with ethyl benzoylacetate in triethylamine and chloroform (as base and solvent, respectively) at room temperature [11]. Surprisingly, after seven days of reaction, the desired product, 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide (**4**), was obtained in very low yield (Table 1). In an attempt to significantly improve this yield, triethylamine was substituted for morpholine or piperidine but without success (Table 1). The attempts to change the solvent and the reaction temperature failed to give (**4**) in good yields (Table 1). Therefore, the use of sodium ethoxide in ethanol for the formation of (**4**) was studied [15]; the results obtained were unexpected. In fact, using this methodology, it was impossible to isolate the desired derivative (**4**). After acidification of the aqueous phase, a complex mixture of compounds was obtained but the separation of these compounds by silica gel column chromatography was not possible.

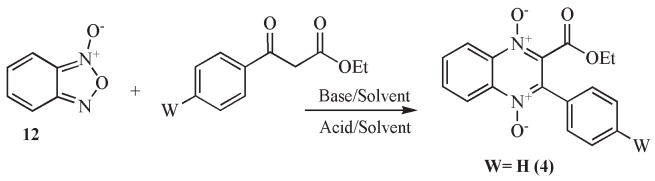
The next step taken was to investigate the use of an inorganic base as catalyst for the aforementioned chemical transformation. Condensation of benzofurazan oxide (**12**) with ethyl benzoylacetate was carried out in the presence of potassium carbonate at room temperature, using acetone as the solvent. The result was the formation of (**4**) in 50% yield (Table 1). With this promising result, an attempt was made to improve the yield using a more polar solvent, such as *N*,*N*-dimethylformamide (DMF). No significant differences were observed in the reactions carried out in the presence of acetone or DMF (Table 1).

Considering the versatility of potassium fluoride on alumina (KF/Al_2O_3), as an agent for inducing different chemical transformations [16], the use of KF/Al_2O_3 as a base and solid support, in the absence of an organic solvent, in the condensation of **12** with ethyl benzoylacetate was studied. Interestingly, the condensation step was carried out spontaneously, resulting in the formation of derivative (**4**) in 38% yield (Table 1).

In the condensation of **12** with ethyl benzoylacetate in an acid catalytic version, ammonium acetate in a mixture of

Table 1

Different Conditions for the Synthesis of 2-(Carboethoxy)-3-phenylquinoxaline 1,4-Dioxide



W	Reagent	Solvent	Temperature	Time	Yield (%)
H	Et_3N	$CHCl_3$	r.t.	7 days	5
H	Morpholine	$CHCl_3$	r.t.	7 days	7
H	Piperidine	$CHCl_3$	r.t.	7 days	5
H	Et_3N	$CHCl_3$	reflux	30 h	0*
H	Et_3N	EtOH	reflux	30 h	8
H	Morpholine	EtOH	reflux	30 h	3
H	NaOEt	EtOH	r.t.	1 h	0
H	K_2CO_3	acetone	r.t.	2 h	50
H	K_2CO_3	DMF	r.t.	2 h	53
H	$KF\text{-}Al_2O_3$	XX	r.t.	spontaneous	38
H	$Ac(NH_4)_2$	toluene/AcOH	reflux	7 days	13

*complex mixture of product soluble in aqueous basic phase

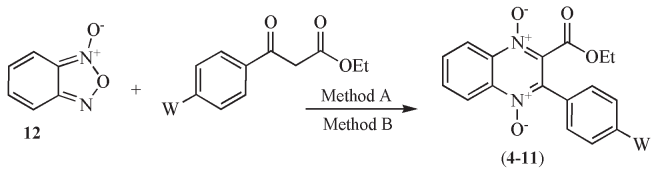
toluene and acetic acid [17], under reflux for seven days, resulted in the formation of (**4**) in only 13% yield.

Once the systematic study of the condensation of benzofurazan oxide (**12**) with ethyl benzoylacetate under different conditions was concluded, the methodologies that had led to better yields of **4** were selected. A study in which the electronic character of the β-keto esters was varied was then carried out (Table 2). As shown in Table 2, the condensation of benzofurazan oxide (**12**) with *para*-substituted ethyl benzoylacetate, using K_2CO_3 in acetone at room temperature for two hours, resulted in the formation of the corresponding quinoxaline di-*N*-oxides (**4-11**) in moderate to good yields. These results appear to indicate that the condensation step was influenced by the electronic profile of the β-keto-ester because significant differences were found upon comparing the condensation of **12** with that of ethyl-(4-nitrobenzoyl)acetate (σ_p = 0.81) and with that of ethyl-(4-methoxylbenzoyl) acetate (σ_p = -0.28)]. These results suggest that β-keto-ester attaches to an electron-withdrawing group (positive value of σ_p), facilitating the condensation step with benzofurazan oxide (**12**) and resulting in the formation of quinoxaline 1,4-dioxide in superior yields. In contrast, no significative differences were observed for the condensation when using KF/Al_2O_3 as the catalyst, in the absence of organic solvent. However, this transformation seemed to depend on the physical state of the β-keto-ester. In other words, it appears that at least one of the reagents used in this transformation step must be a liquid in order for the chemical conversion to be a success; no reaction was found when a solid β-keto-ester, such as (4-nitrobenzoyl)acetate, was used (Table 2).

The assignment of gross structural features for each 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide derivative was unequivocally determined by ^{1}H-NMR, ^{13}C-NMR, IR, mass spectra and elemental analyses.

Table 2

Synthesis of 2-(Carboethoxy)-3-phenylquinoxaline 1,4-Dioxide Derivatives Applying Methods A and B. **Method A: 12**+ Functionalized Ethyl Benzoylacetate/K_2CO_3/acetone/r.t.; **Method B: 12** + Functionalized Ethyl Benzoylacetate//KF-Al_2O_3 40% w/t; r.t



Compounds	W	s_p	Method	Time (hr)	Yield (%)	Method	Time (hr)	Yield (%)
4	H	0	A	2	50	B	spontaneous	38
5	F	0.15	A	2	35	B	spontaneous	34
6	Cl	0.24	A	2	34	B	spontaneous	48
7	Br	0.26	A	2	64	B	spontaneous	40
8	CH_3	-0.14	A	2	46	B	spontaneous	36
9	CF_3	0.53	A	2	60	B	spontaneous	31
10	NO_2	0.81	A	2	60	B	No reaction	0
11	OCH_3	-0,28	A	2	15	B	spontaneous	33

Conclusions.

This study permitted the identification of two new basic conditions for the synthesis of quinoxaline 1,4-dioxide derivatives in moderate to good yields. These conditions, exemplified by the use of K_2CO_3 in acetone or by the use of KF/Al_2O_3, in the absence of an organic solvent, were reproducible and applicable to the synthesis of 2-(carboethoxy)-3-phenylquinoxaline 1,4-dioxide derivatives substituted in position 4 with electron-donating or electron-withdrawing groups. In terms of simplicity, cost, and availability of reagents, the use of potassium carbonate in acetone appeared to be the method of choice for large-scale applications. The reaction which was carried out using 73.4 mmol of benzofurazan oxide (**12**) and 73.4 mmol of β-keto-ester resulted in the formation of the desired product without a significant loss of yield.

EXPERIMENTAL

Chemistry.

Melting points were determined with a Mettler FP82+FP80 apparatus (Greifense, Switzerland) and have not been corrected. The ^{1}H NMR spectra were recorded on a Bruker AC-200E instrument (200 MHz) and Bruker 400 Ultrashield™ (400 MHz), using TMS as the internal standard and with DMSO-d_6 and $CDCl_3$ as the solvent; 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 performed on a Perkin Elmer 1600 FTIR (Norwalk, CT, USA) in KBr pellets; the frequencies are expressed in cm^{-1}. Elemental microanalyses were obtained on an Elemental Analyzer (Carlo Erba 1106, Milan, Italy) from vacuum-dried samples. The analytical results for C, H, and N, were within ± 0.4 of the theoretical values.

Alugram® SIL G/UV_{254} (Layer: 0.2 mm) (Macherey-Nagel GmbH & Co. KG. Postfach 101352. D-52313 Düren, Germany) was used for Thin Layer Chromatography and Silica gel 60 (0.040-0.063 mm) for Column flash Chromatography (Merck). HPLC conditions: Column Nova Pack C18 60 A 4 µm (3.9x150 mm); mobile phase: acetonitrile/water (60:40); flux: 1 mL/min.

Chemicals were purchased from E. Merck (Darmstadt, Germany), Scharlau (F.E.R.O.S.A., Barcelona, Spain), Panreac Química S.A. (Montcada i Reixac, Barcelona, Spain), Sigma-Aldrich Química, S.A., (Alcobendas, Madrid), Acros Organics (Janssen Pharmaceuticalaan 3a, 2440 Geel, België) and Lancaster (Bischheim-Strasbourg, France).

Benzofurazan oxide (**12**) was prepared as reported [4].

General Procedure for the Preparation of 2-(Carboethoxy)-3-phenylquinoxaline 1,4-Dioxide 4'-Functionalized Derivatives (**4-11**).

Metho d A.

The corresponding functionalized ethyl benzoylacetate (7.34 mmol) and 9.55 mmol of potassium carbonate were added to a solution of 7.34 mmol of benzofurazan oxide (**12**) in 50 mL of acetone. The suspension was stirred at room temperature for two hours. The quinoxaline 1,4-dioxide derivatives (**4-11**) were isolated by adding 50 mL of water, followed by extraction with dichlorometane (5 x 40 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by recrystallization from a mixture of methanol/ether/*n*-hexane (2:4:4). Yields 15-64%.

Method B.

Appropriate stoichometric quantities of benzofurazan oxide (**12**) (7.34 mmol) and of functionalized ethyl benzoylacetate (7.34 mmol) with 1 g of KF-Al_2O_3 (40% w/t) were thoroughly mixed in an agate mortar; an instantaneous change of color was observed in the mixture. The quinoxaline 1,4-dioxide derivatives (**4-11**) were isolated by adding 100 mL of dichoromethane, followed by filtration and evaporation of the organic layer under reduced pressure. The residue was purified by recrystallization from a mixture of methanol/ether/*n*-hexane (2:4:4). Yields 31-48%.

2-(Carboethoxy)-3-phenylquinoxaline 1,4-Dioxide (**4**).

The derivative (**4**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl benzoylacetate as yellow powder (Methods A and B: 50% and 38% yields, respectively). ^1H NMR ($CDCl_3$): δ 1.08 (t, J= 7.2 Hz, OCH_2CH_3); 4.25 (t, J= 7.2 Hz, OCH_2CH_3); 7.53 (m, H3'-H5'); 7.61 (m, H2' and H6'); 7.91 (m, H6 and H7); 8.65 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 13.98 (OCH_2CH_3), 63.65 (OCH_2CH_3), 120.89 (C5), 121.08 (C8), 127.84 (C1'), 129.16 (C3' and C5'), 130.15 (C2' and C6'), 131.26 (C4'), 132.51 (C6), 132.53 (C7), 136.53 (C2), 137.73 (C10), 138.81 (C3), 140.08 (C9), 159.66 (CO_2Et) ppm. Ir (KBr): 2978 (ArC-H), 1746 (C=O), 1352 (N-oxide), 701 and 666 (mono-substituted phenyl) cm^{-1}. Mass: 310 (m/z, 100%), 294 (M^+, 6%), 249 (M^+, 51%), 221 (M^+, 46%), 77 (M^+, 46%).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.52; N, 9.03. Found: C, 65.65; H, 4.57; N, 8.98.

2-(Carboethoxy)-3-(4'-fluoro)phenylquinoxaline 1,4-Dioxide (**5**).

The derivative (**5**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-fluorobenzoyl)acetate as yellow powder (Methods A and B: 35% and 34% yields, respectively). ^1H NMR ($DMSOd_6$): δ 1.15 (t, J= 7.2 Hz, OCH_2CH_3); 4.30 (t, J= 7.2 Hz, OCH_2CH_3); 7.21 (t, J= 8.6 Hz, H3' and H5'); 7.64 (m, H6 and H7); 7.93 (dd, J= 8.6 Hz and 4.0 Hz, H2' and H6'); 8.66 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 14.07 (OCH_2CH_3), 63.81 (OCH_2CH_3), 116.41 (C3' and C5'), 120.93 (C5), 121.18 (C8), 125.77 (C1'), 132.53 (C6), 132.63 (C2' and C6'), 133.24 (C7), 136.46 (C2), 137.78 (C10), 138.76 (C3), 139.13 (C9), 159.65 (CO_2Et), 163.11 (C4') ppm. Ir (KBr): 3036 (ArC-H), 1741 (C=O), 1348 (N-oxide), 1319 (C-F), 771 and 834 (*p*-substituted phenyl) cm^{-1}. Mass: 328 (m/z, 100%), 312 (M^+, 7%), 267 (M^+, 54%), 239 (M^+, 62%), 95 (M^+, 29%).

Anal. Calcd. for $C_{17}H_{13}N_2O_4F$: C, 62.19; H, 3.96; N, 8.54. Found: C, 62.15; H, 3.82; N, 8.37.

2-(Carboethoxy)-3-(4'-chloro)phenylquinoxaline 1,4-Dioxide (**6**).

The derivative (**6**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-chlorobenzoyl)acetate as yellow powder (Methods A and B: 34% and 48% yields, respectively). ^1H NMR ($CDCl_3$): δ 1.18 (t, J= 7.2 Hz, OCH_2CH_3); 4.32 (t, J= 7.2 Hz, OCH_2CH_3); 7.53 (dd, J= 8.8 Hz and 1.6 Hz, H3' and H5'); 7.58 (dd, J= 8.8 Hz and 1.6 Hz, H2' and H6'); 7.95 (m, H6 and H7); 8.68 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 14.07 (OCH_2CH_3), 63.86 (OCH_2CH_3), 120.94 (C5), 121.18 (C8), 126.19 (C1'), 129.54 (C2' and C6'), 131.19 (C3' and C5'), 132.69 (C6), 133.26 (C7), 136.59 (C2), 137.61 (C4'), 137.82 (C10), 138.76 (C3), 139.01 (C9), 159.59 (CO_2Et) ppm. Ir (KBr): 3029 (ArC-H), 1745 (C=O), 1341 (N-oxide), 1090 (C-Cl), 771 and 822 (*p*-substituted phenyl) cm^{-1}. Mass: 344 (m/z, 6%), 328 (M^+, 2%), 151 (M^+, 10%), 139 (M^+, 100%), 111 (M^+, 19%).

Anal. Calcd. for $C_{17}H_{13}N_2O_4Cl$: C, 59.30; H, 3.78; N, 8.14. Found: C, 58.99; H, 3.83; N, 8.17.

2-(Carboethoxy)-3-(4'-bromo)phenylquinoxaline 1,4-Dioxide (**7**).

The derivative (**7**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-bromobenzoyl)acetate as yellow powder (Methods A and B: 64% and 40% yields, respectively). ^1H NMR ($CDCl_3$): δ 1.18 (t, J= 7.2 Hz, OCH_2CH_3); 4.31 (t, J= 7.2 Hz, OCH_2CH_3); 7.52 (dd, J= 8.4 Hz and 1.6 Hz, H3' and H5'); 7.69 (dd, J= 8.4 Hz and 1.6 Hz, H2' and H6'); 7.94 (m, H6 and H7); 8.66 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 14.08 (OCH_2CH_3), 63.89 (OCH_2CH_3), 120.96 (C5), 121.19 (C8), 126.00 (C4'), 126.67 (C1'), 131.84 (C2' and C6'), 132.51 (C3' and C5'), 132.70 (C6), 133.27 (C7), 136.28 (C2), 137.83 (C10), 138.78 (C3), 139.05 (C9), 159.58 (CO_2Et) ppm. Ir (KBr): 2985 (ArC-H), 1742 (C=O), 1349 (N-oxide), 1013 (C-Br), 779 and 821 (*p*-substituted phenyl) cm^{-1}. Mass: 390 (m/z, 25%), 325 (M^+, 26%), 220 (M^+, 53%), 91 (M^+, 95%).

Anal. Calcd. for $C_{17}H_{13}N_2O_4Br$: C, 52.44; H, 3.34; N, 7.20. Found: C, 52.28; H, 3.37; N, 7.13.

2-(Carboethoxy)-3-(4'-methyl)phenylquinoxaline 1,4-Dioxide (**8**).

The derivative (**8**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-methylbenzoyl)acetate as yellow powder (Methods A and B: 46% and 36% yields, respectively). ^{1}H NMR ($CDCl_3$): δ 1.15 (t, J= 7.2 Hz, OCH_2CH_3); 2, 47 (s, $ArCH_3$); 4.30 (t, J= 7.2 Hz, OCH_2CH_3); 7.35 (d, J= 8.0 Hz, H3' and H5'); 7.52 (d, J= 8.0 Hz, H2' and H6'); 7.91 (m, H6 and H7); 8.69 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 14.03 (OCH_2CH_3), 22.02 ($ArCH_3$), 63.64 (OCH_2CH_3), 120.89 (C5), 121.21 (C8), 124.83 (C1'), 129.88 (C3' and C5'), 130.01 (C2' and C6'), 132.07 (C6), 132.39 (C7), 136.60 (C2), 137.64 (C10), 138.83 (C3), 140.26 (C9), 141.65 (C4'), 159.79 (CO_2Et) ppm. Ir (KBr): 3023 (ArC-H), 1745 (C=O), 1349 (N-oxide), 777 and 818 (*p*-substituted phenyl) cm^{-1}. Mass: 324 (m/z, 100%), 308 (M^+, 7%), 263 (M^+, 40%), 235 (M^+, 30%), 105 (M^+, 44%).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.94; N, 8.64. Found: C, 66.39; H, 4.96; N, 8.52.

2-(Carboethoxy)-3-(4'-trifluoromethyl)phenylquinoxaline 1,4-Dioxide (**9**).

The derivative (**9**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-trifluoromethylbenzoyl)acetate as orange crystals (Methods A and B: 60% and 31% yields, respectively). ^{1}H NMR ($DMSOd_6$): δ 1.12 (t, J= 7.2 Hz, OCH_2CH_3); 4.29 (t, J= 7.2 Hz, OCH_2CH_3); 7.77 (d, J= 8.8 Hz, H2' and H6'); 7.82 (dd, J= 8.8 Hz, H3' and H5'); 7.94 (m, H6 and H7); 8.67 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 13.94 (OCH_2CH_3), 63.92 (OCH_2CH_3), 120.60 ($ArCF_3$), 120.99 (C5), 121.19 (C8), 125.31 (C4'), 126.14 (C3' and C5'), 130.85 (C2' and C6'), 131.48 (C1'), 132.87 (C6), 133.36 (C7), 136.23 (C2), 137.99 (C10), 138.66 (C9), 138.77 (C3), 159.42 (CO_2Et) ppm. Ir (KBr): 2955 (ArC-H), 1747 (C=O), 1350 (N-oxide), 1319 (C-F), 771 and 834 (*p*-substituted phenyl) cm^{-1}. Mass: 378 (m/z, 64%), 362 (M^+, 5%), 317 (M^+, 39%), 289 (M^+, 57%), 179 (M^+, 100%).

Anal. Calcd. for $C_{18}H_{13}N_2O_4F_3$: C, 57.14; H, 3.44; N, 7.41. Found: C, 57.12; H, 3.36; N, 7.29.

2-(Carboethoxy)-3-(4'-nitro)phenylquinoxaline 1,4-dioxide (**10**).

The derivative (**10**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-nitrobenzoyl)acetate as yellow powder (Methods A and B: 60% and 0% yields, respectively). ^{1}H NMR ($DMSOd_6$): δ 1.17 (t, J= 7.2 Hz, OCH_2CH_3); 4.30 (t, J= 7.2 Hz, OCH_2CH_3); 7.85 (dd, J= 8.8 Hz and 1.6 Hz, H2' and H6'); 7.97 (m, H6 and H7); 8.40 (dd, J= 8.8 Hz and 1.6 Hz, H3' and H5'); 8.68 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 14.09 (OCH_2CH_3), 64.11 (OCH_2CH_3), 121.03 (C5), 121.18 (C8), 124.25 (C2' and C6'), 131.77 (C1'), 131.79 (C3' and C5'), 133.13 (C6), 133.52 (C7), 135.99 (C2), 137.92 (C10), 138.11 (C3), 138.75 (C9), 149.41 (C4'), 159.34 (CO_2Et) ppm. Ir (KBr): 2981 (ArC-H), 1740 (C=O), 1521 (C-NO_2), 1342 (N-oxide), 777 and 851 (*p*-substituted phenyl) cm^{-1}. Mass: 355 (m/z, 26%), 339 (M^+, 4%), 294 (M^+, 10%), 179 (M^+, 100%), 144 (M^+, 33%).

Anal. Calcd. for $C_{17}H_{13}N_3O_6$: C, 57.46; H, 3.66; N, 11.83. Found: C, 57.38; H, 3.72; N, 11.74.

2-(Carboethoxy)-3-(4'-methoxy)phenylquinoxaline 1,4-Dioxide (**11**).

The derivative (**11**) was obtained by condensation of benzofurazan oxide (**12**) with ethyl (4-methoxybenzoyl)acetate as yellow powder (Methods A and B: 15% and 33% yields, respectively). ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J= 7.2 Hz, OCH_2CH_3); 3.89 (s, OCH_3); 4.31 (t, J= 7.2 Hz, OCH_2CH_3); 7.05 (dd, J= 8.8 Hz and 1.6 Hz, H3' and H5'); 7.60 (dd, J= 8.8 Hz and 1.6 Hz, H2' and H6'); 7.91 (m, H6 and H7); 8.66 (m, H5 and H8) ppm. ^{13}C NMR ($CDCl_3$): δ 14.13 (OCH_2CH_3), 55.84 ($ArOCH_3$), 63.66 (OCH_2CH_3), 114.63 (C3' and C5'), 119.71 (C1'), 120.86 (C5), 121.17 (C8), 131.83 (C2' and C6'), 132.89 (C6), 133.06 (C7), 136.62 (C2), 137.53 (C10), 138.78 (C3), 139.97 (C9), 159.89 (CO_2Et), 161.82 (C4') ppm. Ir (KBr): 3090 (ArC-H), 1740 (C=O), 1343 (N-oxide), 1261 (C-O-C), 777 and 829 (*p*-substituted phenyl) cm^{-1}. Mass: 340 (m/z, 100%), 324 (M^+, 15%), 262 (M^+, 39%), 235 (M^+, 31%), 179 (M^+, 96%).

Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.53; H, 4.71; N, 8.23. Found: C, 63.37; H, 4.72; N, 8.13.

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