6-FLUORO-7-(1-PIPERAZINYL)QUINOXALINE 1,4-DIOXIDES. PART I. 2-(*N*-2-HYDROXYALKYLCARBAMOYL) DERIVATIVES

Mustafa M. El-Abadelah*[a], Musa Z. Nazer[a], Naser S. El-Abadla[a], and Herbert Meier*[b]

[a] Chemistry Department, University of Jordan, Amman, Jordan

[b] Johannes Gutenberg-Universität Mainz, Institut für Organische Chemie, D-55099 Mainz, Germany

Abstract —A series of *N*-[6-fluoro-7-(4-methyl-1-piperazinyl)-3-methyl-2-quinoxaloyl]-*β*-aminoalkanol 1,4-dioxides (**12a-h**) have been synthesized for bioassay *via* the Beirut reaction of 5(6)-fluoro-6(5)-(4-methyl-1-piperazinyl)benzofuroxan (**9**) with the appropriate *N*-acetoacetyl-*β*-aminoalkanol in the presence of triethylamine. Preliminary *in vitro* investigations have indicated that none of the title compounds exhibits any significant antibacterial potency at concentrations ≤ 200 μg / ml.

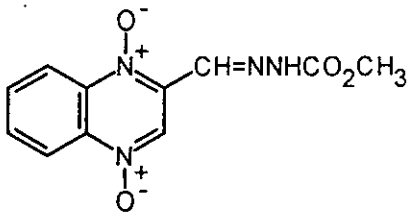
Introduction

Substantial development in the chemistry of amine *N*-oxides began some fifty years ago by the work of Ochiai's group in Japan.[1] Interest in the chemistry of heteroaromatic *N*-oxides was spurred by the early findings that some of the naturally occurring *N*-oxides, such as iodinin[2] and aspergillic acid,[3] possess antibacterial potency.[4]

Quinoxaline-1,4-dioxides were long known to exhibit antibacterial activity.[1,5] An elegant and versatile route towards their synthesis, known as the Beirut reaction,[6] involves the

interaction of benzofuroxans with enolate anions,[7] or with enamines.[8] Over the years, a significant number of substituted quinoxaline 1,4-dioxides was synthesized and bioassayed.[9,10] Compound (**1**) was found active *in vitro* against *streptococcus pyogenes* and *Proteus vulgaris*, and was commercialized as feed additive / growth-promoting factor (Mecadox).[11] Compound (**2**) showed a much greater spectrum of antibacterial activity than **1**, being particularly effective against pathogens of the gastrointestinal tract as *P. vulgaris, Escherichia coli, Enterobacter aerogenes* and *Pseudomonus aeruginosa*.[12]

Currently, the second generation fluoroquinolone-antimicrobial drugs, such as norfloxacin (**3a**)[13] and ciprofloxacin (**3b**),[14] are receiving much attention; their high level of antibacterial potency is associated with the presence of 6-fluoro and 7-(1-piperazinyl) grouping.[15]



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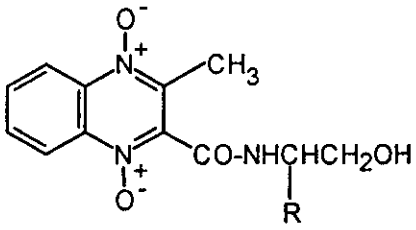

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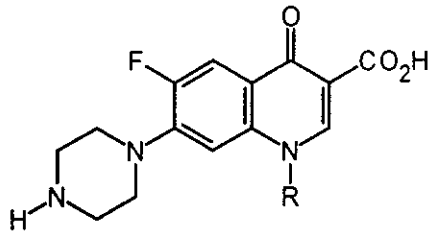


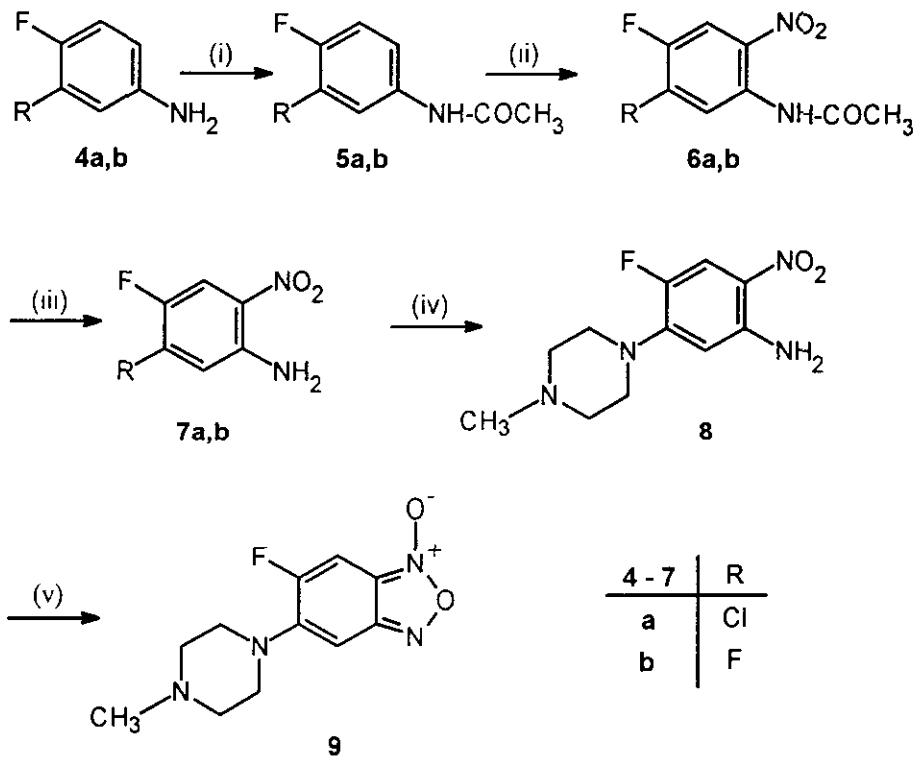
	R
3a	$-C_2H_5$
3b	

Previously, we reported[16] data on some β-aminoalkanol analogues of **2** ($R \neq H$). We also sought to prepare relevant quinoxaline 1,4-dioxides with the concept of introducing fluorine and *N*-methylpiperazine at the 6- and 7-positions, respectively; such substituents might enhance the antibacterial action of the derivatised quinoxaline 1,4-dioxides. In particular, we prepare some *N*-[6-fluoro-7-(4-methyl-1-piperazinyl)-3-methyl-2-quinoxaloyl]-β-aminoalkanol 1,4-dioxides (**12a-h**) for bioassay. Herein we report their synthesis and properties.

Results and Discussion

Syntheses . Our approach to the synthesis of the target quinoxaline 1,4-dioxides **(12a-h)** is *via* application of the Beirut reaction[8] of the appropriately substituted benzofuroxan **(9)** with the particular *N*-acetoacetyl-*β*-aminoalkanol **(11a-h)**. The required 5(6)-fluoro-6(5)-(4-methyl-1-piperazinyl)benzofuroxan **(9)** is prepared by the general route (Scheme 1) involving hypochlorite oxidative cyclization[17,18] of 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline **(8)**. The latter compound was obtained by the reaction of

Scheme I



Reaction conditions :

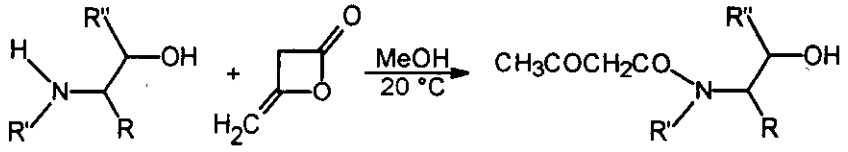
(i) $(Ac)_2O$ / 20 °C ; 30 min. (ii) conc. H_2SO_4 + conc. HNO_3 / 0-5 °C ; 2 h.

(iii) conc. HCl + EtOH / reflux ; 3 h. (iv) HN⌒N–CH_3 + DMSO / 140 - 145 °C ; 2 h.

(v) Ethanolic KOH (2%) + NaOCl (Hypex) / 0 °C ; 2 h.

N-methylpiperazine with 5-chloro-4-fluoro-2-nitroaniline (**7a**) or with 4,5-difluoro-2-nitroaniline (**7b**), following a reported procedure[19,20] that employs standard reaction conditions for related systems. Compound (**7a**) is readily accessible[21] from 3-chloro-4-fluoroaniline (**4a**) *via* *N*-acylation, followed by nitration and subsequent deacylation as shown in Scheme I. 3,4-Difluoroaniline (**4b**) was likewise converted into 4,5-difluoro-2-nitroaniline (**7b**) following reported procedures.[22] The *N*-acetoacetyl-*β*-aminoalkanols (**11a-h**) were prepared by the reaction of diketene with the corresponding *β*-aminoalkanol (**10a-h**).[16,23] (Scheme II).

Scheme II



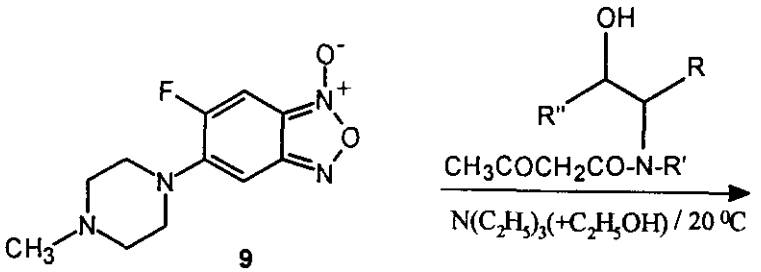
10a-h **11a-h**

A series of *N*-[6-fluoro-7-(4-methyl-1-piperazinyl)-3-methyl-2-quinoxaloyl]-*β*-aminoalkanol-1,4-dioxides (**12a-h**) was synthesized by the reaction of benzofuroxan (**9**) with the appropriate *N*-acetoacetyl-*β*-aminoalkanol (**11a-h**) in the presence of triethylamine (Scheme III). The desired quinoxaline 1,4-dioxides crystallized within 1-3 days as yellow solids. Compounds (**9**) and (**12a-h**) were characterized by elemental analyses (Table 1) and spectral data (*vida infra*).

In principle the Beirut reaction, exemplified here between the unsymmetrically 5,6-disubstituted benzofuroxan (**9**) and the enolate form of **11**, should give two isomeric products (**12**) and (**13**) (Scheme III) as has been realized in a number of related cases.[6,8] In the present work we have been able to isolate only compounds (**12a-h**), as the major isomeric products. In support of the assigned substitution pattern for compounds (**12a-h**), selective monodeoxygenation was performed on compound (**12f**), as a model of the series, using trimethylphosphite. This reagent was reported to remove selectively the *N*-oxygen nearest to the electron-withdrawing group in 2,3-disubstituted quinoxaline-1,4-dioxides.[24,25] In the present work, this reagent displayed similar selectivity towards compound (**12f**) leading to the removal of the *N*-1-oxygen adjacent to the 2-carboxamido group with ultimate

production of the corresponding 4-monoxide **(14f)** (Scheme IV) as evidenced from its nmr spectral data (*vide infra*).

Scheme III



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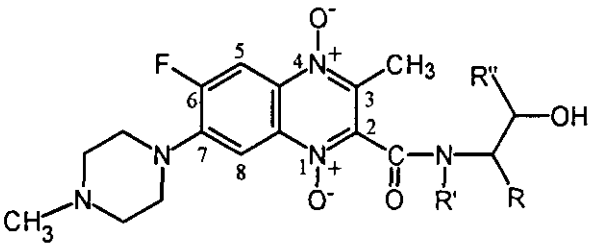
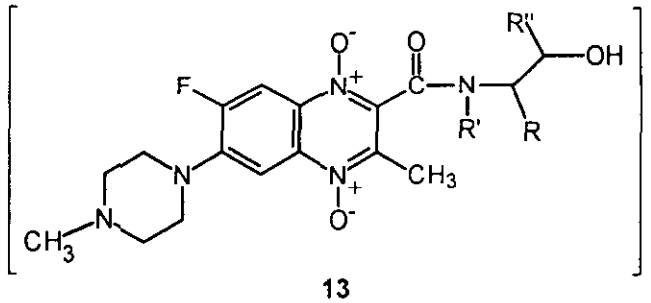


12a-h

+



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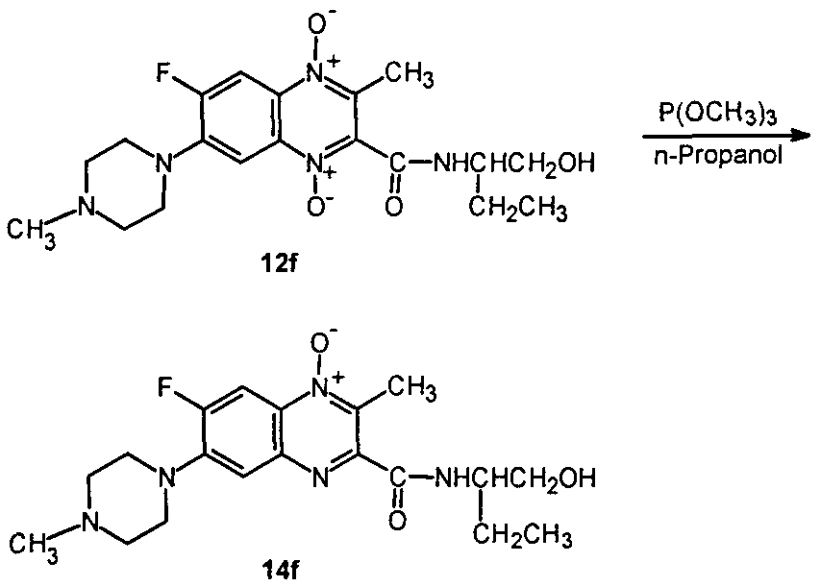
Compounds **(10-12)** and **(13)**

No.	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R	H	H	CH_3	CH_2Ph	$CH(CH_3)C_2H_5$	CH_2CH_3	$CH_2CH(CH_3)_2$	CH_3
R'	H	CH_3	H	H	H	H	H	CH_3
R"	H	H	H	H	H	H	H	Ph

Table 1. Physical and Analytical Data for Compounds (**9, 12a-h, 14f**).

Compd No	mp (°C)	Yield (%)	Mol. Formula	$[M]^{+\cdot}$	% Analysis (Calcd / Found) C	H	N
9	96-97	76	$C_{11}H_{13}N_4O_2F$	252	52.38	5.19	22.21
					52.18	5.15	22.08
12 a	192-193	55	$C_{17}H_{22}N_5O_4F$	379	53.82	5.84	18.46
					53.69	5.91	18.34
12 b	104-105	45	$C_{18}H_{24}N_5O_4F$	393	54.95	6.15	17.80
					55.19	6.12	17.67
12 c	207-208	53	$C_{18}H_{24}N_5O_4F$	393	54.95	6.15	17.80
					54.73	6.00	17.54
12 d	179-180	60	$C_{24}H_{28}N_5O_4F$	469	61.40	6.01	14.92
					61.21	6.00	14.86
12 e	220-221	58	$C_{21}H_{30}N_5O_4F$	435	57.92	6.94	16.08
					58.24	7.10	16.25
12 f	223-224	72	$C_{19}H_{26}N_5O_4F$	407	56.01	6.43	17.19
					55.86	6.33	17.00
12 g	212-213	70	$C_{20}H_{28}N_5O_4F$	421	57.00	6.70	16.62
					56.79	6.78	16.46
12 h	180-182	41	$C_{25}H_{30}N_5O_4F$	485	62.09	6.25	14.48
					61.85	6.42	14.50
14 f	179-180	72	$C_{19}H_{26}N_5O_3F$	391	58.30	6.69	17.89
					58.16	6.65	17.81

Scheme IV

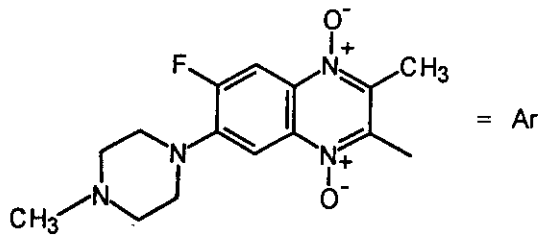


Spectral Data . The nmr and ms spectra for the new quinoxaline-1,4-dioxide derivatives (**12a-h**) are in agreement with the assigned structures.

(i) H-nmr Spectra (Table 2) : The peri-positioned aromatic protons (H-5 and H-8) appear around δ 7.8 and δ 7.3 , respectively, as two doublets due to coupling with the fluorine atom. The H-5 is more deshielded and shows a larger *ortho*-coupling constant value ($J_{H5\text{-}F} \approx 14$ Hz) than the H-8 with *meta*-coupling ($J_{H8\text{-}F} \approx 8$ Hz). The signal of the N_{10}-H proton appears as a triplet (δ 8.5) in compound **(12a)**, and as a doublet (δ 8.1) in compounds **(12c-g)** due to vicinal coupling with the α-protons. The methyl protons at C-3 and N-4 appear as singlets around δ 2.5 and 2.3, respectively. The methylene protons of the piperazine moiety form an 'AA'BB' pattern around δ 3.3 (H-2' / H-6') and δ 2.6 (H-3' / H-5'). Assignments of the remaining protons (H-11, CH_2OH, R and R') are also straightforward.

(ii) ^{13}C-nmr Spectra (Table 3): The ^{13}C-nmr spectra of the individual compounds (**12a-h**) exhibit signals that account for the different carbon atoms comprising the molecular structures. Gated Spin Echo (GASPE) measurement is utilized to differentiate secondary (C_{12}, $C_{2'}$ / $C_{6'}$, $C_{3'}$ / $C_{5'}$) and quaternary carbon atoms (C_2, C_3, C_6, C_7, C_{4a}, C_{8a}) from primary (C_3 - $\underline{CH_3}$, N-$\underline{CH_3}$) and tertiary (C_5, C_8, C_{11} " where R ≠ H ") which appear as inverted signals. Each of the benzenoid ring carbons (C_5 - C_8, C_{4a}, C_{8a}) appear as doublets due to coupling with fluorine.

It is worth noting that the ^{13}C-nmr spectrum of compound (**12b**) displays signal doubling for certain carbons. Such signal doubling is also observed for the various protons of this compound (Table 2), and is the result of slow rotation around the tertiary amide (-CO — N ⟨) bond[26] which leads to the existence of two rotamers represented by the following structures :



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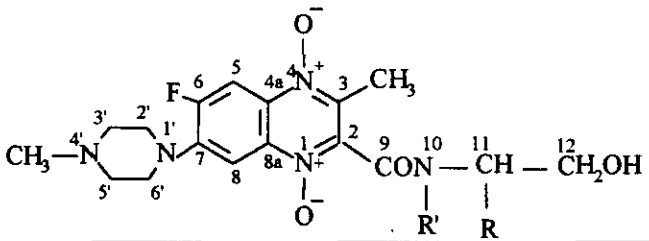
Nmr spectrum of the *N*-4-monoxide (**14f**) (Tables 2 and 3) : The C_3 - methyl protons' singlet in the ^{1}H-nmr spectrum of this monoxide is shifted downfield (δ 2.95) as compared to that of the parent 1,4-dioxide (**12f**) (δ 2.49); this sizable shift ($\Delta\delta \approx 0.46$ ppm) is characteristic of related quinoxaline *N*-4-monoxides.[25] Moreover, the aromatic C_8-proton has a lower δ value (7.12) than that of the corresponding 1,4-dioxide (**12f**) (δ 7.31); this upfield shift for the H-8 proton is indicative of the absence of the *N*-1-oxide function.[25] The ^{13}C-nmr spectrum of the monoxide (**14f**) shows a singnificant deshielding of the signals belonging to C_3, C_{8a}, C_9 and C_8 ($^3J_{C\text{-}F} \approx 4.5$ Hz) as compared to those of the parent dioxide (**12f**), in agreement with previous observations for related quinoxaline *N*-4-monoxides.[27] As expected, the chemical shift for the C-5 doublet ($^2J_{C\text{-}F} \approx 28.3$ Hz) in the monoxide (**14f**) is almost the same as that of the corresponding 1,4-dioxide (**12f**). Again, the chemical shift for the H-5 doublet ($^2J_{5\text{-}F} \approx 13$ Hz) in the monoxide (**14f**) is invariant as compared to that of the parent 1,4-dioxide (**12f**). These spectral data are consistent with the assigned structures for the 4-monoxide (**14f**), and for the 1,4-dioxides (**12a-h**).

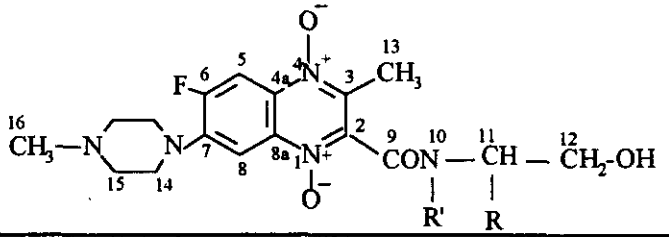
Table 2 . The Chemical Shifts (ppm) of the Different Protons for Model Compounds **(12a-c, e, f and 14f)**



Compd No	$\frac{C_5-H^{i}}{C_8-H}$	$\frac{C_{3'}-H / C_{5'}-H}{C_{2'}-H / C_{6'}-H}$	C_3-CH_3	$N_{10}-H^{k}$	$C_{11}-H$	$N-CH_3$	$C_{12}-H^{z}_2$
12 a	7.77 (d) 7.37 (d)	2.62 3.34	2.62 (s)	8.52 (t)	3.87 (m)	2.35 (s)	3.65 (m)
12 b	8.11 (d) / 8.17 (d) 7.78 (d) / 7.82 (d)	2.61 3.37	2.58 (s) 2.62 (s)	–	3.84 (m) 4.01 (m)	2.34 (s) 2.51 (s)	3.35 (m) 3.56 (m)
12 c	7.80 (d) 7.37 (d)	2.62 3.34	2.56 (s)	8.20 (d)	4.28 (m)	2.37 (s)	3.75 (m)
12 e	7.85 (d) 7.43 (d)	2.62 3.37	2.59 (s)	8.05 (d)	4.08 (m)	2.38 (s)	3.85 (m)
12 f	7.87 (d) 7.31 (d)	2.61 3.32	2.49 (s)	8.12 (d)	4.04 (m)	2.33 (s)	3.75 (m)
14 f	7.91 (d) 7.12 (d)	2.62 3.25	2.95 (s)	8.09 (d)	4.05 (m)	2.47 (s)	3.80 (m)

[i] $J_{H_5-F} \sim 14$ Hz; $J_{H_8-F} \sim 8$ Hz. [k] $J_{NH-CH} \sim 8.5$ Hz. [z] The geminal protons in **12c,e,f** and **14f** are not chemically equivalent, but the differences in chemical shifts are small.

Table 3 . The Chemical shifts (ppm) of the Different Carbons for Model Compounds **(12a-c, e, f and 14f)**



Compd No	C – 2	C – 3	C – 4a [i] / C – 8a	C – 5 [k] / C – 8	C – 6 [l] / C – 7	C – 9	C – 11	C – 12	C – 13	C – 14	C – 15	C – 16
12 a	133.71	139.60	132.20 (d) 137.03	106.04 (d) 105.23 (d)	158.42 (d) 145 02 (d)	159.90	42.91	60.98	14.71	49.85	54.68	46 06
12 b	134.19	139 11	133.04 (d) 137.63	106 57 (d) 106.23	159.76 (d) 144.81 (d)	161.15 160.05	53.34 50.31	59.60 57.91	14.20 14.13	49.84	54.58	46.00
12 c	133 64	139.67	132.02 (d) 136.79	105 91 (d) 105 35 (d)	158.11 (d) 144 79 (d)	159.65	48.63	65.46	14.60	49.77	54.58	45.97
12 e	133.71	139.62	132 00 (d) 136.87	105.88 (d) 105.56 (d)	158.34 (d) 144 71 (d)	159.59	57 12	62.59	14.63	49.78	45.57	45.98
12 f	133.69	139.41	132.01 (d) 136.95	105 92 (d) 105.31 (d)	158.25 (d) 144 68 (d)	159.59	54.37	63.78	14.53	49.69	54.56	45.95
14 f	140.37 (d)	139.30 (d)	132.43 (d) 145.67	104.51 (d) 115.64 (d)	158.45 (d) 144.66 (d)	164.38	53.58	64.52	13.60	50 02	54.73	46.00

[i] J_{C4a-F} ~ 11 Hz. [k] J_{C5-F} ~ 29 Hz; J_{C8-F} ~ 4.5 Hz. [l] J_{C6-F} ~ 260 Hz; J_{C7-F} ~ 11 Hz.

(iii) Mass spectra (Table 4) : The ms spectra of the dioxides (**12a-h**) display the correct molecular ions, $[M]^{+\cdot}$, as suggested by their molecular formulas, albeit of low relative abundance. The intense fragment ions at M-16 arise by the elimination of an *N*-oxide oxygen from the molecular ion. These are accompanied by strong peaks at M-17 arising via the net loss of an OH radical. The occurrence of both cations was observed in the ms of related heterocyclic *N*-oxides.[28,29] The amide bond does not suffer cleavage to any appreciable extent prior to loss of an *N*-oxide oxygen, a trend that had been noted earlier for related systems.[25,29] The base peak at m/z = 43 (100%) together with a prominent peak at m/z = 71 (> 50%) correspond to the respective ions $[C_2H_5N]^{+\cdot}$ and $[C_4H_9N]^{+\cdot}$ arising *via* two -bond rupture of the *N*-methylpiperazine ring, A comparable fragmentation pattern is also observed for the monoxide (**14f**) whose $[M]^{+\cdot}$ shows a relatively high abundance (~ 48%).

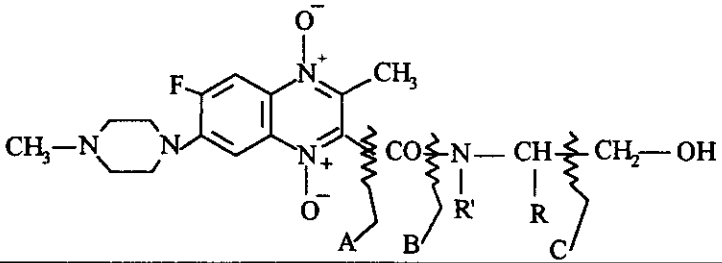
Bioassay

The antimicrobial susceptibility of certain bacteria and fungi was tested by the agar diffusion method using Mueller-Hinton agar plates. Aqueous solutions of the quinoxaline 1,4-dioxides (**12a-h**) (in the form of their monohydrochloride salts) were prepared and introduced into wells digged on agar so as to obtain 200 µg of substance in each well.
Under these conditions, the following compounds were slightly active against *Bacillus Cereus* :

Compound No	**12b**	**12c**	**12d**	**12e**	**12f**	**12h**
Growth inhibition zone diameter (mm)	10	13	9	13	11	10

Compound (**12h**) also exhibited slight activity against *Staphylococcus aureus* (inhibition zone diameter = 12 mm), and against *Aspergillus Parasiticus* (inhibition zone diameter = 7 mm). However, compounds (**12b-f**) were inactive against *E. coli*, *Ps. aeruginosa*, *S. aureus*, and *A. parasiticus;* similarly compounds (**12a-h**) were inactive against *Candida* albicans, and *Fusarium oxysporum.*

Table 4 . The m/z Values and Relative Intensities (given in parentheses) of the Principal Fragment Ions in the Mass Spectra of Compounds **(12a - f)**



Compd No	$M^{+\cdot}$	M - [O] M - [OH]	M - [O_2 H] M - [O_2]	A - [O] A - [O_2]	B - [O]	C - [O] C - [O_2]
12 a	379 (22)	363 (47) 362 (62)	346 (32) 347 (9)	275 (15) 259 (13)	303 (6)	332 (4) 316 (3)
12 b	393 (13)	377 (35) 376 (40)	360 (20) 361 (8)	275 (2) 259 (4)	303 (2)	346 (6) 330 (5)
12 c	393 (14)	377 (51) 376 (32)	360 (27) 361 (11)	275 (14) 259 (27)	303 (4)	346 (14) 330 (4)
12 d	469 (3)	453 (23) 452 (15)	436 (12) 437 (8)	257 (9) 259 (31)	303 (7)	422 (8) 406 (3)
12 e	435 (28)	419 (57) 418 (74)	402 (21) 403 (9)	275 (26) 259 (39)	303 (8)	388 (39) 372 (8)
12 f	407 (20)	391 (35) 390 (48)	374 (18) 375 (7)	275 (13) 259 (18)	303 (6)	360 (17) 344 (4)

EXPERIMENTAL

3-Chloro-4-fluoroaniline (**4a**), 3,4-difluoroaniline (**4b**), *N*-methylpiperazine, 2-aminoethanol (**10a**), 2-(*N*-methylamino)ethanol (**10b**), *L*-2-amino-1-butanol (**10f**) and *L*-ephedrine (**10h**), used in this study, were purchased from Janssen Chimica. *L*-Alaninol (**10c**), *L*-phenylalaninol (**10d**), *L*-valinol (**10e**), and *L*-isoleucinol (**10g**) were prepared by $LiAlH_4$ reduction of the respective *L*-α-amino acids according to a reported procedure.[30] Diketene (Fluka) was distilled before use (bp 68 °C / 90 mmHg).

Melting points were measured on an electrothermal Mel-Temp. apparatus, and are uncorrected. ^1H- and ^{13}C-nmr spectra were recorded on a Bruker AM 400 spectrometer for solutions in $CDCl_3$. Electron impact mass spectra were obtained using a Finnigan MAT 731 at 70 eV. Microanalyses were carried out by M. H. W. Laboratories at Arizona, U. S. A.

***N*-(3-Chloro-4-fluorophenyl)acetamide (5a).**

This compound was prepared from 3-chloro-4-fluoroaniline (**4a**) and acetic anhydride following a previously described procedure.[21] Yield 96%; mp 117-118 °C (lit.,[21] mp 118 - 119 °C).

***N*-(5-Chloro-4-fluoro-2-nitrophenyl)acetamide (6a).**

This compound was prepared by nitration of **5a**, prepared above, following reported conditions.[21] Yield 70%; mp 112-113 °C (lit.,[21] Yield 72%; mp 114 - 115 °C).

5-Chloro-4-fluoro-2-nitroaniline (7a).

This compound was obtained by deacetylation of **6a**, obtained above, following a reported procedure.[21] Yield 98%; mp 148 - 149 °C (lit.,[21] mp 149.5 - 150 °C).

The title compound (**7a**) was also prepared directly from **5a** in a one-pot step following reported conditions.[31]

***N*-(3,4-Difluorophenyl)acetamide (5b).**

The title compound was obtained by acetylation of 3,4-difluoroaniline (**4b**) following an established procedure.[22] Yield 95 %; mp 126 - 127 °C (lit.,[22] mp 127 - 127.5 °C).

***N*-(4,5-Difluoro-2-nitrophenyl)acetamide (6b).**

The title compound was prepared by nitration of **5b** under reported reaction conditions.[22] Yield 72%; mp 113-114 °C. Anal. Calcd for $C_8H_6N_2O_3F_2$: C, 44.46 ; H, 2.80 ; N, 12.96.

Found : C, 44.28 ; H, 2.77 ; N, 12.85.

4,5-Diflluoro-2-nitroaniline (7b).

The title compound was obtained *via* deacetylation of **6b** following reported reaction conditions.[22] Yield 93 %; mp 108 - 109 °C (lit.,[22] mp 109 - 109.5 °C).

4-Fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (8).

This compound was prepared from **7a** (7.6 g , 40 mmol) and *N*-methylpiperazine (20.0 g , 200 mmol) following reported procedure.[19,20] The product was recrystallized from chloroform / benzene. Yield 85%; mp 152 - 153 °C. Anal. Calcd for $C_{11}H_{15}N_4O_2F$: C, 51.96 ; H, 5.95; N, 22.03. Found : C, 51.81 ; H,5.85 ; N, 21.89 .

Under similar reaction conditions, the title compound was also prepared from **7b** (7.0 g , 40 mmol) and *N*-methylpiperazine (20.0 g, 200 mmol). Yield 83%; mp 152 - 153 °C (undepressed upon admixture with a sample prepared above *via* compound (**7a**).

5(6)-Fluoro-6(5)-(4-methyl-1-piperazinyl)benzofuroxan (9)

This compound was prepared by the following procedure which is analogous to that reported for the parent furoxan[18] : To a solution of compound (**8**) (5.1g ; 20 mmol) and KOH (2.5 g ; 44 mmol) in ethanol (120 ml) was slowly added 7% sodium hypochlorite solution (30 ml, 28 mmol , commercial Hypex) at 0 to 3 °C with vigorous stirring. After the addition was complete, the reaction mixture was stirred for two h at the same temperature. To the resulting reaction mixture was then added cold water (200 ml) to assist further precipitation of the title compound (**9**) as yellow solid which was collected by suction and recrystallized from ethanol (cooling to -20 °C). The product was further recrystallized from $CHCl_3$ / pet. ether (bp 40-60 °C). The physical and analytical data of the title compound are shown in Table 1.

***N*-Acetoacetyl-*β*-aminoalkanols (11a-h).**

The title compounds, employed in this work, were prepared from the corresponding *β*-aminoalkanols (**10a-h**) by *N*-acetoacetylation with diketene following a standard procedure.[16,23] These derivatives were previously described.[23]

***N*-[6-Fluoro-7-(4-methyl-1-piperazinyl)-3-methyl-2-quinoxaloyl]-*β*-aminoalkanol 1,4-dioxides (12a-h).**

To a filtered solution of 5(6)-fluoro-6(5)-(4-methyl-1-piperazinyl)benzofuroxan (**9**) (2.5 g ,

10 mmol) in triethyamine (120 ml) was added a solution of the particular *N*-acetoacetyl-*β*-aminoalkanol (**11**) (12 mmol) in methanol (20 ml). The resulting clear mixture was set aside at room temperature for 1-3 days. The yellow insoluble products that formed slowly were collected by suction, washed with cold ethanol (5-10 ml), and recrystallized from the appropriate solvent.

Analytical samples of the title compounds were obtained using preparative tlc, with silica gel as the adsorbent and $CHCl_3$ / MeOH (95 : 5 v/v) as the developing solvent. The physical and analytical data of compounds (**12a-h**) are shown in Table 1.

***N*-[6-Fluoro-7-(4-methyl-1-piperazinyl)-3-methyl-2-quinoxaloyl]-2-aminobutanol 4-oxide (14f).**

A mixture of the quinoxaline 1,4-dioxide (**12f**) (4.0 g ; 10 mmol) and trimethylphosphite (2.5 g ; 20 mmol) in 1-propanol (100 ml) was refluxed for five h. The solvent was evaporated and the residue was washed with ether to give the title compound (**14f**) which was purified on preparative tlc plates, using silica gel as the adsorbent and $CHCl_3$ / MeOH (95 : 5 v/v) as the developing solvent. The physical and analytical data of the title monoxide are shown in Table 1.

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