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Original article

Novel substituted quinoxaline 1,4-dioxides with in vitro antimycobacterial and anticandida activity

Antonio Carta [a], Giuseppe Paglietti [a], Mohammad E. Rahbar Nikookar [a], Paolo Sanna [a,*], Leonardo Sechi [b], Stefania Zanetti [b]

[a] *Dipartimento Farmaco Chimico Tossicologico, via Muroni 23/a, 07100 Sassari, Italy*
[b] *Dipartimento di Scienze Biomediche, viale S. Pietro, 07100 Sassari, Italy*

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Abstract

Thirty-six 6(7)-substituted-3-methyl- or 3-halogenomethyl-2-phenylthio–phenylsulphonyl–chloro-quinoxaline 1,4-dioxides belonging to series **3**–**6** were synthesised and submitted to a preliminary in vitro evaluation for antimycobacterial, anticandida and antibacterial activities. Antitubercular screening showed a generally good activity of 3-methyl-2-phenylthioquinoxaline 1,4-dioxides (**3d**,**e**,**h**–**j**) against *Mycobacterium tuberculosis*, and exhibited MIC between 0.39 and 0.78 μg mL^{-1} (rifampicin MIC = 0.25 μg mL^{-1}), whereas in compounds **4d**,**e**, **5a**,**b**,**d**,**e**,**l** and **6b**–**e**,**j**,**l** MIC ranged between 1.56 and 6.25 μg mL^{-1}. Results of the antibacterial and anticandida screening showed that **6e** and **6l** exhibited MIC = 0.4 and 1.9 μg mL^{-1}, respectively, against *Candida krusei* (miconazole MIC = 0.9 μg mL^{-1}), and **4i**, **5b**,**d**, **6e**, MIC = 3.9 μg mL^{-1} against *Candida glabrata* (miconazole MIC = 0.4 μg mL^{-1}), while compounds **3d**,**l**, **5e**,**l**, and **6b**,**d**,**e**,**l** showed MIC = 15.6 μg mL^{-1} against *Vibrio alginolyticus*. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: Quinoxaline 1,4-dioxides; Antimycobacterial; Anticandida; Antibacterial activity

1. Introduction

The quinoxaline derivatives show very interesting biological properties (antibacterial, antiviral, anticancer, antifungal, anthelmintic, insecticidal) and their interest in medicinal chemistry is far to come to an end [1,2]. In the last two decades, many *mono*- and *di*-*N*-oxides and 2-oxo derivatives of this heterocyclic system have appeared and their biological activities reported. Thus, for some quinoxalin-2-ones it was evidenced antifungal activity [3,4], whereas the quinoxaline 1-oxides have shown antibacterial activity [5]. Oxidation of both ring nitrogen of quinoxaline enormously widens the diversity of the biological properties, among these antibacterial activity [6–9], animal growth promoting in feed additives [10–12], hypoxia-selective activity [13], genotoxycity against *Escherichia coli* and *S. typhimurium* [14], etc. Recently, some researchers have reported antibacterial [15] and antimycobacterial [16] activities of various 2-methylquinoxaline 1,4-dioxides, confirming that the presence of a methyl (or halogenomethyl) group at 2(3) position of this ring, as previously reported also by other authors [6,8,9,17,18], is favourable for antimicrobial activity. Interestingly, some 2-sulphonylquinoxalines [19] and 3-[(alkylthio)methyl]quinoxaline 1-oxide derivatives [5] were reported to be endowed with antibacterial and antifungal activities.

In this context as contribution in the development of quinoxaline derivatives, some of us have recently reported the preparation and in vitro antitumoral and antifungal activities of a large series of variously substituted quinoxalines [20–23] as well as the synthesis and anticancer, antibacterial and antifungal activities of a series of 2(3)-oxo-quinoxalines [4,24,25], and antibacterial activity of quinoxaline-*N*-oxides [26]. Now, as a further contribution in this field, we have designed the series of 6(7)-substituted-3-methyl(halogenomethyl)-2-phenylthio(sulphonyl)(chloro)quinoxaline 1,4-dioxides (**3**–**6**) summarised in Fig. 1. Substituent at 6 and/or 7 positions in the benzene moiety, was chosen in order to

* Correspondence and reprints.
E-mail address: psanna@ssmain.uniss.it (P. Sanna).

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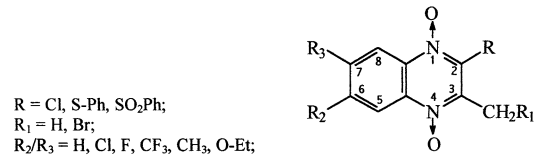


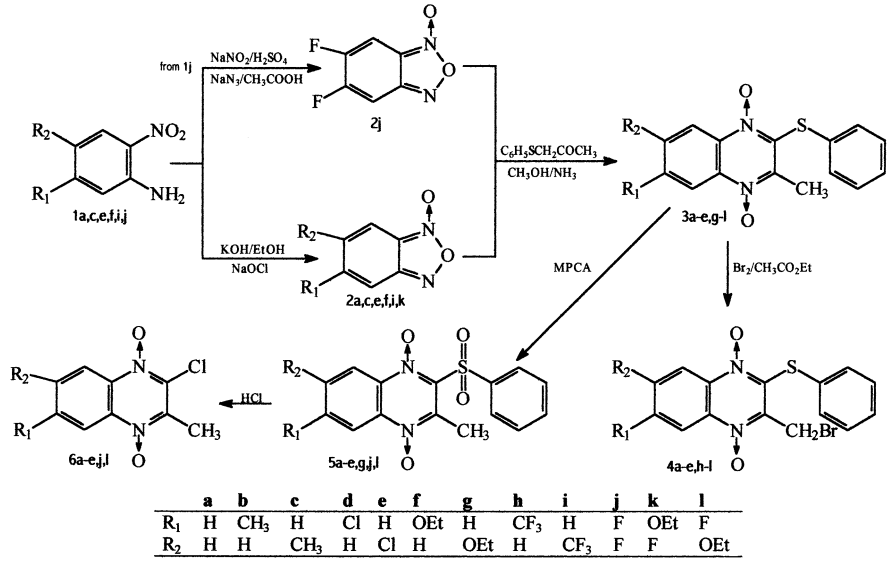
Fig. 1. Quinoxaline 1,4-dioxides (**3**–**6**).

evaluate the effect of an electron-withdrawing group (CF_3, Cl, *di*F) or electron-releasing group (CH_3, EtO) on the biological activities.

2. Chemistry

The synthetic approach for the preparation of the quinoxalines 1,4-dioxides (**3**–**6**) is depicted in Fig. 2. The 3-methyl-2-phenylthioquinoxaline 1,4-dioxides (**3a**–**e**,**g**–**l**) were obtained according to the known Beirut reaction, by condensation of benzofuroxan derivatives **2a**,**c**,**e**,**f**,**i**–**k** with acetonylphenyl sulphide in the presence of methanolic ammonia. Formation of isomeric quinoxaline 1,4-dioxides was observed in the case of monosubstituted benzofuroxans **2c**,**e**,**f**,**i** and of the non-symmetrical disubstituted compound **2k**. According to previous reports by Abushanab and Alteri for similar cases [27], we have observed that when an electron-releasing substituent is present on benzofuroxan ring the 7-substituted-quinoxaline 1,4-dioxides (**3c**,**l**) were prevailing over the 6-isomers **3b**,**k** or the only isomer formed was **3g**. These results were reversed when electron-withdrawing substituents were present. Compounds **3d**,**h** were prevailing over the isomers **3e**,**i**, respectively. The 3-bromomethyl-2-phenylthioquinoxaline 1,4-dioxides (**4a**–**e**,**h**–**l**) were obtained in good yield (83–88%), starting from **3a**–**e**,**h**–**l** by addition of a solution of bromine in ethyl acetate and heating the mixture at reflux temperature [28]. The 3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxides (**5a**–**e**,**g**,**j**,**l**) were in turn obtained, generally in good yield, by oxidation of the 2-phenylthio derivatives (**3a**–**e**,**g**,**j**,**l**) with a solution of 3-chloroperoxybenzoic acid (MCPBA) in chloroform according to a described method [29]. Conversion of the sulphonylquinoxaline derivatives **5a**–**e**,**j**,**l** into the 2-chloro-3-methylquinoxaline 1,4-dioxides (**6a**–**e**,**j**,**l**) was performed, with good yield (78–93%), carrying out the reaction in concentrated hydrochloric acid, under stirring at 70 °C for 15 min.

Preparation of the benzofuroxan intermediates **2a**,**c**,**e**,**f**,**i**,**k** was achieved, following the procedure previously described by Mallory [30], by means of a sodium hypochlorite solution added to a suspension of the appropriate *o*-nitroaniline **1a**,**c**,**e**,**f**,**i**,**j** in a mixture of potassium hydroxide and absolute ethanol. In the case of 4,5-difluoro-2-nitroaniline (**1j**), the reaction afforded the 5-ethoxy-6-fluorobenzofuroxan (**2k**), in 84% yield, instead of the desired 5,6-difluorobenzofuroxan (**2j**). This behaviour clearly indicates that a nucleophilic displacement of fluorine atom at C-5 of the compound **1j** by ethoxyde, was taking place during cyclisation to **2k**. Conversion of the intermediate **1j** into **2j** was obtained following a previous described alternative route [31]. Compound **1j**, in glacial acetic acid, was first diazotised with nitrosyl sulphuric acid and the resulting diazonium salt was added to an aqueous solution of sodium azide (Fig. 2) to give **2j** in 67% yield.



	a	b	c	d	e	f	g	h	i	j	k	l
R_1	H	CH_3	H	Cl	H	OEt	H	CF_3	H	F	OEt	F
R_2	H	H	CH_3	H	Cl	H	OEt	H	CF_3	F	F	OEt

Fig. 2. Method of preparation of quinoxaline 1,4-dioxides (**3**–**6**).

3. Microbiology

Microbiological screening of the described compounds was performed against mycobacteria (*Mycobacterium tuberculosis*), Gram positive (*Staphylococcus aureus*) and Gram negative (*E. coli*, *Vibrio alginolyticus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) bacteria, and yeasts (*Candida albicans*, *Candida glabrata*, *Candida krusei* and *Candida parapsilosis*).

4. Results and discussion

Quinoxaline 1,4-dioxides (**3a**–**e**,**g**–**l**, **4a**–**e**,**h**–**l**, **5a**–**e**,**g**,**j**,**l** and **6a**–**e**,**j**,**l**) were evaluated in vitro for antibacterial (*S. aureus*, *E. coli*, *V. alginolyticus*, *K. pneumoniae* and *P. aeruginosa*), antifungal (*C. albicans*, *C. glabrata*, *C. krusei* and *C. parapsilosis*), and antimycobacterial (*M. tuberculosis*) activities and results are reported in Tables 1–4. These data show that various compounds possess an interesting activity against several tested strains. In general, compounds of the series **3**, **5** and **6** resulted more active against *M. tuberculosis*, *V. alginolyticus* and various strains of *Candida* compared with those of the series **4**.

With regard to antibacterial activity, the obtained results mainly indicate that most of tested compounds exhibited scarce activity against Gram positive and -negative bacteria showing MIC values ranging from 62.5 to 500 μg mL^{-1} with a few exceptions. Compounds **4a**, **5a**,**b** and **6d** (MIC = 31.25 μg mL^{-1}) and **5c** and **5d** (MIC = 15.6 μg mL^{-1}) were the most active against *S. aureus*, while only compounds **5a** (MIC = 7.8 μg mL^{-1} against *E. coli*) and **4j** (MIC = 31.25 μg mL^{-1} against *P. aeruginosa*), display significant activity versus the mentioned Gram negative bacteria. However, the titled compounds **3d**,**l**, **5e**,**l** and **6b**,**d**,**e**,**l** exhibited significant activity against environment Gram

Table 1
In vitro evaluation of anticandida activity on 24 clinical isolated strains of *C. albicans* of tested compounds (**3d**,**e**,**i**, **4a**, **5a**,**e**,**l**, **6e**,**l**) MIC (μg mL^{-1}), miconazole MIC = 3.9 μg mL^{-1}

Strains	3d	3e	3i	4a	5a	5e	5l	6e	6l
1	62.5	31.25	31.25	7.8	31.25	62.5	62.5	15.6	62.5
2	15.6	62.5	31.25	15.6	31.25	15.6	15.6	15.6	15.6
3	15.6	62.5	62.5	62.5	62.5	62.5	15.6	15.6	62.5
4	15.6	31.25	15.6	15.6	31.25	15.6	15.6	15.6	15.6
5	15.6	31.25	15.6	31.25	31.25	31.25	15.6	7.8	31.25
6	31.25	15.6	15.6	15.6	7.8	31.25	15.6	31.25	15.6
7	31.25	15.6	31.25	31.25	15.6	31.25	15.6	7.8	15.6
8	31.25	31.25	31.25	31.25	15.6	31.25	15.6	15.6	15.6
9	31.25	31.25	31.25	31.25	31.25	31.25	15.6	15.6	62.5
10	31.25	31.25	31.25	31.25	31.25	15.6	31.25	7.8	15.6
11	31.25	31.25	62.5	31.25	31.25	31.25	15.6	7.8	62.5
12	62.5	31.25	31.25	31.25	31.25	31.25	15.6	7.8	62.5
13	31.25	15.6	15.6	15.6	15.6	31.25	15.6	7.8	62.5
14	31.25	15.6	15.6	15.6	15.6	31.25	31.25	31.25	62.5
15	62.5	15.6	15.6	31.25	31.25	62.5	15.6	15.6	62.5
16	62.5	15.6	15.6	31.25	31.25	62.5	15.6	7.8	62.5
17	31.25	31.25	31.25	15.6	15.6	31.25	31.25	31.25	62.5
18	7.8	31.25	15.6	15.6	31.25	7.8	7.8	7.8	7.8
19	31.25	7.8	7.8	7.8	7.8	62.5	7.8	7.8	15.6
20	15.6	15.6	15.6	15.6	15.6	62.5	7.8	7.8	15.6
21	62.5	31.25	7.8	31.25	15.6	15.6	15.6	7.8	31.25
22	31.5	7.8	7.8	15.6	7.8	31.25	15.6	7.8	31.25
23	15.6	31.25	15.6	31.25	15.6	15.6	15.6	15.6	15.6
24	31.25	31.25	15.6	31.25	31.25	31.25	15.6	15.6	31.25

Table 2
In vitro evaluation of anticandida activity on *C. glabrata*, *C. krusei* and *C. parapsilosis* (clinical isolated) of tested compounds (**3d**,**k**,**j**, **4b**,**i**, **5b**,**d**,**l**, **6e**,**l**) MIC (μg mL^{-1})

	3d	3k	3j	4b	4i	5b	5d	5l	6e	6l	Miconazole
C. glabrata	31.25	62.5	62.5	31.25	3.9	3.9	3.9	7.8	3.9	15.6	0.4
C. krusei	31.25	62.5	31.25	62.5	31.25	31.25	7.8	31.25	0.4	1.9	0.9
C. parapsilosis	62.5	62.5	62.5	62.5	31.25	62.5	15.6	62.5	15.6	62.5	0.4

Table 3
In vitro evaluation of antitubercular activity as % growth inhibition at 6.25 μg mL^{-1} of concentration against *M. tuberculosis* of compounds **3a–e,h–l**, **4a–e,h–j**, **5a–e,j,l** and **6b–e,j,l**

Compound	MIC (μg mL^{-1})	% Inhibition	Compound	MIC (μg mL^{-1})	% Inhibition	Compound	MIC (μg mL^{-1})	% Inhibition
3a	>6.25	88	**4b**	>6.25	0	**5e**	<6.25	100
3b	>6.25	19	**4c**	>6.25	17	**5j**	>6.25	27
3c	>6.25	27	**4d**	<6.25	96	**5l**	<6.25	100
3d	<6.25	100	**4e**	<6.25	99	**6b**	<6.25	100
3e	<6.25	100	**4h**	>6.25	88	**6c**	<6.25	100
3h	<6.25	100	**4i**	>6.25	77	**6d**	<6.25	99
3i	<6.25	100	**4j**	>6.25	48	**6e**	<6.25	100
3j	<6.25	100	**5a**	<6.25	100	**6j**	<6.25	100
3k	>6.25	0	**5b**	<6.25	99	**6l**	<6.25	99
3l	>6.25	19	**5c**	>6.25	79			
4a	>6.25	28	**5d**	<6.25	100			

Table 4
Actual MIC against *M. tuberculosis* (rifampicin MIC = 0.25 μg mL^{-1}) of compounds exhibiting >95% growth inhibition at 6.25 μg mL^{-1} of compounds **3d,e,h–j**, **4d,e**, **5a,b,d,e,l** and **6b–e,j,l**

Compound	Actual MIC against *M. tuberculosis* (μg mL^{-1})	Compound	Actual MIC against *M. tuberculosis* (μg mL^{-1})	Compound	Actual MIC against *M. tuberculosis* (μg mL^{-1})
Rifampicin	0.25	**4e**	3.13	**6c**	3.13
3d	0.78	**5a**	6.25	**6d**	6.25
3e	0.39	**5b**	3.13	**6e**	1.56
3h	0.39	**5d**	6.25	**6j**	1.56
3i	0.78	**5e**	6.25	**6l**	3.13
3j	0.78	**5l**	6.25		
4d	6.25	**6b**	3.13		

negative bacterium *V. alginolyticus* with a MIC = 15.6 μg mL^{-1} compared with ciprofloxacin (MIC = 0.5 μg mL^{-1}).

The in vitro anticandida activity was first tested against a clinically isolated strains of *C. albicans*, using miconazole as reference drug (MIC = 3.9 μg mL^{-1}). The result of this preliminary test shows that none of the tested compounds exhibited a better activity than that of miconazole, even if several compounds showed MIC values in the range 7.8–15.6 μg mL^{-1}. In particular, among these compounds **3i**, **4b,i** and **5d** exhibited MIC = 7.8 μg mL^{-1}, and **3d,e,j,k**, **4a**, **5a,b,e** and **6e,l** MIC = 15.6 μg mL^{-1}. In Table 1, we have reported the results of a screening carried out over nine of these derivatives (**3d,e,i**, **4a**, **5a,e,l** and **6e,l**) against an additional 24 clinically isolated strains of *C. albicans*. The data reported seem to confirm that the quinoxaline 1,4-dioxide derivatives have in general a good activity against *C. albicans*. Of these compounds **5l** and **6e** exhibited MIC ≤ 15.6 μg mL^{-1} (miconazole MIC = 3.9 μg mL^{-1}) versus several strains. In the light of these results the compounds **5l** and **6e**, along with **3d,j,k**, **4b,i**, **5b,d,l** and **6e,l** were tested against other clinically isolated species of *Candida* (*C. glabrata*, *C. krusei* and *C. parapsilosis*). The results reported in Table 2 show a general good activity. Among these compounds, the derivatives **6e** and **6l** resulted the most active exhibiting MIC = 0.4 and 1.9 μg mL^{-1}, respectively against *C. krusei* (miconazole MIC = 0.9 μg mL^{-1}), whereas **4i**, **5b,d** and **6e** recorded MIC = 3.9 μg mL^{-1} against *C. glabrata* (miconazole MIC = 0.4 μg mL^{-1}).

In Table 3, we have reported the results of an in vitro antitubercular screening of 31 derivatives that showed a general good activity against *M. tuberculosis*. In particular, the compounds **3d,e,h–j**, **4d,e**, **5a,b,d,e,l** and **6b–d,e,j,l** exhibited at 6.25 μg mL^{-1} a growth inhibition in the range 96–100%. For these derivatives, a confirmatory advanced screening was performed in order to determine their actual MICs, that are reported in Table 4. Among these, 3-methyl-2-phenylthioquinoxaline 1,4-dioxides (**3d,e,h,i,j**) exhibited the best activity with MIC between 0.39 and 0.78 μg mL^{-1} (rifampicin MIC = 0.25 μg mL^{-1}), whereas for compounds **4d,e**, **5a,b,d,e,l** and **6b–d,e,j,l** MIC ranged between 1.56 and 6.25 μg mL^{-1}.

In conclusion, the overall biological data allowed us to make some observations on structure–activity relationships. Antitubercular assays seem to confirm that the quinoxaline 1,4-dioxide system is a good scaffold for this type of activity. This resulted very high when

the phenylthio group in C-2 was associated with the presence of an electron-withdrawing group in the benzene moiety (CF_3, Cl, *di*F), while combination of the phenylthio group with a ring electron-releasing group (CH_3, EtO), as well as with the bromomethyl substituent at C-3, reduces this activity. Both oxidation of the sulphide bridge to sulphonyl derivative and replacement of phenylthio group with a chlorine generally decreases the antitubercular activity, although in these cases the type of the substituent in the benzene moiety was generally not significant. On the contrary, the results of antibacterial tests seem to put in evidence that the highest activity is exhibited from those derivatives bearing a chlorine or a phenylsulphonyl group at C-2 beside a methyl group in C-3, while the position and the type of the substituents in the benzene moiety were generally not relevant. As regards the anticandida test, we can notice that the presence of chlorine atom at position 2 (compounds **6e** and **6l**) favourably increases the activity against these fungi.

5. Conclusions

The screening on the in vitro antimicrobial activity of these novel series of 6(7)-substituted-3-methyl- or 3 - halogenomethyl - 2 - phenylthio–phenylsulphonyl–chloro-quinoxaline 1,4-dioxides has evidenced that the 3-methyl-2-phenylthioquinoxaline 1,4-dioxides (**3d**, **3e**, **3h**, **3i**, **3j**) have emerged as new compounds endowed with antitubercular activity exhibiting MIC between 0.39 and 0.78 μg mL^{-1} (rifampicin MIC = 0.25 μg mL^{-1}). This result is most encouraging for the development of some compounds as antitubercular agents. In addition, the quinoxaline 1,4-dioxide derivatives have a general good anticandida activity. In particular, compounds **6e** and **6l** were the most active against *C. krusei* exhibiting MIC = 0.4 and 1.9 μg mL^{-1}, respectively, (miconazole MIC = 0.9 μg mL^{-1}).

6. Experimental

6.1. Chemistry

M.p.s were determined by a Kofler hot stage or Digital Electrothermal apparatus, and are uncorrected. IR spectra are in nujol mulls and were recorded using a Perkin–Elmer 781 spectrophotometer. UV spectra are qualitative and were recorded in nm for solutions in EtOH with a Perkin–Elmer Lambda 5 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian XL-200 (200 MHz) instrument, using TMS as internal standard. The chemical shift values are reported in ppm (δ) and coupling constants (J) in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), dd (double doublet), m (multiplet), and br s (broad singlet). Column chromatographies were performed using 230–400 mesh silica gel (Merck silica gel 60). Light petroleum refers to the fraction with b.p. 40–60 °C. Elemental analyses were performed by the Laboratorio di Microanalisi, Dipartimento di Scienze Farmaceutiche, Università di Padova (Italy). The analytical results for C, H, N, and halogen (Cl, Br), when present, were within $\pm 0.4\%$ of the theoretical values.

6.1.1. Starting materials

The *o*-nitroaniline derivatives **1a**,**c**,**e**,**i**,**j** were commercially available, **1f** was known [32] but it was now prepared, in 85% yield, by an alternative route by nucleophilic displacement of the chlorine by EtONa–EtOH starting from commercial 5-chloro-2-nitroaniline, (m.p. 102–103 °C; literature [32]: m.p. 105–106 °C). Acetonylphenyl sulphide was prepared following the procedure previously described [33].

6.1.2. Intermediate benzofuroxans

(i) The benzofuroxan derivatives **2a**,**c**,**e**,**f**,**i**,**k** were prepared following the procedure previously described by Mallory [30]. To a suspension of the appropriate *o*-nitroaniline **1a**,**c**,**e**,**f**,**i**,**j** (28.9–72.7 mmol), in a mixture of KOH (32–80 mmol) and absolute EtOH (25–60 mL) cooled at 0 °C, was slowly added under vigorous stirring a freshly prepared NaClO solution. After the addition was complete, the reaction mixture was stirred at 0 °C for an additional 1–2 h and then allowed to reach room temperature (r.t.). The resulting precipitate was filtered off and crystallised from EtOH.

(ii) Compound **2j** was in turn obtained following the procedure described by Ghosh et al. [31] for the monofluoro derivative. The *o*-nitroaniline (**1j**) (57.4 mmol) in glacial AcOH (50 mL) was added dropwise to ice-cooled stirred nitrosyl sulphuric acid (4.26 g of $NaNO_2$ in 50 mL of concd. H_2SO_4). When the addition was complete, stirring was continued for an additional 1 h at 0 °C and the resulting solution was poured onto crushed ice (100 g). Then the reaction mixture was added to a solution of NaN_3 (4.10 g of NaN_3 in 100 mL of H_2O) under stirring for 30 min, the resulting precipitate was filtered off, added of glacial AcOH (50 mL) and refluxed under stirring for 2 h. Eventually, the AcOH was removed in vacuo and the remaining solution poured onto H_2O. The precipitate obtained was filtered off and thoroughly dried.

*6.1.2.1. Benzofuroxan (**2a**).* This compound was obtained in 74% yield; m.p. 69–70 °C (from EtOH), (literature [30,34]: m.p. 72–73 °C).

*6.1.2.2. 6-Methylbenzofuroxan (**2c**).* This compound was obtained in 72% yield; m.p. 95–96 °C (from EtOH), (literature [34]: m.p. 98 °C).

*6.1.2.3. 6-Chlorobenzofuroxan (**2e**).* This compound was obtained in 79% yield; m.p. 47–48 °C (from EtOH), (literature [34]: m.p. 48 °C).

*6.1.2.4. 5-Ethoxybenzofuroxan (**2f**).* This is a new compound and was obtained in 56% yield; m.p. > 300 °C (from EtOH); IR (cm^{-1}): *v* 1620, 1600, 1520; UV: λ_{max} 372, 323, 309, 219 nm; ^{1}H-NMR (DMSO-d_6): δ 7.49 (1H, d, $J = 8.8$, H-5), 7.37 (1H, s, H-7), 6.98 (1H, d, $J = 8.8$, H-4), 4.13 (2H, q, $J = 7.0$, CH_2), 1.36 (3H, t, $J = 7.0$, CH_3). Anal. $C_8H_8N_2O_3$ (C, H, N).

*6.1.2.5. 6-Trifluoromethylbenzofuroxan (**2i**).* This compound was obtained in 80% yield; m.p. 108–110 °C (from EtOH), (literature [31]: b.p. 118–120 °C/1 mmHg).

*6.1.2.6. 5,6-Difluorobenzofuroxan (**2j**).* This compound was obtained in 67% yield; m.p. 55–56 °C (from EtOH), (literature [35]: m.p. 56–58 °C).

*6.1.2.7. 6-Fluoro-5-ethoxybenzofuroxan (**2k**).* This is a new compound and was obtained in 84% yield; m.p. 75–76 °C (from EtOH); IR (cm^{-1}): *v* 1600, 1520, 1330; UV: λ_{max} 352, 320, 306, 214 nm; ^{1}H-NMR ($CDCl_3$): δ 7.25 (1H, d, $J = 10.4$, H-7), 6.70 (1H, d, $J = 7.4$, H-4), 4.17 (2H, q, $J = 7.0$, CH_2), 1.54 (3H, t, $J = 7.0$, CH_3). Anal. $C_8H_7FN_2O_3$ (C, H, N).

*6.1.3. General procedure for preparation of 3-methyl-2-phenylthioquinoxaline 1,4-dioxides (**3a–e,g–l**)*

The title compounds were prepared following the known Beirut reaction. Equimolar amounts (3.0–117.0 mmol) of the appropriate benzofuroxan **2a**,**c**,**e**,**f**,**i**,**j**,**k** and acetonylphenyl sulphide in MeOH (10–150 mL) were bubbled in with ammonia gas for 10 min. Then, the reaction mixture was stirred at r.t. for an additional time, as indicated below. The resulting precipitate was filtered off, washed with Et_2O and dried. Separation of the couple of two isomers, when present in the crude mixture, was achieved by fractional crystallisation (**3b**/**3c**) or by chromatography (**3d**/**3e**, **3h**/**3i** and **3k**/**3l**), as indicated below.

*6.1.3.1. 3-Methyl-2-phenylthioquinoxaline 1,4-dioxide (**3a**).* This compound was obtained in 69% yield; m.p. 154–156 °C (from MeOH), (literature [29]: m.p. 153–154 °C).

*6.1.3.2. 3,6-Dimethyl-2-phenylthioquinoxaline 1,4-dioxide (**3b**).* This compound was obtained in 21% yield after stirring for 16 h and crystallisation from MeOH; m.p. 159–161 °C; IR (cm^{-1}): *v* 1620, 1600, 1350, 1310; UV: λ_{max} 378, 296, 268, 242, 200 nm; ^{1}H-NMR ($CDCl_3$): δ 8.44 (1H, d, $J = 9.0$, H-8), 8.41 (1H, s, H-5), 7.60 (1H, d, $J = 9.0$, H-7), 7.32 (5H, m, 5 phenyl-H), 2.87 (3H, s, 3-CH_3), 2.61 (3H, s, 6-CH_3). Anal. $C_{16}H_{14}N_2O_2S$ (C, H, N).

*6.1.3.3. 3,7-Dimethyl-2-phenylthioquinoxaline 1,4-dioxide (**3c**).* This compound was obtained in 34% yield after stirring for 16 h and crystallisation from MeOH; m.p. 137–139 °C; IR (cm^{-1}): *v* 1620, 1600, 1340, 1310; UV: λ_{max} 381, 297, 268, 242, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.51 (1H, d, $J = 8.8$, H-5), 8.34 (1H, d, $J = 1.8$, H-8), 7.65 (1H, dd, $J = 8.8$ and 1.8, H-6), 7.33 (5H, m, 5 phenyl-H), 2.85 (3H, s, 3-CH_3), 2.58 (3H, s, 7-CH_3). Anal. $C_{16}H_{14}N_2O_2S$ (C, H, N).

*6.1.3.4. 6-Chloro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3d**).* This compound was obtained in 29% yield after stirring for 12 h and chromatography on silica gel column (eluent Et_2O–light petroleum 70:30); m.p. 134–136 °C (from MeOH); IR (cm^{-1}): *v* 1620, 1350, 1310; UV: λ_{max} 387, 304, 274, 243, 203 nm; ^{1}H-NMR ($CDCl_3$): δ 8.64 (1H, d, $J = 2.2$, H-5), 8.48 (1H, d, $J = 9.2$, H-8), 7.72 (1H, dd, $J = 9.2$ and 2.2, H-7), 7.34 (5H, m, 5 phenyl-H), 2.86 (3H, s, CH_3). Anal. $C_{15}H_{11}ClN_2O_2S$ (C, H, Cl, N).

*6.1.3.5. 7-Chloro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3e**).* This compound was obtained in 26% yield after stirring for 12 h and chromatography on silica gel column (eluent Et_2O–light petroleum 70:30); m.p. 152–154 °C (from MeOH); IR (cm^{-1}): *v* 1620, 1600, 1340, 1310; UV: λ_{max} 389, 300, 272, 242, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.56 (1H, d, $J = 9.2$, H-5), 8.53 (1H, d, $J = 2.2$, H-8), 7.75 (1H, dd, $J = 9.2$ and 2.2, H-6), 7.34 (5H, m, 5 phenyl-H), 2.85 (3H, s, CH_3). Anal. $C_{15}H_{11}ClN_2O_2S$ (C, H, Cl, N).

*6.1.3.6. 7-Ethoxy-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3g**).* This compound was obtained in 49% yield after stirring for 16 h and crystallisation from MeOH; m.p. 250–251 °C; IR (cm^{-1}): *v* 1620, 1580, 1330, 1320; UV: λ_{max} 389, 306, 284, 253, 205 nm; ^{1}H-NMR ($CDCl_3$): δ 8.41 (1H, d, $J = 9.6$, H-5), 7.69 (1H, d, $J = 2.2$, H-8), 7.55 (1H, dd, $J = 9.6$ and 2.2, H-6), 7.33 (5H, m, 5 phenyl-H), 4.22 (2H, q, $J = 7.0$, CH_2), 2.68 (3H, s, 3-CH_3), 1.41 (3H, t, $J = 7.0$, CH_3–CH_2). Anal. $C_{17}H_{16}N_2O_3S$ (C, H, N).

*6.1.3.7. 6-Trifluoromethyl-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3h**).* This compound was obtained in 12% yield after stirring for 11 h and chromatography on silica gel column (eluent Et_2O–light petroleum 50:50); m.p. 144–145 °C (from MeOH); IR (cm^{-1}): *v*

1600, 1330, 1310, 1150, 1040; UV: λ_{max} 389, 300, 272, 236, 204 nm; ^{1}H-NMR ($CDCl_3$): δ 8.85 (1H, d, $J = 2.2$, H-5), 8.76 (1H, d, $J = 9.2$, H-8), 8.00 (1H, dd, $J = 9.2$ and 2.2, H-7), 7.35 (5H, m, 5 phenyl-H), 2.89 (3H, s, CH_3). Anal. $C_{16}H_{11}F_3N_2O_2S$ (C, H, N).

*6.1.3.8. 7-Trifluoromethyl-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3i**).* This compound was obtained in 2.4% yield after stirring for 11 h and chromatography on silica gel column (eluent Et_2O–light petroleum 50:50); m.p. 128–129 °C (from MeOH); IR (cm^{-1}): *v* 1620, 1330, 1300; UV: λ_{max} 396, 342, 300, 270, 235, 207 nm; ^{1}H-NMR ($CDCl_3$): δ 8.95 (1H, d, $J = 1.6$, H-8), 8.66 (1H, d, $J = 8.8$, H-5), 7.97 (1H, dd, $J = 8.8$ and 1.6, H-6), 7.35 (5H, m, 5 phenyl-H), 2.86 (3H, s, CH_3). Anal. $C_{16}H_{11}F_3N_2O_2S$ (C, H, N).

*6.1.3.9. 6,7-Difluoro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3j**).* This compound was obtained in 82% yield after stirring for 12 h and crystallisation from MeOH; m.p. 186–187 °C; IR (cm^{-1}): *v* 1620, 1340, 1320; UV: λ_{max} 386, 298, 270, 236, 213 nm; ^{1}H-NMR ($CDCl_3$): δ 8.39 (2H, m, H-5 + H-8), 7.34 (5H, m, 5 phenyl-H), 2.85 (3H, s, CH_3). Anal. $C_{15}H_{10}F_2N_2O_2S$ (C, H, N).

*6.1.3.10. 6-Ethoxy-7-fluoro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3k**).* This compound was obtained in 13% yield after stirring for 16 h and chromatography on silica gel column (eluent $CHCl_3$–light petroleum–EtOAc 50:20:30); m.p. 168–169 °C (from MeOH); IR (cm^{-1}): *v* 1620, 1500, 1400, 1330, 1310; UV: λ_{max} 378, 305, 271, 249, 204 nm; ^{1}H-NMR ($CDCl_3$): δ 8.21 (1H, d, $J = 10.8$, H-8), 8.02 (1H, d, $J = 7.4$, H-5), 7.32 (5H, m, 5 phenyl-H), 4.32 (2H, q, $J = 7.0$, CH_2), 2.88 (3H, s, 3-CH_3), 1.57 (3H, t, $J = 7.0$, CH_3–CH_2). Anal. $C_{17}H_{15}FN_2O_3S$ (C, H, N).

*6.1.3.11. 7-Ethoxy-6-fluoro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3l**).* This compound was obtained in 47% yield after stirring for 16 h and chromatography on silica gel column (eluent $CHCl_3$–light petroleum–EtOAc 50:20:30); m.p. 157–158 °C (from MeOH); IR (cm^{-1}): *v* 1620, 1500, 1410, 1330, 1320; UV: λ_{max} 396, 382, 303, 268, 246, 204 nm; ^{1}H-NMR ($CDCl_3$): δ 8.28 (1H, d, $J = 10.8$, H-5), 7.94 (1H, d, $J = 7.8$, H-8), 7.32 (5H, m, 5 phenyl-H), 4.26 (2H, q, $J = 7.0$, CH_2), 2.86 (3H, s, 3-CH_3), 1.54 (3H, t, $J = 7.0$, CH_3–CH_2). Anal. $C_{17}H_{15}FN_2O_3S$ (C, H, N).

*6.1.4. General procedure for preparation of 3-bromomethyl-2-phenylthioquinoxaline 1,4-dioxides (**4a**–**e**,**h**–**l**)*

The title compounds were prepared following the procedure previously described by Haddadin et al. [28]. A solution of the appropriate 3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3a**–**e**,**h**–**l**) (1.5–2.0 mmol) in EtOAc (50 mL) was heated to reflux temperature, when a solution of Br (2.25–3.0 mmol) in EtOAc (5 mL) was slowly (30–230 min) added dropwise. After the addition was complete, the reaction mixture was stirred under reflux for an additional 15 min. The volume of the solution was then concentrated in vacuo, to 5 mL, and the solid precipitate was filtered off, washed with Et_2O, dried and crystallised from a suitable solvent.

*6.1.4.1. 3-Bromomethyl-2-phenylthioquinoxaline 1,4-dioxide (**4a**).* This compound was obtained in 87% yield (after addition of Br solution within 75 min); m.p. 167–169 °C (from EtOAc); IR (cm^{-1}): *v* 1610, 1350, 1320; UV: λ_{max} 382, 309, 274, 242, 205 nm; ^{1}H-NMR ($CDCl_3$): δ 8.66 (1H, dd, $J = 8.4$ and 2.2, H-5), 8.51 (1H, dd, $J = 8.4$ and 2.2, H-8), 7.84 (2H, m, H-6 + H-7), 7.51 (2H, m, 2 phenyl-H), 7.35 (3H, m, 3 phenyl-H), 5.20 (2H, s, CH_2). Anal. $C_{15}H_{11}BrN_2O_2S$ (C, H, Br, N).

*6.1.4.2. 3-Bromomethyl-6-methyl-2-phenylthioquinoxaline 1,4-dioxide (**4b**).* This compound was obtained in 87% yield (after addition of Br solution within 70 min); m.p. 165–166 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1350, 1320; UV: λ_{max} 381, 312, 275, 246, 203 nm; ^{1}H-NMR ($CDCl_3$): δ 8.45 (1H, d, $J = 2.2$, H-5), 8.40 (1H, d, $J = 8.6$, H-8), 7.64 (1H, dd, $J = 8.6$ and 2.2, H-7), 7.49 (2H, m, 2 phenyl-H), 7.33 (3H, m, 3 phenyl-H), 5.22 (2H, s, CH_2), 2.63 (3H, s, CH_3). Anal. $C_{16}H_{13}BrN_2O_2S$ (C, H, Br, N).

*6.1.4.3. 3-Bromomethyl-7-methyl-2-phenylthioquinoxaline 1,4-dioxide (**4c**).* This compound was obtained in 83% yield (after addition of Br solution within 110 min); m.p. 186–187 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1330, 1310; UV: λ_{max} 382, 311, 275, 246, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.55 (1H, d, $J = 8.8$, H-5), 8.32 (1H, d, $J = 2.2$, H-8), 7.68 (1H, dd, $J = 8.8$ and 2.2, H-6), 7.52 (2H, m, 2 phenyl-H), 7.35 (3H, m, 3 phenyl-H), 5.21 (2H, s, CH_2), 2.58 (3H, s, CH_3). Anal. $C_{16}H_{13}BrN_2O_2S$ (C, H, Br, N).

*6.1.4.4. 3-Bromomethyl-6-chloro-2-phenylthioquinoxaline 1,4-dioxide (**4d**).* This compound was obtained in 85% yield (after addition of Br solution within 60 min); m.p. 188–190 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1340, 1320; UV: λ_{max} 387, 317, 280, 245, 203 nm; ^{1}H-NMR ($CDCl_3$): δ 8.64 (1H, d, $J = 2.2$, H-5), 8.44 (1H, d, $J = 9.2$, H-8), 7.74 (1H, dd, $J = 9.2$ and 2.2, H-7), 7.49 (2H, m, 2 phenyl-H), 7.34 (3H, m, 3 phenyl-H), 5.17 (2H, s, CH_2). Anal. $C_{15}H_{10}BrClN_2O_2S$ (C, H, Br, Cl, N).

*6.1.4.5. 3-Bromomethyl-7-chloro-2-phenylthioquinoxaline 1,4-dioxide (**4e**).* This compound was obtained in 86% yield (after addition of Br solution within 60 min);

m.p. 198–199 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1350, 1330; UV: λ_{max} 388, 314, 278, 245, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.59 (1H, d, $J = 9.2$, H-5), 8.49 (1H, d, $J = 2.4$, H-8), 7.77 (1H, dd, $J = 9.2$ and 2.4, H-6), 7.53 (2H, m, 2 phenyl-H), 7.34 (3H, m, 3 phenyl-H), 5.17 (2H, s, CH_2). Anal. $C_{15}H_{10}BrClN_2O_2S$ (C, H, Br, Cl, N).

*6.1.4.6. 3-Bromomethyl-6-trifluoromethyl-2-phenylthioquinoxaline 1,4-dioxide (**4h**).* This compound was obtained in 86% yield (after addition of Br solution within 30 min); m.p. 185–186 °C (from EtOAc); IR (cm^{-1}): *v* 1610, 1330, 1310; UV: λ_{max} 394, 276, 237, 203 nm; ^{1}H-NMR ($CDCl_3$): δ 8.81 (1H, d, $J = 2.2$, H-5), 8.79 (1H, d, $J = 8.8$, H-8), 8.02 (1H, dd, $J = 8.8$ and 2.2, H-7), 7.58 (2H, m, 2 phenyl-H), 7.38 (3H, m, 3 phenyl-H), 5.20 (2H, s, CH_2). Anal. $C_{16}H_{10}BrF_3N_2O_2S$ (C, H, Br, N).

*6.1.4.7. 3-Bromomethyl-7-trifluoromethyl-2-phenylthioquinoxaline 1,4-dioxide (**4i**).* This compound was obtained in 85% yield (after addition of Br solution within 30 min); m.p. 175–176 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1350, 1310; UV: λ_{max} 389, 277, 237, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.97 (1H, d, $J = 2.2$, H-8), 8.62 (1H, d, $J = 8.8$, H-5), 7.99 (1H, dd, $J = 8.8$ and 2.2, H-6), 7.52 (2H, m, 2 phenyl-H), 7.37 (3H, m, 3 phenyl-H), 5.18 (2H, s, CH_2). Anal. $C_{16}H_{10}BrF_3N_2O_2S$ (C, H, Br, N).

*6.1.4.8. 3-Bromomethyl-6,7-difluoro-2-phenylthioquinoxaline 1,4-dioxide (**4j**).* This compound was obtained in 87% yield (after addition of Br solution within 30 min); m.p. 181–182 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1340, 1310; UV: λ_{max} 384, 306, 275, 236, 203 nm; ^{1}H-NMR ($CDCl_3$): δ 8.46 (1H, t, $J = 8.6$, H-5), 8.31 (1H, t, $J = 8.6$, H-8), 7.52 (2H, m, 2 phenyl-H), 7.36 (3H, m, 3 phenyl-H), 5.17 (2H, s, CH_2). Anal. $C_{15}H_9BrF_2N_2O_2S$ (C, H, Br, N).

*6.1.4.9. 3-Bromomethyl-6-ethoxy-7-fluoro-2-phenylthioquinoxaline 1,4-dioxide (**4k**).* This compound was obtained in 84% yield (after addition of Br solution within 120 min); m.p. 165–166 °C (from EtOAc); IR (cm^{-1}): *v* 1610, 1330; UV: λ_{max} 378, 316, 273, 250, 204 nm; ^{1}H-NMR ($CDCl_3$): δ 8.19 (1H, d, $J = 10.2$, H-8), 8.06 (1H, d, $J = 8.0$, H-5), 7.48 (2H, m, 2 phenyl-H), 7.33 (3H, m, 3 phenyl-H), 5.22 (2H, s, CH_2Br), 4.32 (2H, q, $J = 6.8$, CH_2O), 1.57 (3H, t, $J = 6.8$, CH_3). Anal. $C_{17}H_{14}BrFN_2O_3S$ (C, H, Br, N).

*6.1.4.10. 3-Bromomethyl-7-ethoxy-6-fluoro-2-phenylthioquinoxaline 1,4-dioxide (**4l**).* This compound was obtained in 88% yield (after addition of Br solution within 230 min); m.p. 180–181 °C (from EtOAc); IR (cm^{-1}): *v* 1600, 1330; UV: λ_{max} 382, 319, 274, 253, 204 nm; ^{1}H-NMR ($CDCl_3$): δ 8.30 (1H, d, $J = 10.4$, H-5), 7.90 (1H, d, $J = 7.8$, H-8), 7.51 (2H, m, 2 phenyl-H), 7.35 (3H, m, 3 phenyl-H), 5.19 (2H, s, CH_2Br), 4.24 (2H, q, $J = 7.0$, CH_2O), 1.53 (3H, t, $J = 7.0$, CH_3). Anal. $C_{17}H_{14}BrFN_2O_3S$ (C, H, Br, N).

*6.1.5. General procedure for preparation of 3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxides (**5a–e,g,j,l**)*

The title compounds were prepared following the procedure previously described by Abushanab [29]. To a solution of the appropriate 3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3a–e,g,j,k**) (6.25–18.5 mmol) in $CHCl_3$ (50–100 mL) a solution of 3-chloroperoxybenzoic acid (MCPBA) (12.5–37.0 mmol) in $CHCl_3$ (30–60 mL) was slowly added. After the addition was complete, the reaction mixture was stirred at r.t. for an additional 16 h, then the $CHCl_3$ solution was washed with 10% $NaHCO_3$ aq. solution, dried over $MgSO_4$, filtered off and evaporated. A solid was obtained and purified as indicated below.

*6.1.5.1. 3-Methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5a**).* This compound was obtained in 94% yield; m.p. 158–160 °C (from $CHCl_3$), (literature [29]: m.p. 180–181 °C).

*6.1.5.2. 3,6-Dimethyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5b**).* This compound was obtained in 77% yield; m.p. 179–180 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1600, 1350, 1310; UV: λ_{max} 398, 274, 247, 201 nm; ^{1}H-NMR ($CDCl_3$): δ 8.40 (1H, d, $J = 2.2$, H-5), 8.28 (1H, d, $J = 8.8$, H-8), 8.15 (1H, dd, $J = 8.8$ and 2.2, H-7), 7.63 (5H, m, 5 phenyl-H), 3.21 (3H, d, $J = 2.2$, 3-CH_3), 2.60 (3H, s, 6-CH_3). Anal. $C_{16}H_{14}N_2O_4S$ (C, H, N).

*6.1.5.3. 3,7-Dimethyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5c**).* This compound was obtained in 74% yield; m.p. 180–181 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1600, 1350, 1300; UV: λ_{max} 410, 362, 272, 240, 201 nm; ^{1}H-NMR ($CDCl_3$): δ 8.49 (1H, d, $J = 8.8$, H-5), 8.14 (2H, m, H-6 + H-8), 7.65 (5H, m, 5 phenyl-H), 3.20 (3H, s, 3-CH_3), 2.53 (3H, s, 7-CH_3). Anal. $C_{16}H_{14}N_2O_4S$ (C, H, N).

*6.1.5.4. 6-Chloro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5d**).* This compound was obtained in 72% yield; m.p. 148–150 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1600, 1330, 1310; UV: λ_{max} 396, 281, 244, 203 nm; ^{1}H-NMR ($CDCl_3$): δ 8.61 (1H, d, $J = 2.0$, H-5), 8.43 (1H, d, $J = 9.0$, H-8), 8.14 (1H, dd, $J = 9.0$ and 2.0, H-7), 7.73 (2H, m, 2 phenyl-H), 7.54 (3H, m, 3 phenyl-H), 3.21 (3H, s, CH_3). Anal. $C_{15}H_{11}ClN_2O_4S$ (C, H, Cl, N).

*6.1.5.5. 7-Chloro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5e**).* This compound was obtained in 80% yield; m.p. 158–160 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1600, 1330, 1310; UV: λ_{max} 403, 282, 237, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.53 (1H, d, $J = 8.8$, H-5), 8.49 (1H, d, $J = 2.2$, H-8), 8.08 (2H, m, 2 phenyl-H), 7.78 (1H, dd, $J = 8.8$ and 2.2, H-6), 7.54 (3H, m, 3 phenyl-H), 2.95 (3H, s, CH_3). Anal. $C_{15}H_{11}ClN_2O_4S$ (C, H, Cl, N).

*6.1.5.6. 7-Ethoxy-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5g**).* This compound was obtained in 5% yield; m.p. 146–148 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1620, 1330, 1310; UV: λ_{max} 402, 280, 230, 211 nm; ^{1}H-NMR ($CDCl_3$): δ 8.06 (1H, d, $J = 2.0$, H-8), 7.97 (1H, d, $J = 8.4$, H-5), 7.91 (1H, dd, $J = 8.4$ and 2.0, H-6), 7.64 (2H, m, 2 phenyl-H), 7.48 (3H, m, 3 phenyl-H), 4.42 (2H, q, $J = 7.0$, CH_2), 2.28 (3H, s, 3-CH_3), 1.41 (3H, t, $J = 7.0$, CH_3–CH_2). Anal. $C_{17}H_{16}N_2O_5S$ (C, H, N).

*6.1.5.7. 6,7-Difluoro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5j**).* This compound was obtained in 74% yield; m.p. 179–180 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1610, 1340, 1310; UV: λ_{max} 405, 368, 274, 230 nm; ^{1}H-NMR ($CDCl_3$): δ 8.43 (1H, t, $J = 8.6$, H-8), 8.21 (1H, t, $J = 8.6$, H-5), 8.14 (2H, m, 2 phenyl-H), 7.62 (3H, m, 3 phenyl-H), 3.20 (3H, s, CH_3). Anal. $C_{15}H_{10}F_2N_2O_4S$ (C, H, N).

*6.1.5.8. 7-Ethoxy-6-fluoro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5l**).* This compound was obtained in 89% yield; m.p. 150–152 °C (from $CHCl_3$); IR (cm^{-1}): *v* 1620, 1330, 1320; UV: λ_{max} 402, 367, 318, 274, 245, 208 nm; ^{1}H-NMR ($CDCl_3$): δ 8.28 (1H, d, $J = 10.2$, H-5), 7.84 (1H, d, $J = 7.6$, H-8), 7.66 (5H, m, 5 phenyl-H), 4.29 (2H, q, $J = 7.0$, CH_2), 3.20 (3H, s, 3-CH_3), 1.56 (3H, t, $J = 7.0$, CH_3–CH_2). Anal. $C_{17}H_{15}FN_2O_5S$ (C, H, N).

*6.1.6. General procedure for preparation of 2-chloro-3-methylquinoxaline 1,4-dioxides (**6a–e,j,l**)*

The title compounds were prepared by an adaptation of the procedure described by Abushanab [29]. A mixture of the appropriate sulphonylquinoxaline derivative **5a–e,j,l** (3.1–15.8 mmol) in concd. HCl (6–32 mL) was warmed up at 70 °C under stirring for 15 min. After the excess of the acid was removed in vacuo, the aq. solution was poured onto ice (about 20 g) and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$, filtered off and evaporated. The solid residue obtained was chromatographed on silica gel, eluting by ethyl ether–EtOH 90:10, to give the desired compounds.

*6.1.6.1. 2-Chloro-3-methylquinoxaline 1,4-dioxide (**6a**).* This compound was obtained in 87% yield; m.p. 132–133 °C (from ether–EtOH), (literature [29]: m.p. 166–68 °C).

*6.1.6.2. 2-Chloro-3,6-dimethylquinoxaline 1,4-dioxide (**6b**).* This compound was obtained in 91% yield; m.p. 153–154 °C (from ether–EtOH); IR (cm^{-1}): *v* 1600, 1320, 1260; UV: λ_{max} 379, 363, 266, 240, 216 nm; ^{1}H-NMR ($CDCl_3$): δ 8.51 (1H, d, $J = 8.8$, H-8), 8.41 (1H, d, $J = 2.0$, H-5), 7.67 (1H, dd, $J = 8.8$ and 2.0, H-7), 2.84 (3H, s, 3-CH_3), 2.63 (3H, s, 6-CH_3). Anal. $C_{10}H_9ClN_2O_2$ (C, H, Cl, N).

*6.1.6.3. 2-Chloro-3,7-dimethylquinoxaline 1,4-dioxide (**6c**).* This compound was obtained in 92% yield; m.p. 152–153 °C (from ether–EtOH); IR (cm^{-1}): *v* 1600, 1320, 1260; UV: λ_{max} 379, 361, 266, 240, 216 nm; ^{1}H-NMR ($CDCl_3$): δ 8.50 (1H, d, $J = 8.8$, H-5), 8.41 (1H, d, $J = 2.0$, H-8), 7.67 (1H, dd, $J = 8.8$ and 2.0, H-6), 2.83 (3H, s, 3-CH_3), 2.63 (3H, s, 7-CH_3). Anal. $C_{10}H_9ClN_2O_2$ (C, H, Cl, N).

*6.1.6.4. 2,6-Dichloro-3-methylquinoxaline 1,4-dioxide (**6d**).* This compound was obtained in 84% yield; m.p. 151–153 °C (from ether–EtOH); IR (cm^{-1}): *v* 1620, 1320, 1270; UV: λ_{max} 382, 370, 272, 230, 205 nm; ^{1}H-NMR ($CDCl_3$): δ 8.61 (1H, d, $J = 2.0$, H-5) 8.58 (1H, d, $J = 9.2$, H-8), 7.79 (1H, dd, $J = 9.2$ and 2.0, H-7), 2.84 (3H, s, CH_3). Anal. $C_9H_6Cl_2N_2O_2$ (C, H, Cl, N).

*6.1.6.5. 2,7-Dichloro-3-methylquinoxaline 1,4-dioxide (**6e**).* This compound was obtained in 88% yield; m.p. 178–179 °C (from ether–EtOH); IR (cm^{-1}): *v* 1600, 1310, 1250; UV: λ_{max} 368, 272, 240, 212 nm; ^{1}H-NMR ($CDCl_3$): δ 8.63 (1H, d, $J = 2.0$, H-8), 8.57 (1H, d, $J = 9.2$, H-5), 7.80 (1H, dd, $J = 9.2$ and 2.0, H-6), 2.83 (3H, s, CH_3). Anal. $C_9H_6Cl_2N_2O_2$ (C, H, Cl, N).

*6.1.6.6. 2-Chloro-6,7-difluoro-3-methylquinoxaline 1,4-dioxide (**6j**).* This compound was obtained in 78% yield; m.p. 202–203 °C (from ether–EtOH); IR (cm^{-1}): *v* 1620, 1600, 1320, 1270; UV: λ_{max} 379, 268, 231 nm; ^{1}H-NMR ($CDCl_3$): δ 8.44 (2H, m, H-5 + H-8), 2.83 (3H, s, CH_3). Anal. $C_9H_5ClF_2N_2O_2$ (C, H, Cl, N).

*6.1.6.7. 2-Chloro-7-ethoxy-6-fluoro-3-methylquinoxaline 1,4-dioxide (**6l**).* This compound was obtained in 93% yield; m.p. 180–181 °C (from ether–EtOH); IR (cm^{-1}): *v* 1610, 1310, 1260; UV: λ_{max} 384, 362, 300, 267, 244, 202 nm; ^{1}H-NMR ($CDCl_3$): δ 8.26 (1H, d, $J = 10.4$, H-5), 7.99 (1H, d, $J = 7.6$, H-8), 4.33 (2H, q, $J = 7.0$, CH_2), 2.81 (3H, s, 3-CH_3), 1.58 (3H, t, $J = 7.0$, CH_3–CH_2). Anal. $C_{11}H_{10}ClFN_2O_3$ (C, H, Cl, N).

6.2. Microbiological assays

All the synthetised compounds were evaluated in vitro for their antimicrobial activity against Gram positive (*S. aureus*) and Gram negative (*E. coli*, *V. alginolyticus*, *K. pneumoniae* and *P. aeruginosa*) bacteria, yeasts (*C. albicans*, *C. glabrata*, *C. krusei* and *C. parapsilosis*), and mycobacteria (*M. tuberculosis*).

6.2.1. Antibacterial assays

The strains used in these tests were from American Type Culture Collection (ATCC): *S. aureus* ATCC 2913, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853, or are environmental isolate (*V. alginolyticus*). A logarithmic phase culture of each bacterial strain was diluted with Luria broth in order to obtain a density of 10^6 CFU mL^{-1}. The test was performed in a 96 well microtitre plate in a final volume of 100 μL. Test compounds were dissolved in dimethyl sulphoxide at an initial concentration of 1000 μg mL^{-1} and serially diluted in the plate (500–7.8 μg mL^{-1}) using Luria broth. Each well was then inoculated with the standardised bacterial suspension and incubated at 37 °C for 18–24 h. One well containing bacteria without sample (growth control), and one well containing broth only (sterility control) were also used. After the incubation the growth (or its lack) of the bacteria was determined visually in both containing compound well and control well. The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC. In addition 5 μL of suspension from each well was inoculated in a Mueller Hinton agar plate to control bacterial viability.

6.2.2. Antimycotic assay

Antifungal activity was determined by the tube dilution method on clinical isolates of *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. albicans* (24 strains). These clinical isolates were from a variety of patient types including patients with AIDS, candidaemia, and tissue disease. Yeast inocula were obtained by properly diluting cultures incubated at 35 °C for 48 h in Sabouraud Dextran agar to obtain a density of 10^6 CFU mL^{-1}. Test compounds were dissolved in dimethyl sulphoxide at an initial concentration of 1000 μg mL^{-1} and then were serially diluted in culture medium to 15.6 μg mL^{-1}. Then, 0.5 mL of the above serial dilutions of test compounds were added, in sterile polystirene tubes, with an equal volume of fungal suspension and incubated at 35 °C for 48 h. The MIC determination was performed in duplicate, and defined as the lowest concentration of the compound which produced no visible growth. A sample of compound free growth control and a set of tubes with sample alone for monitoring contamination of the medium were used.

6.2.3. Antimycobacterial assay

The described compounds were tested in vitro for their antitubercular activity at Southern Research Institute, GWL Hansen's Disease Center (Colorado State University) within the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) screening program for the discovery of novel drugs for treatment of tuberculosis.

Primary screening was conducted at 6.25 μg mL^{-1} for **3a**–**e**,**h**–**l**, **4a**–**e**,**h**–**j**, **5a**–**e**,**j**,**l**, and **6b**–**e**,**j**,**l**, against the virulent strain *M. tuberculosis* H37Rv (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue assay (MABA). Compounds exhibiting fluorescence were tested in the Bactec 460 radiometric system. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. Compounds showing at least 90% inhibition in the primary screen are re-tested at lower concentration againt *M. tuberculosis* H37Rv to determine the actual minimum inhibitory concentration in a broth microdilution Alamar Blue assay (MABA) [36]. Compounds effecting $< 90\%$ inhibition in the primary screening (MIC > 6.25 μg mL^{-1}) were not evaluated further. The standard compound used in this primary assay was rifampicin (MIC $= 0.25$ μg mL^{-1}).

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Appendix A. Analytical data

5-Ethoxybenzofuroxan (**2f**): Anal. Calc. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.11; H, 4.63; N, 15.32%.

6-Fluoro-5-ethoxybenzofuroxan (**2k**): Anal. Calc. for $C_8H_7FN_2O_3$: C, 48.49; H, 3.56; N, 14.14. Found: C, 48.37; H, 3.48; N, 14.02%.

3,6-Dimethyl-2-phenylthioquinoxaline 1,4-dioxide (**3b**): Anal. Calc. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.32; H, 4.63; N, 9.24%.

3,7-Dimethyl-2-phenylthioquinoxaline 1,4-dioxide (**3c**): Anal. Calc. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.33; H, 4.66; N, 9.23%.

6-Chloro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3d**): Anal. Calc. for $C_{15}H_{11}ClN_2O_2S$: C, 56.51; H, 3.48; Cl, 11.12; N, 8.79. Found: C, 56.43; H, 3.39; Cl, 11.07; N, 8.62%.

7-Chloro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3e**): Anal. Calc. for $C_{15}H_{11}ClN_2O_2S$: C, 56.51; H,

3.48; Cl, 11.12; N, 8.79. Found: C, 56.34; H, 3.35; Cl, 11.02; N, 8.64%.

7-Ethoxy-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3g**): Anal. Calc. for $C_{17}H_{16}N_2O_3S$: C, 62.17; H, 4.91; N, 8.53. Found: C, 62.07; H, 5.19; N, 8.32%.

6-Trifluoromethyl-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3h**): Anal. Calc. for $C_{16}H_{11}F_3N_2O_2S$: C, 54.54; H, 3.15; N, 7.95. Found: C, 54.49; H, 16.12; N, 7.84%.

7-Trifluoromethyl-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3i**): Anal. Calc. for $C_{16}H_{11}F_3N_2O_2S$: C, 54.54; H, 3.15; N, 7.95. Found: C, 54.38; H, 3.09; N, 7.80%.

6,7-Difluoro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3j**): Anal. Calc. for $C_{15}H_{10}F_2N_2O_2S$: C, 56.24; H, 3.15; N, 8.75. Found: C, 56.17; H, 3.02; N, 8.67%.

6-Ethoxy-7-fluoro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3k**): Anal. Calc. for $C_{17}H_{15}FN_2O_3S$: C, 58.94; H, 4.37; N, 8.09. Found: C, 58.83; H, 4.29; N, 7.96%.

7-Ethoxy-6-fluoro-3-methyl-2-phenylthioquinoxaline 1,4-dioxide (**3l**): Anal. Calc. for $C_{17}H_{15}FN_2O_3S$: C, 58.95; H, 4.36; N, 8.09. Found: C, 58.87; H, 4.27; N, 8.02%.

3-Bromomethyl-2-phenylthioquinoxaline 1,4-dioxide (**4a**): Anal. Calc. for $C_{15}H_{11}BrN_2O_2S$: C, 49.60; H, 3.06; Br, 22.00; N, 7.71. Found: C, 49.57; H, 2.98; Br, 21.93; N, 7.64%.

3-Bromomethyl-6-methyl-2-phenylthioquinoxaline 1,4-dioxide (**4b**): Anal. Calc. for $C_{16}H_{13}BrN_2O_2S$: C, 50.94; H, 3.47; Br, 21.18; N, 7.42. Found: C, 50.86; H, 3.39; Br, 21.07; N, 7.69%.

3-Bromomethyl-7-methyl-2-phenylthioquinoxaline 1,4-dioxide (**4c**): Anal. Calc. for $C_{16}H_{13}BrN_2O_2S$: C, 50.94; H, 3.47; Br, 21.18; N, 7.42. Found: C, 50.77; H, 3.42; Br, 21.02; N, 7.30%.

3-Bromomethyl-6-chloro-2-phenylthioquinoxaline 1,4-dioxide (**4d**): Anal. Calc. for $C_{15}H_{10}BrClN_2O_2S$: C, 45.30; H, 2.53; Br, 20.10; Cl, 8.92; N, 7.05. Found: C, 45.24; H, 2.48; Br, 19.93; Cl, 8.83; N, 6.97%.

3-Bromomethyl-7-chloro-2-phenylthioquinoxaline 1,4-dioxide (**4e**): Anal. Calc. for $C_{15}H_{10}BrClN_2O_2S$: C, 45.30; H, 2.53; Br, 20.10; Cl, 8.92; N, 7.05. Found: C, 45.16; H, 2.41; Br, 19.90; Cl, 8.78; N, 6.91%.

3-Bromomethyl-6-trifluoromethyl-2-phenylthioquinoxaline 1,4-dioxide (**4h**): Anal. Calc. for $C_{16}H_{10}BrF_3N_2O_2S$: C, 44.56; H, 2.34; Br, 18.53; N, 6.50. Found: C, 44.27; H, 2.42; Br, 18.44; N, 6.36%.

3-Bromomethyl-7-trifluoromethyl-2-phenylthioquinoxaline 1,4-dioxide (**4i**): Anal. Calc. for $C_{16}H_{10}BrF_3N_2O_2S$: C, 44.56; H, 2.34; Br, 18.53; N, 6.50. Found: C, 44.48; H, 2.28; Br, 18.39; N, 6.47%.

3-Bromomethyl-6,7-difluoro-2-phenylthioquinoxaline 1,4-dioxide (**4j**): Anal. Calc. for $C_{15}H_9BrF_2N_2O_2S$: C, 45.13; H, 2.27; Br, 20.02; N, 7.02. Found: C, 44.79; H, 2.42; Br, 19.73; N, 6.84%.

3-Bromomethyl-6-ethoxy-7-fluoro-2-phenylthioquinoxaline 1,4-dioxide (**4k**): Anal. Calc. for $C_{17}H_{14}BrFN_2O_3S$: C, 48.01; H, 3.32; Br, 18.79; N, 6.59. Found: C, 47.86; H, 3.57; Br, 18.62; N, 6.33%.

3-Bromomethyl-7-ethoxy-6-fluoro-2-phenylthioquinoxaline 1,4-dioxide (**4l**): Anal. Calc. for $C_{17}H_{14}BrFN_2O_3S$: C, 48.01; H, 3.32; Br, 18.79; N, 6.59. Found: C, 47.93; H, 3.29; Br, 18.83; N, 6.47%.

3,6-Dimethyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5b**): Anal. Calc. for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.06; H, 4.19; N, 8.41%.

3,7-Dimethyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5c**): Anal. Calc. for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.11; H, 4.34; N, 8.37%.

6-Chloro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5d**): Anal. Calc. for $C_{15}H_{11}ClN_2O_4S$: C, 51.36; H, 3.16; Cl, 10.11; N, 7.99. Found: C, 51.29; H, 3.11; Cl, 9.98; N, 7.87%.

7-Chloro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5e**): Anal. Calc. for $C_{15}H_{11}ClN_2O_4S$: C, 51.36; H, 3.16; Cl, 10.11; N, 7.99. Found: C, 51.18; H, 3.28; Cl, 10.03; N, 7.84%.

7-Ethoxy-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5g**): Anal. Calc. for $C_{17}H_{16}N_2O_5S$: C, 56.65; H, 4.48; N, 7.77. Found: C, 56.41; H, 4.74; N, 7.51%.

6,7-Difluoro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5j**): Anal. Calc. for $C_{15}H_{10}F_2N_2O_4S$: C, 51.13; H, 2.86; N, 7.95. Found: C, 51.06; H, 2.72; N, 7.84%.

7-Ethoxy-6-fluoro-3-methyl-2-phenylsulphonylquinoxaline 1,4-dioxide (**5l**): Anal. Calc. for $C_{17}H_{15}FN_2O_5S$: C, 53.96; H, 4.00; N, 7.40. Found: C, 53.89; H, 3.97; N, 7.31%.

2-Chloro-3,6-dimethylquinoxaline 1,4-dioxide (**6b**): Anal. Calc. for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.04; Cl, 15.78; N, 12.47. Found: C, 53.39; H, 3.96; Cl, 15.66; N, 12.36%.

2-Chloro-3,7-dimethylquinoxaline 1,4-dioxide (**6c**): Anal. Calc. for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.04; Cl, 15.78; N, 12.47. Found: C, 53.26; H, 3.99; Cl, 15.51; N, 12.32%.

2,6-Dichloro-3-methylquinoxaline 1,4-dioxide (**6d**): Anal. Calc. for $C_9H_6Cl_2N_2O_2$: C, 44.11; H, 2.47; Cl, 28.93; N, 11.43. Found: C, 44.07; H, 2.41; Cl, 28.89; N, 11.36%.

2,7-Dichloro-3-methylquinoxaline 1,4-dioxide (**6e**): Anal. Calc. for $C_9H_6Cl_2N_2O_2$: C, 44.11; H, 2.47; Cl, 28.93; N, 11.43. Found: C, 43.93; H, 2.53; Cl, 28.88; N, 11.27%.

2-Chloro-6,7-difluoro-3-methylquinoxaline 1,4-dioxide (**6j**): Anal. Calc. for $C_9H_5ClF_2N_2O_2$: C, 43.83; H, 2.04; Cl, 14.38; N, 11.36. Found: C, 43.76; H, 1.99; Cl, 14.32; N, 11.29%.

2-Chloro-7-ethoxy-6-fluoro-3-methylquinoxaline 1,4-dioxide (**6l**): Anal. Calc. for $C_{11}H_{10}ClFN_2O_3$: C, 48.45;

H, 3.70; Cl, 13.00; N, 10.28. Found: C, 48.37; H, 3.68; Cl, 12.94; N, 10.23%.

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