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Original article

Synthesis and antimycobacterial activity of new quinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives

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ABSTRACT

As a continuation of our research and with the aim of obtaining new anti-tuberculosis agents which can improve the current chemotherapeutic anti-tuberculosis treatments, forty-three new quinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives were synthesized and evaluated for *in vitro* anti-tuberculosis activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$. Active compounds were also screened to assess toxicity to a VERO cell line. Results indicate that compounds with a methyl moiety substituted in position 3 and unsubstituted benzyl substituted on the carboxamide group provide an efficient approach for further development of anti-tuberculosis agents.

1. Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium Tuberculosis (M.Tbc)*. The report published by WHO in 2009 established that there were an estimated 9.27 million incident cases of TB in 2007. This means an increase from the 9.24 million cases in 2006, the 8.3 million cases in 2000 and the 6.6 million cases in 1990. Although the total number of incident cases of TB is increasing, it must be said that the number of cases per capita is slowly decreasing [1]. Nevertheless, the continuing emergence of multidrug-resistant strains of *M. tuberculosis* (MDR-TB) will inevitably make it more difficult in the future to control TB.

The global epidemiology of drug-resistant TB, particularly extremely drug-resistant TB (XDR-TB), is unknown and the true magnitude of the problem is probably quite underestimated. MDR-TB, which is defined as TB caused by organisms that are resistant to isoniazid and rifampicin, continues to threaten the progress being made in controlling the disease. The emergence of XDR-TB, defined as a less common form of MDR-TB that is resistant not only to isoniazid and rifampicin but also to any one of the fluoroquinolones and to at least one of the second-line drugs (amikacin, capreomycin or kanamycin), has heightened this threat [2]. The recent influx of immigrants from countries endemic for disease and co-infection with human immunodeficiency virus (HIV) turns TB into a serious problem in developed countries [3,4]. The development of HIV co-infection with MDR-TB and XDR-TB highlights the urgent need for new drugs to extend the range of effective TB treatment options.

Quinoxaline derivatives are a class of compounds that show very interesting biological properties and the interest in these compounds is growing within the field of medicinal chemistry. Quinoxaline-1,4-di-*N*-oxide derivatives even improve the biological results shown by their reduced analogues and are endowed with antiviral, anticancer, antibacterial and antiprotozoal activities [5–9]. There are many publications regarding 1,4-di-*N*-oxide derivatives, and more specifically alkyl and arylcarboxamide derivatives, in which their antibacterial and antimicrobial activities [10–14] have been reported or their capability to act as antitumoral agents [15,16] has been clearly demonstrated, thereby reflecting the growing interest in these structures over the past forty years.

As a result of the anti-tuberculosis research project, our group has published several papers reporting a wide range of quinoxaline-1,4-di-*N*-oxide derivatives (Fig. 1) including a great variety of substituents in positions 2, 3, 6 and 7. With regard to position 2, carbonitrile derivatives appeared to be quite toxic [17–21]. Moreover, ketone, carboxylate and carboxamide quinoxaline-1,4-dioxydes derivatives were actually patented in the 70s for their antibacterial activity [12–15].

These studies have facilitated a wide structure-activity relationship (SAR) analysis which lead us to design a group of thirty-six 3-methylquinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives that were prepared and tested against *M.Tbc* and to justify the design of the compounds presented in this paper [22].

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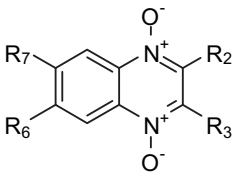


Fig. 1. General structure and numeration of quinoxaline-1,4-di-*N*-oxide.

Continuing with the anti-tuberculosis project and in an attempt to establish the structural requirements necessary for the development of anti-tuberculosis drugs, nine series of quinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives were proposed (Fig. 2). Several structural modifications were designed and can be summarized as follows: a) variation in the length of the aliphatic linker between the carboxamide group and the aromatic ring; b) modification of the substituent in position 3 by a phenyl (Series **1**–**3**) and a methyl moiety (Series **4**–**9**); c) substitution of a variety of aromatic rings (Series **4**–**9**).

2. Chemistry

Forty-three new 1,4-di-*N*-oxide-quinoxaline-2-carboxylic acid aryl amide derivatives were prepared according to the synthetic process illustrated in Scheme 1:

The synthesis of the new 1,4-di-*N*-oxide-quinoxaline derivatives (Series **1**–**9**) was carried out by a variation of the Beirut reaction [23], where the appropriate benzofuroxanes (BFX) react with the corresponding β-ketoamide in the presence of calcium chloride and ethanolamine as catalysts [22,24].

The starting compounds, BFX, were obtained by previously described methods [18,25]. Compound **1** was commercially available whereas the rest of the β-ketoamides were synthesized as follows: compound **2** was synthesized by Passerini reaction between the appropriate glyoxal and isocyanide [26]; compound **3** was synthesized by condensation of the corresponding ester and the appropriate aryl amine [27]. Compounds **4**–**9** were obtained through the acetoacetylation of corresponding aryl amines by diketene [22,28].

Quinoxaline derivatives were unsubstituted or substituted in positions 6 and 7 by chloro, fluoro or trifluoromethyl moiety as electron-withdrawing groups and by methyl or methoxy moiety as electron-releasing groups. When quinoxalines were prepared from monosubstituted-BFX, the formation of isomeric quinoxalines 1,4-di-*N*-oxide was observed. In most cases, the 7-substituted isomer prevailed over 6-substituted isomer, and when the methoxy substituted quinoxalines were prepared, only the 7-isomer was obtained, as previously described [29,30].

3. Pharmacology

In vitro evaluation of the anti-tuberculosis activity was carried out within the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) screening program for the discovery of novel drugs for the treatment of tuberculosis [31]. The Southern Research Institute coordinates the overall program under the direction of the U.S. National Institute of Allergy and Infectious Disease (NIAID).

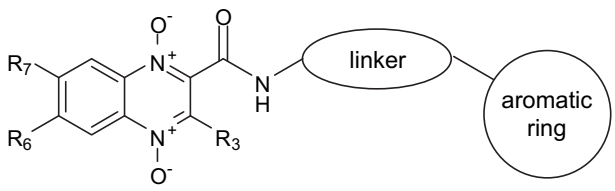


Fig. 2. Design of the new series of quinoxaline-2-carboxamide 1,4-di-*N*-oxide.

The purpose of the screening program is to provide a resource whereby new experimental compounds can be tested for their ability to inhibit the growth of virulent *M. tuberculosis (M.Tbc.).* Biological tests have been performed according to previously described methods [32].

4. Results and discussion

Structure and biological values of new synthesized quinoxaline-1,4-di-*N*-oxide derivatives are reported in Table 1. Compounds are assayed against *M.Tbc.* $H_{37}Rv$ in order to determine the IC_{90}. Compounds showing values of $\leq$10 μg/mL are considered as active and move on to the secondary screening. Cytotoxicity is assayed in VERO cells and the CC_{50} is determined from the dose–response curve. Next, the IC_{90} and CC_{50} values are formed into a ratio termed Selectivity Index (SI). Compounds showing a SI $\geq$ 10 are considered active for anti-tubercular activity.

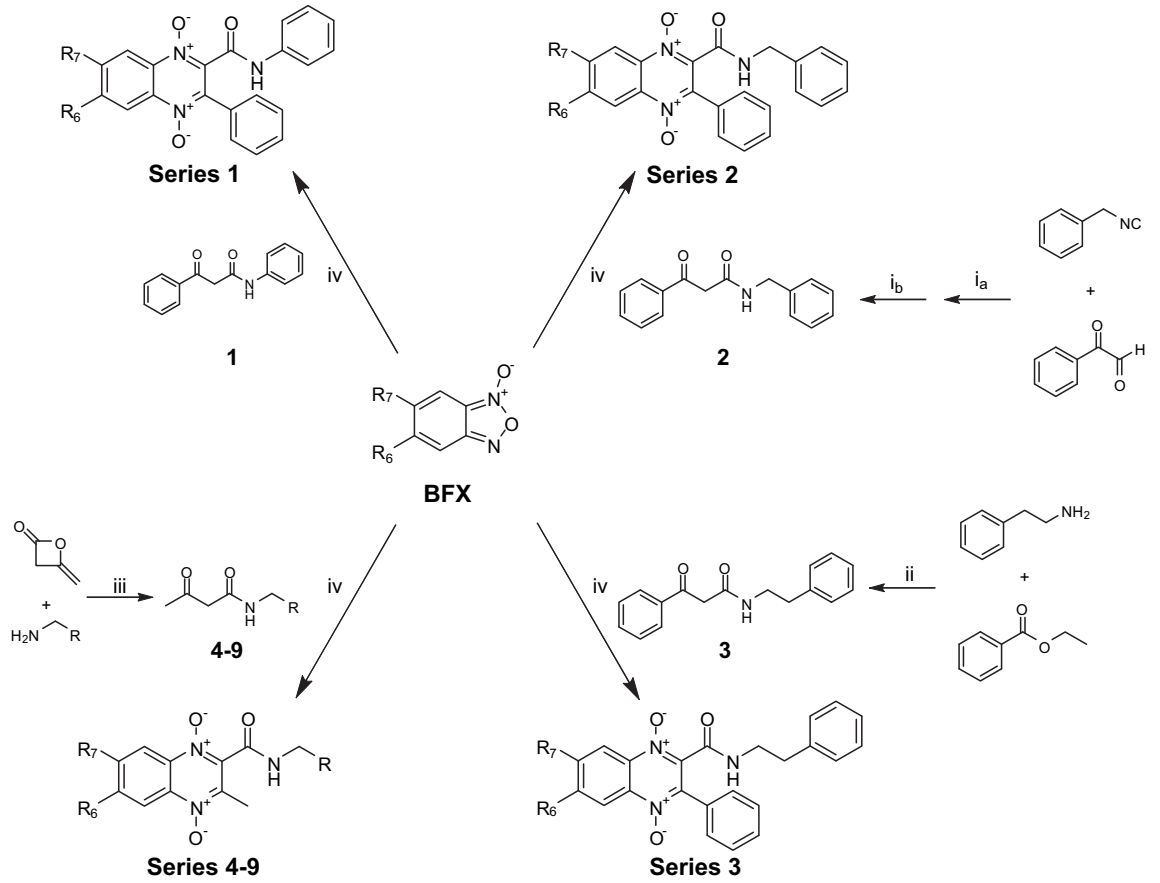
As can be observed in Table 1, thirteen of the forty-three evaluated compounds passed the cut off established by the TAACF at the primary screening level and moved on to the secondary screening level. Compounds **2b** and **4d** were identified as the most interesting with a SI higher than 10.

Some structure–activity relationships were established. Looking at the values of compounds **1b**, **1g**, **2b**, **4b**, **4c**, **4d**, **4g**, **6b**, **6g**, **7b** and **9b**, it can be said that the insertion of a halogen moiety, increases the anti-tubercular activity. Taking into account the biological values reported in Table 1, it can be concluded that the insertion of a electron-withdrawing moiety, especially that of chlorine atom, is an essential requirement for the anti-tubercular activity, as previously established by our group [21,22].

With the aim of corroborating previous preliminary structure–activity relationship observed by our group and identifying the most suitable length for the aliphatic chain between the carboxamide group and the aromatic ring, three series of compounds (Series **1, 2** and **3**) were prepared. Comparing the biological values shown by these compounds, it can be said that the preferred length for the aliphatic chain is one methylene group. This data corroborates the hypothesis established in a previous report on analogue structures published by our group [22].

In previous investigations carried out by our group, three series of 1,4-di-*N*-oxide-quinoxaline-2-carboxylic acid aryl amide derivatives were synthesized, containing a methyl moiety in position 3 [21,22]. To further explore the SAR of these types of compounds, a phenyl group was substituted in position 3 of the quinoxaline ring (Series **1**, **2** and **3**) and reported in this paper. This modification led to a reduction of the anti-tubercular activity as can be observed by comparing the biological values of compounds from Series **1**, **2** and **3** with their analogues containing a methyl group in position 3, described in previous reports [21,22].

Taking into account the biological values of the structures which present a phenyl group substituted in position 3 and the compounds with a methyl group in this position, [22] we decided to keep the methyl moiety in position 3 and modify the substitution on the aromatic ring. Different substituents were introduced on *para* position of the phenyl ring considering chloro, bromo or trifluoromethyl moiety as electron-withdrawing groups and methyl as electron-releasing group (Series **4**, **5**, **6**, **7**). In this fragment of the structure other substituents as byphenyl or a benzodioxol have been considered (Series **8**, **9**). Taking into account the biological values showed by these derivatives, it can be said that the insertion



Scheme 1. General scheme of synthesis. Reagents and conditions: i_a) acetic acid, diethyl ether, rt.; i_b) methanol, Zn/NH_4Cl aq.; ii) 2-hydroxypyridine, reflux; iii) methanol, 0 °C, N_2 atmosphere; iv) methanol, $CaCl_2$, ethanolamine.

of a substituent on *para* position of the phenyl group did not improve the anti-tubercular activity suggesting that the most suitable aromatic ring is the unsubstituted phenyl.

5. Conclusions

Forty-three new 1,4-di-*N*-oxide-quinoxaline-2-carboxylic acid aryl amide derivatives were synthesized using a variation of the Beirut reaction. All of the compounds were evaluated against *M.Tbc*. $H_{37}Rv$ stain; thirteen were active in the primary screening, showing an $IC_{90} \leq 10$ μg/mL, and were then moved on to the secondary screening level. Two of the compounds were active at this level, showing a $SI \geq 10$.

Taking into account the biological values obtained, it can be said that the lead general structure for developing new anti-tubercular agents should consider the 1,4-di-*N*-oxide-quinoxaline ring with a carboxamide functionalized on position 2 and a methyl moiety on position 3. The most suitable substituent on positions 6 or/and 7 should be an electron-withdrawing group and a methyl moiety on position 3. With regard to the linker and the aromatic ring attached to it, one methylene group and an unsubstituted phenyl ring are considered to be the most appropriate substituents.

6. Experimental protocols

6.1. Chemistry

6.1.1. General remarks

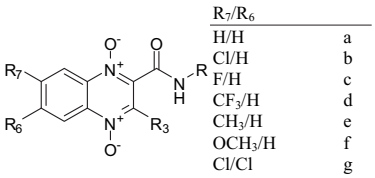
All of the synthesized compounds were chemically characterized by thin layer chromatography (TLC), infrared (IR), proton nuclear magnetic resonance (^1H NMR) and elemental microanalyses (CHN).

Alugram SIL G/UV254 (Layer: 0.2 mm) (Macherey-Nagel GmbH & Co. KG., Düren, Germany) was used for TLC, and Silica gel 60 (0.040–0.063 mm, Merck) was used for Conventional Flash Column Chromatography. Flash Column Chromatography was developed on a CombiFlash® R_f (TELEDYNE ISCO, Lincoln, USA) instrument with Silica RediSep® R_f columns. The ^1H NMR spectra were recorded on a Bruker 400 Ultrashield instrument (400 MHz), using TMS as internal standard and with DMSO-d_6 as solvent; the chemical shifts are reported in ppm (δ) and coupling constant (J) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), ddd (double double doublet), t (triplet), tt (triple triplet) and m (multiplet). The IR spectra were recorded on a Nicolet Nexus FTIR (Thermo, Madison, USA) in KBr pellets. Elemental microanalyses were obtained on a CHN-900 Elemental Analyzer (Leco, Tres Cantos, Spain) from vacuum-dried samples. The analytical results for C, H and N, were within ±0.4 of the theoretical values. Chemicals were purchased from Panreac Química S.A. (Barcelona, Spain), Sigma–Aldrich Química, S.A. (Alcobendas, Spain), Acros Organics (Janssen Pharmaceuticalaan, Geel, Belgium) and Lancaster (Bischheim-Strasbourg, France).

6.1.2. General procedure of the synthesis of 3-oxo-N-benzyl-3-phenylpropanamide (**2**)

Acetic acid (5.0 mmol) and phenylglyoxal were diluted in diethyl ether (25 mL) under N_2 atmosphere. Once dissolved, the benzylisocyanide (5.0 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 72 h. The residue

Table 1
Anti-tubercular activity of compounds (Series **1**–**9**).



R_7/R_6	
H/H	a
Cl/H	b
F/H	c
CF_3/H	d
CH_3/H	e
OCH_3/H	f
Cl/Cl	g

Comp.	R_3	R	Anti-tubercular activity IC_{90}[a] $H_{37}Rv$	Cytotoxicity CC_{50}[b] VERO	SI[c] CC_{50}/MIC
1a	C_6H_5	C_6H_5	26.99	N.T.[d]	N.T.
1b			6.71	8.97	1.34
1c			17.93	N.T.	N.T.
1d			19.10	N.T.	N.T.
1e			24.65	N.T.	N.T.
1f			26.84	N.T.	N.T.
1g			6.63	5.541	0.84
2a	C_6H_5	$CH_2-C_6H_5$	6.71	>40	>5.96
2b			3.39	>40	>11.79
2c			3.86	17.86	4.62
2d			>100	N.T.	N.T.
2e			13.91	N.T.	N.T.
2f			14.58	N.T.	N.T.
2g			25.45	N.T.	N.T.
3a	C_6H_5	$CH_2-CH_2-C_6H_5$	18.61	N.T.	N.T.
3b			15.42	N.T.	N.T.
4a	CH_3	$CH_2-C_6H_5-4-CF_3$	16.81	N.T.	N.T.
4b			6.13	>40	>6.52
4c			4.48	>40	>8.94
4d			3.38	>40	>11.82
4e			>100	N.T.	N.T.
4f			>100	N.T.	N.T.
4g			6.58	>40	>6.08
5a	CH_3	$CH_2-C_6H_5-4-Cl$	11.04	N.T.	N.T.
5b			29.68	N.T.	N.T.
5e			14.56	N.T.	N.T.
5g			51.86	N.T.	N.T.
6a	CH_3	$CH_2-C_6H_5-4-Br$	15.61	N.T.	N.T.
6b			5.33	>40	>7.50
6e			78.22	N.T.	N.T.
6g			6.92	>40	>5.78
7a	CH_3	$CH_2-C_6H_5-4-CH_3$	6.76	>40	>5.92
7b			32.04	N.T.	N.T.
7e			99.91	N.T.	N.T.
7g			>100	N.T.	N.T.
8a	CH_3	$CH_2-CH-(C_6H_5)_2$	15.99	N.T.	N.T.
8b			60.43	N.T.	N.T.
8e			16.79	N.T.	N.T.
8g			66.54	N.T.	N.T.
9a	CH_3	CH_2-benzo[*d*][1,3]dioxol	22.75	N.T.	N.T.
9b			6.99	>40	>5.72
9e			13.22	N.T.	N.T.
9g			34.92	N.T.	N.T.
RIF[e]			0.015–0.125	>100	>800

[a] IC_{90} against *M.tb* $H_{37}Rv$.
[b] Cytotoxicity in VERO cells.
[c] Selectivity index.
[d] Not tested.
[e] Rifampin.

obtained was filtered and washed with isopropanol. The solid was dissolved in methanol (32.0 mL) and added dropwise to a solution of Zn dust (8.0 mmol) in saturated aqueous NH_4Cl (8.0 mL) previously activated in a sonication bath for 5 min. The mixture was stirred at room temperature for 30 min and filtered in order to eliminate the Zn. Water (100 mL) was added to the mixture and the solid obtained was filtered and washed with water. The solid was used without further purification [26].

*6.1.2.1. 3-oxo-N-benzyl-3-phenylpropanamide (**2**).* Yield: 25%. IR (KBr): 3290 (m, ν_{N-H}); 3060 (w, ν_{arC-H}); 1687 (s, $\nu_{C=O\ ketone}$); 1635 (s, $\nu_{C=O\ amide}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.66 (bs, 1H, N**H**); 7.99 (d, 2H, **H$_2$** + **H$_6$**-phCO, $J_{2-3'} = 7.2$ Hz); 7.66–7.52 (m, 3H, **H$_3$**–**H$_5$**-phCO); 7.37–7.25 (m, 5H, **H$_2$**–**H$_6$**-phCH2); 4.32 (d, 2H, C**H$_2$**–NH, $J_{CH2-NH} = 5.9$ Hz); 3.92 (s, 2H, CO–C**H$_2$**–CO).

*6.1.3. General procedure of the synthesis of 3-oxo-N-(2-phenylethyl)-3-phenyl propanamide (**3**)*

Ethyl benzoylacetate (6.0 mmol), 2-phenethylamine (15.0 mmol) and 2-hydroxypyridine (6.0 mmol) were refluxed at 130 °C under N_2 atmosphere for 48 h. The mixture reaction was dissolved in dichloromethane and quenched with water. The organic phase was dried with anhydrous sodium sulphate and filtered. The solvent was removed in vacuo and precipitated with cold isopropanol in order to obtain a white solid. The solid was used without further purification. [27]

*6.1.3.1. 3-oxo-N-(2-phenylethyl)-3-phenylpropanamide (**3**).* Yield: 62%. IR (KBr): 3336 (s, ν_{N-H}); 3032 (w, ν_{arC-H}); 1614 (s, $\nu_{C=O}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.01 (bs, 1H, N**H**); 7.43–7.35 (m, 2H, **H$_2$** + **H$_6$**-phCO); 7.30–7.25 (m, 2H, **H$_3$** + **H$_5$**-phCO); 7.24–7.14 (m, 5H, **H$_4$**-phCO + **H$_{2+3+5+6}$**-phCH2); 7.05–7.03 (m, 1H, **H$_4$**-phCH2); 3.82 (s, 2H, CO–C**H$_2$**–CO); 3.30–3.21 (m, 2H, C**H$_2$**–NH); 3.08–2.67 (m, 2H, C**H$_2$**-ph).

*6.1.4. General procedure of the synthesis of 3-oxobutanamide derivatives (**4**–**9**)*

The corresponding aryl amines (20.0 mmol) were diluted in methanol (10 mL) under N_2 atmosphere and cooled in an ice bath until 0 °C. Next, diketene (25.0 mmol) was added dropwise and the reaction was stirred for 1–3 h. The residue obtained was precipitated with cold diethyl ether and filtered in order to obtain a red–brown solid. The compound was used without further purification [28].

*6.1.4.1. 3-oxo-N-(p-(trifluoromethyl)benzyl)butanamide (**4**).* Yield: 84%. IR (KBr): 3259 (m, ν_{N-H}); 3090 (w, ν_{arC-H}); 1716 (s, $\nu_{C=O\ ketone}$); 1644 (s, $\nu_{C=O\ amide}$); 1106 (m, $\nu_{arC-CF3}$); 1111 (s, $\nu_{arC-CF3}$); 1069 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.64 (t, 1H, N**H**, $J_{NH-CH2} = 5.5$ Hz); 7.70 (d, 2H, **H$_{3'}$** + **H$_{5'}$**, $J_{3'-2'} = 7.9$ Hz); 7.50 (d, 2H, **H$_{2'}$** + **H$_{6'}$**); 4.38 (d, 2H, C**H$_2$**–NH); 3.41 (s, 2H, CO–C**H$_2$**–CO); 2.16 (s, 3H, C**H$_3$**–CO).

*6.1.4.2. 3-oxo-N-(p-chlorobenzyl)butanamide (**5**).* Yield: 59%. IR (KBr): 3253 (s, ν_{N-H}); 3085 (m, ν_{arC-H}); 1714 (s, $\nu_{C=O\ ketone}$); 1642 (s, $\nu_{C=O\ amide}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.55 (bs, 1H, N**H**); 7.39 (dd, 2H, **H$_{3'}$** + **H$_{5'}$**, $J_{3'-2'} = 8.5$ Hz, $J_{3'-Cl} = 1.9$ Hz); 7.30 (d, 2H, **H$_{2'}$** + **H$_{6'}$**); 4.28 (d, 2H, C**H$_2$**–NH, $J_{CH2-NH} = 5.9$ Hz); 3.38 (s, 2H, CO–C**H$_2$**–CO); 2.15 (s, 3H, C**H$_3$**–CO).

*6.1.4.3. 3-oxo-N-(p-bromobenzyl)butanamide (**6**).* Yield: 57%. IR (KBr): 3253 (s, ν_{N-H}); 3085 (m, ν_{arC-H}); 1714 (s, $\nu_{C=O\ ketone}$); 1642 (s, $\nu_{C=O\ amide}$); 1015 (m, ν_{arC-Br}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.55 (bs, 1H, N**H**); 7.52 (d, 2H, **H$_{3'}$** + **H$_{5'}$**, $J_{3'-2'} = 8.2$ Hz); 7.24 (d, 2H, **H$_{2'}$** + **H$_{6'}$**); 4.26 (d, 2H, C**H$_2$**–NH, $J_{CH2-NH} = 5.5$ Hz); 3.38 (s, 2H, CO–C**H$_2$**–CO); 2.15 (s, 3H, C**H$_3$**–CO).

*6.1.4.4. 3-oxo-N-(p-methylbenzyl)butanamide (**7**).* Yield: 40%. IR (KBr): 3254 (m, ν_{N-H}); 3088 (m, ν_{arC-H}); 1715 (m, $\nu_{C=O\ ketone}$); 1641 (s, $\nu_{C=O\ amide}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.47 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 7.20–7.10 (m, 4H, **H$_{2'}$** + **H$_{3'}$** + **H$_{5'}$** + **H$_{6'}$**); 4.24 (d, 2H, C**H$_2$**–NH); 3.36 (s, 2H, CO–C**H$_2$**–CO); 2.28 (s, 3H, C**H$_3$**-ph); 2.15 (s, 3H, C**H$_3$**-CO).

*6.1.4.5. N-(2,2-diphenylethyl)-3-oxobutanamide (**8**).* Yield: 32%. IR (KBr): 3276 (s, ν_{N-H}); 3020 (w, ν_{arC-H}); 1710 (m, $\nu_{C=O\ ketone}$); 1668 (s, $\nu_{C=O\ amide}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.14 (t, 1H, N**H**, $J_{NH-CH2} = 5.6$ Hz); 7.34–7.24 (m, 10H, 2**ph**); 4.19 (t, 1H, C**H**, $J_{CH-CH2} = 7.9$ Hz); 3.73 (dd, 2H, C**H$_2$**–NH); 3.19 (s, 2H, CO–C**H$_2$**–CO); 1.96 (s, 3H, C**H$_3$**–CO).

*6.1.4.6. N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-oxobutanamide (**9**).* Yield: 33%. IR (KBr): 3290 (m, ν_{N-H}); 3064 (w, ν_{arC-H}); 1758 (m, $\nu_{C=O\ ketone}$); 1615 (s, $\nu_{C=O\ amide}$); 1241 (m, $\nu_{C=O}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.50 (t, 1H, N**H**, $J_{NH-CH2} = 5.6$ Hz); 7.02 (bs, 1H, **H$_{2'}$**); 6.91 (bs, 2H, **H$_{5'}$** + **H$_{6'}$**); 6.01 (s, 2H, O–C**H$_2$**–O); 4.27 (d, 2H, C**H$_2$**–NH); 3.37 (s, 2H, CO–C**H$_2$**–CO); 2.15 (s, 3H, C**H$_3$**–CO).

*6.1.5. General procedure of the synthesis of 1,4-di-N-oxide-quinoxaline-2-carboxylic acid aryl amide derivatives (Series **1**–**9**)*

The appropriate BFX (1.0 mmol) and the corresponding β-ketoamide (1.2 mmol) were dissolved in a minimum amount of methanol. Next, calcium chloride (0.1 mmol) and ethanolamine (5 drops) were added as catalysts [22,23]. The mixture reaction was stirred at room temperature from 1 to 48 h, depending on the BFX substituents used; it was then filtered and washed with cold diethyl ether. The solid was dissolved in dichloromethane and quenched with water. The organic phase was dried with anhydrous sodium sulphate and filtered. The solvent was removed in vacuo and precipitated with cold diethyl ether in order to obtain a yellow solid. The solid was purified by column chromatography, if necessary.

*6.1.5.1. 3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1a**).* Yield: 17%. IR (KBr): 3256 (w, ν_{NH}); 3077 (w, ν_{arC-H}); 1693 (s, $\nu_{C=O}$); 1348 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 10.80 (s, 1H, N**H**); 8.60–8.56 (m, 2H, **H$_5$** + **H$_8$**); 8.10–8.07 (m, 2H, **H$_6$** + **H$_7$**); 7.62–7.60 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{QX}$); 7.49–7.47 (m; 3H, **H$_3$**–**H$_5$**–ph-$_{QX}$); 7.39 (dd, 2H, **H$_2$** + **H$_6$**–ph-$_{NH}$, $J_{2-3} = 8.5$ Hz, $J_{2-4} = 1.0$ Hz); 7.33–7.28 (m, 2H, **H$_3$** + **H$_5$**–ph-$_{NH}$); 7.10 (tt, 1H, **H$_4$**–ph-$_{NH}$, $J_{4-3} = 7.2$ Hz). Anal. Calcd. for $C_{21}H_{15}N_3O_3$: C, 70.58%; H, 4.23%; N, 11.76%. Found: C, 70.72%; H, 4.48%; N, 11.99%.

*6.1.5.2. 7-chloro-3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1b**).* Yield: 18%. IR (KBr): 3256 (w, ν_{NH}); 3058 (w, ν_{arC-H}); 1686 (s, $\nu_{C=O}$); 1330 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 10.82 (s, 1H, N**H**); 8.57–8.56 (m; 2H, **H$_5$** + **H$_8$**); 8.11 (dd, 1H, **H$_6$**, $J_{6-5} = 9.0$ Hz, $J_{6-8} = 1.7$ Hz); 7.61–7.59 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{QX}$); 7.49–7.48 (m, 3H, **H$_3$**–**H$_5$**–ph-$_{QX}$); 7.38 (d, 2H, **H$_2$** + **H$_6$**–ph-$_{NH}$, $J_{2-3} = 7.9$ Hz); 7.31 (t, 2H, **H$_3$** + **H$_5$**–ph-$_{NH}$, $J_{3-4} = 7.9$ Hz); 7.11 (t, 1H, **H$_4$**–ph-$_{NH}$). Anal. Calcd. for $C_{21}H_{14}ClN_3O_3$: C, 64.38%; H, 3.60%; N, 10.72%. Found: C, 64.30%; H, 3.96%; N, 10.48%.

*6.1.5.3. 7-fluoro-3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1c**).* Yield: 17%. IR (KBr): 3244 (m, ν_{NH}); 3058 (w, ν_{arC-H}); 1658 (s, $\nu_{C=O}$); 1339 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 10.83 (s, 1H, N**H**); 8.66–8.62 (m, 1H, **H$_5$**); 8.34–8.32 (m, 1H, **H$_8$**); 8.02–7.98 (m, 1H, **H$_6$**); 7.60–7.59 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{QX}$); 7.49–7.47 (m, 3H, **H$_3$**-**H$_5$**–ph-$_{QX}$); 7.39–7.37 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{NH}$); 7.32–7.28 (m, 2H, **H$_3$** + **H$_5$**–ph-$_{NH}$); 7.12–7.09 (m, 1H, **H$_4$**–ph-$_{NH}$). Anal. Calcd. for $C_{21}H_{14}FN_3O_3$: C, 67.20%; H, 3.76%; N, 11.20%. Found: C, 66.85%; H, 3.95%; N, 11.00%.

*6.1.5.4. 7-trifluoromethyl-3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1d**).* Yield: 18%. IR (KBr): 3250 (w, ν_{NH}); 3058 (w, ν_{arC-H}); 1686 (s, $\nu_{C=O}$); 1345 (s, ν_{N+O-}); 1140 (s, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 10.82 (s, 1H, N**H**); 8.83 (s, 1H, **H$_8$**); 8.77 (d, 1H, **H$_5$**, $J_{5-6} = 9.0$ Hz); 8.39 (dd, 1H, **H$_6$**, $J_{6-8} = 1.6$ Hz); 7.64–7.62 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{QX}$); 7.51–7.49 (m, 3H, **H$_3$**–**H$_5$**–ph-$_{QX}$); 7.39–7.37 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{NH}$); 7.33–7.29 (m, 2H, **H$_3$** + **H$_5$**–ph-$_{NH}$); 7.13–7.10 (m, 1H, **H$_4$**–ph-$_{NH}$). Anal. Calcd. for

$C_{22}H_{14}F_3N_3O_3$: C, 62.12%; H, 3.32%; N, 9.88%. Found: C, 61.83%; H, 3.37%; N, 9.58%.

*6.1.5.5. 7-methyl-3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1e**).* Yield: 9%. IR (KBr): 3256 (w, ν_{NH}); 3064 (w, ν_{arC-H}); 1686 (s, $\nu_{C=O}$); 1335 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.80 (s, 1H, N**H**); 8.47 (d, 1H, **H$_5$**, $J_{5-6} = 8.8$ Hz); 8.41–8.35 (m, 1H, **H$_8$**); 7.91 (dd, 1H, **H$_6$**, $J_{6-8} = 1.2$ Hz); 7.63–7.58 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{QX}$); 7.51–7.44 (m, 3H, **H$_3$**–**H$_5$**–ph-$_{QX}$); 7.41–7.36 (m, 2H, **H$_2$** + **H$_6$**–ph-$_{NH}$); 7.33–7.27 (m, 2H, **H$_3$** + **H$_5$**–ph-$_{NH}$); 7.13–7.07 (m, 1H, **H$_4$**-ph-$_{NH}$); 2.65 (s, 3H, C**H$_3$**). Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15%; H, 4.61%; N, 11.31%. Found: C, 71.05%; H, 4.80%; N, 11.01%.

*6.1.5.6. 7-methoxy-3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1f**).* Yield: 77%. IR (KBr): 3250 (m, ν_{NH}); 3077 (m, ν_{arC-H}); 1685 (s, $\nu_{C=O}$); 1335 (s, ν_{N+O-}); 1243 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.81 (s, 1H, N**H**); 8.48 (d, 1H, **H$_5$**, $J_{5-6} = 9.5$ Hz); 7.87 (d, 1H, **H$_8$**, $J_{8-6} = 2.7$ Hz); 7.68 (dd, 1H, **H$_6$**); 7.61–7.58 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{QX}$); 7.48–7.46 (m, 3H, **H$_3$**–**H$_5$**-ph-$_{QX}$); 7.38 (dd, 2H, **H$_2$** + **H$_6$**-ph-$_{NH}$, $J_{2-3} = 8.5$ Hz, $J_{2-4} = 1.1$ Hz); 7.32–7.28 (m, 2H, **H$_3$** + **H$_5$**-ph-$_{NH}$); 7.10 (tt, 1H, **H$_4$**-ph-$_{NH}$, $J_{4-3} = 7.3$ Hz); 4.04 (s, 3H, OC**H$_3$**). Anal. Calcd. for $C_{22}H_{17}N_3O_4$: C, 68.21%; H, 4.42%; N, 10.85%. Found: C, 67.89%; H, 4.42%; N, 10.89%.

*6.1.5.7. 6,7-dichloro-3-phenylquinoxaline-2-carboxylic acid phenylamide 1,4-di-N-oxide (**1g**).* Yield: 46%. IR (KBr): 3308 (m,ν_{NH}); 3071 (m,ν_{arC-H}); 1666 (s, $\nu_{C=O}$); 1332 (s, ν_{N+O-}); 1313 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.88 (s, 1H, N**H**); 8.76 (s, 1H, **H$_5$**); 8.74 (s, 1H, **H$_8$**); 7.61–7.59 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{QX}$); 7.51–7.48 (m, 3H, **H$_3$**–**H$_5$**-ph-$_{QX}$); 7.38 (dd, 2H, **H$_2$** + **H$_6$**-ph-$_{NH}$, $J_{2-3} = 8.5$ Hz, $J_{2-4} = 1.0$ Hz); 7.33–7.29 (m, 2H, **H$_3$** + **H$_5$**-ph-$_{NH}$); 7.11 (tt, 1H, **H$_4$**-ph-$_{NH}$, $J_{4-3} = 7.8$ Hz). Anal. Calcd. for $C_{21}H_{13}Cl_2N_3O_3.1/2H_2O$: C, 57.89%; H, 3.22%; N, 9.65%. Found: C, 57.56%; H, 2.91%; N, 9.54%.

*6.1.5.8. 3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2a**).* Yield: 15%. IR (KBr): 3302 (m,ν_{NH}); 3085 (w, ν_{arC-H}); 1673 (s, $\nu_{C=O}$); 1348 (s, ν_{N+O-}); 1339 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.12 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 8.58–8.53 (m, 2H, **H$_5$** + **H$_8$**); 8.06–8.04 (m, 2H, **H$_6$** + **H$_7$**); 7.57–7.56 (m, 3H, **H$_3$**–**H$_5$**-ph-$_{QX}$); 7.51–7.49 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{QX}$); 7.22–7.21 (m, 3H, **H$_3$**–**H$_5$**-ph–$_{CH2}$); 6.90–6.87 (m, 2H, **H$_2$** + **H$_6$**-ph–$_{CH2}$); 4.28 (d, 2H, C**H$_2$**). Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15%; H, 4.61%; N, 11.31%. Found: C, 71.02%; H, 4.50%; N, 10.94%.

*6.1.5.9. 7-chloro-3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2b**).* Yield: 22%. IR (KBr): 3286 (m, ν_{NH}); 3094 (w, ν_{arC-H}); 1649 (s, $\nu_{C=O}$); 1331 (m, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.12 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.56–8.54 (m, 1H, **H$_5$**), 8.50 (bs; 1H, **H$_8$**); 8.08 (dd, 1H, **H$_6$**, $J_{6-5} = 9.2$ Hz, $J_{6-8} = 2.2$ Hz); 7.58–7.49 (m, 5H, **H$_2$**–**H$_6$**-ph-$_{QX}$); 7.21–7.20 (m, 3H, **H$_3$**–**H$_5$**-ph–$_{CH2}$); 6.89–6.87 (m, 2H, **H$_2$** + **H$_6$**-ph–$_{CH2}$); 4.28 (d, 2H, C**H$_2$**). Anal. Calcd. for $C_{22}H_{16}ClN_3O_3$: C, 65.10%; H, 3.97%; N, 10.35%. Found: C, 65.41%; H, 3.97%; N, 10.16%.

*6.1.5.10. 7-fluoro-3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2c**).* Yield: 22%. IR (KBr): 3312 (m, ν_{NH}); 3059 (w, ν_{arC-H}); 1673 (s, $\nu_{C=O}$); 1335 (m, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.14 (t, 1H, N**H**, $J_{NH-CH2} = 5.7$ Hz); 8.62–8.59 (m, 1H, **H$_5$**); 8.33–8.30 (m, 1H, **H$_8$**); 7.99–7.94 (m, 1H, **H$_6$**); 7.94–7.49 (m, 5H, **H$_2$**–**H$_6$**-ph-$_{QX}$); 7.21–7.20 (m, 3H, **H$_3$**–**H$_5$**-ph–$_{CH2}$); 6.90–6.88 (m, 2H, **H$_2$** + **H$_6$**-ph–$_{CH2}$); 4.28 (d, 2H, C**H$_2$**). Anal. Calcd. for $C_{22}H_{16}FN_3O_3.1/2H_2O$: C, 66.26%; H, 4.27%; N, 10.54%. Found: C, 66.56%; H, 4.04%; N, 10.17%.

*6.1.5.11. 7-trifluoromethyl-3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2d**).* Yield: 6%. IR (KBr): 3287 (m, ν_{NH}); 3093 (w, ν_{arC-H}); 1647 (s, $\nu_{C=O}$); 1350 (s, ν_{N+O-}); 1319 (s,ν_{N+O-}); 1171 (s, ν_{ar-CF3}); 1125 (s, ν_{ar-CF3}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.15–9.10 (m, 1H, N**H**); 8.81–8.77 (m, 1H, **H$_5$**); 8.44–8.28 (m, 2H, **H$_8$** + **H$_6$**); 7.59–7.51 (m, 5H, **H$_2$**–**H$_6$**-ph-$_{QX}$); 7.25–7.21 (m, 5H, **H$_2$**–**H$_6$**-ph–$_{CH2}$); 4.29 (d, 2H, C**H$_2$**, $J_{CH2-NH} = 5.9$ Hz). Anal. Calcd. for $C_{23}H_{16}F_3N_3O_3$: C, 62.87%; H, 3.67%; N, 9.56%. Found: C, 63.03%; H, 3.96%; N, 9.36%.

*6.1.5.12. 7-methyl-3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2e**).* Yield: 36%. IR (KBr): 3224 (m, ν_{NH}); 3058 (w, ν_{arC-H}); 1682 (s, $\nu_{C=O}$); 1355 (s,ν_{N+O-}); 1314 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.13 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.43 (d, 1H, **H$_5$**, $J_{5-6} = 8.8$ Hz); 8.37 (s, 1H, H_8); 7.87 (dd, 1H, **H$_6$**, $J_{6-8} = 1.8$ Hz); 7.59–7.55 (m, 3H, **H$_3$**-**H$_5$**-ph-$_{QX}$); 7.51–7.48 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{QX}$); 7.21–7.19 (m, 3H, **H$_3$**–**H$_5$**-ph–$_{CH2}$); 6.90–6.87 (m, 2H, **H$_2$** + **H$_6$**-ph–$_{CH2}$); 4.28 (d, 2H, C**H$_2$**). Anal. Calcd. for $C_{23}H_{19}N_3O_3.1/2H_2O$: C, 69.97%; H, 5.07%; N, 10.65%. Found: C, 70.35%; H, 5.03%; N, 10.65%.

*6.1.5.13. 6-methoxy-3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2f**).* Yield: 35%. IR (KBr): 3262 (m, ν_{NH}); 3080 (w, ν_{arC-H}); 1689 (s, $\nu_{C=O}$); 1352 (s, ν_{N+O-}); 1328 (s,ν_{N+O-}); 1256 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.14 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.44 (d, 1H, **H$_5$**, $J_{5-6} = 9.5$ Hz); 7.86 (d, 1H, **H$_8$**, $J_{8-6} = 2.7$ Hz); 7.65 (dd, 1H, **H$_6$**); 7.58–7.54 (m, 3H, **H$_3$**–**H$_5$**-ph-$_{QX}$); 7.51–7.48 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{QX}$); 7.22–7.20 (m, 3H, **H$_3$**–**H$_5$**-ph-$_{CH2}$); 6.93–6.90 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{CH2}$); 4.27 (d, 2H, C**H$_2$**); 4.03 (s, 3H, OC**H$_3$**). Anal. Calcd. for $C_{23}H_{19}N_3O_4$: C, 68.82%; H, 4.77%; N, 10.47%. Found: C, 68.94%; H, 4.87%; N, 10.26%.

*6.1.5.14. 6,7-dichloro-3-phenylquinoxaline-2-carboxylic acid benzylamide 1,4-di-N-oxide (**2g**).* Yield: 8%. IR (KBr): 3280 (m, ν_{NH}); 3062 (w, ν_{arC-H}); 1649 (s, $\nu_{C=O}$); 1327 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.15 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.75 (s, 1H, **H$_5$**); 8.70 (s, 1H, **H$_8$**); 7.50–7.48 (m, 5H, **H$_2$**–**H$_6$**-ph-$_{QX}$); 7.22–7.20 (m, 3H, **H$_3$**–**H$_5$**-ph-$_{CH2}$); 6.90–6.88 (m, 2H, **H$_2$** + **H$_6$**-ph-$_{CH2}$); 4.27 (d, 2H, C**H$_2$**). Anal. Calcd. for $C_{22}H_{15}Cl_2N_3O_3$: C, 60.02%; H, 3.43%; N, 9.54%. Found: C, 60.07%; H, 3.56%; N, 9.46%.

*6.1.5.15. 3-phenylquinoxaline-2-carboxylic acid (2-phenylethyl)amide 1,4-di-N-oxide (**3a**).* Yield: 10%. IR (KBr): 3269 (w, ν_{NH}); 3078 (w, ν_{arC-H}); 1679 (s, $\nu_{C=O}$); 1328 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.75 (t, 1H, N**H**, $J_{NH-CH2} = 5.7$ Hz); 8.55–8.52 (m, 2H, **H$_5$** + **H$_8$**); 8.05–8.03 (m, 2H, **H$_6$** + **H$_7$**); 7.57–7.51 (m, 5H, **H$_2$**–**H$_6$**-ph-$_{QX}$); 7.27 (t, 2H, **H$_3$** + **H$_5$**-ph-$_{CH2}$, $J_{3-2} = J_{3-4} = 7.3$ Hz); 7.20 (t, 1H, **H$_4$**-ph-$_{CH2}$); 7.09 (d, 2H, **H$_2$** + **H$_6$**-ph-$_{CH2}$); 3.27–3.21 (m, 2H, C**H$_2$**–NH); 2.39 (t, 2H, C**H$_2$**–ph, $J_{CH2-CH2} = 7.3$ Hz). Anal. Calcd. for $C_{23}H_{19}N_3O_3$: C, 71.68%; H, 4.97%; N, 10.90%. Found: C, 71.72%; H, 5.22%; N, 10.88%.

*6.1.5.16. 7-chloro-3-phenylquinoxaline-2-carboxylic acid (2-phenylethyl)amide 1,4-di-N-oxide (**3b**).* Yield: 8%. IR (KBr): 3304 (w, ν_{NH}); 3056 (wd, ν_{arC-H}); 1668 (s, $\nu_{C=O}$); 1330 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.75 (t, 1H, N**H**, $J_{NH-CH2} = 5.6$ Hz); 8.54–8.52 (m, 2H, **H$_5$** + **H$_8$**); 8.07 (dd, **H$_6$**, $J_{6-5} = 9.3$ Hz, $J_{6-8} = 2.2$ Hz); 7.56–7.51 (m, 5H, **H$_2$**–**H$_6$**-ph-$_{QX}$); 7.27 (t, 2H, **H$_3$** + **H$_5$**-ph-$_{CH2}$, $J_{3-2} = J_{3-4} = 7.3$ Hz); 7.19 (t, 1H, **H$_4$**-ph-$_{CH2}$); 7.09 (d, 2H, **H$_2$** + **H$_6$**-ph-$_{CH2}$); 3.27–3.21 (m, 2H, C**H$_2$**–NH); 2.39 (t, 2H, C**H$_2$**–ph, $J_{CH2-CH2} = 7.4$ Hz). Anal. Calcd. for $C_{23}H_{18}ClN_3O_3$: C, 65.80%; H, 4.32%; N, 10.01%. Found: C, 65.95%; H, 4.46%; N, 10.09%.

*6.1.5.17. 3-methylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4a**).* Yield: 21%. IR (KBr): 3205 (w, ν_{N-H}); 3039 (w, ν_{arC-H}); 1669 (s, $\nu_{C=O}$); 1325 (s, ν_{N+O-}); 1166 (m,

$\nu_{arC-CF3}$); 1101 (m, $\nu_{arC-CF3}$); 1068 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.49 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.53–8.49 (m, 2H, $\mathbf{H_5} + \mathbf{H_8}$); 8.03–7.96 (m, 2H, $\mathbf{H_6} + \mathbf{H_7}$); 7.77 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.2$ Hz); 7.70 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.67 (d, 2H, C**H$_2$**); 2.44 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{18}H_{14}F_3N_3O_3$: C, 57.30%; H, 3.74%; N, 11.14%. Found: C, 57.02%; H, 3.79%; N, 11.00%.

*6.1.5.18. 7-chloro-3-methylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4b**).* Yield: 37%. IR (KBr): 3277 (w, ν_{N-H}); 3103 (w, ν_{arC-H}); 1650 (m, $\nu_{C=O}$); 1328 (s, ν_{N+O-}); 1161 (m, $\nu_{arC-CF3}$); 1109 (m, $\nu_{arC-CF3}$); 1072 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.49 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.50 (s, 2H, $\mathbf{H_5} + \mathbf{H_8}$); 8.04 (dd, 1H, **H$_6$**, $J_{6-5} = 9.1$ Hz, $J_{6-8} = 2.3$ Hz); 7.77 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.1$ Hz); 7.69 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.66 (d, 2H, C**H$_2$**); 2.43 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{18}H_{13}ClF_3N_3O_3$: C, 52.51%; H, 3.18%; N, 10.20%. Found: C, 52.26%; H, 3.19%; N, 9.95%.

*6.1.5.19. 7-fluoro-3-methylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4c**).* Yield: 51%. IR (KBr): 3212 (w, ν_{N-H}); 3079 (w, ν_{arC-H}); 1671 (m, $\nu_{C=O}$); 1327 (s, ν_{N+O-}); 1167 (m, $\nu_{arC-CF3}$); 1101 (m, $\nu_{arC-CF3}$); 1065 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.50 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 8.58 (dd, 1H, **H$_5$**, $J_{5-6} = 9.5$ Hz, $J_{5-F} = 5.1$ Hz); 8.25 (dd, 1H, **H$_8$**, $J_{8-F} = 8.8$ Hz, $J_{8-6} = 2.4$ Hz); 7.93 (ddd, 1H, **H$_6$**, $J_{6-F} = 9.4$ Hz); 7.77 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.1$ Hz); 7.69 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.67 (d, 2H, C**H$_2$**); 2.43 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{18}H_{13}F_4N_3O_3$: C, 54.69%; H, 3.31%; N, 10.63%. Found: C, 54.64%; H, 3.30%; N, 10.36%.

*6.1.5.20. 3-methyl-7-trifluoromethylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4d**).* Yield: 12%. IR (KBr): 3212 (w, ν_{N-H}); 3064 (w, ν_{arC-H}); 1679 (s, $\nu_{C=O}$); 1326 (s, ν_{N+O-}); 1168 (m, $\nu_{arC-CF3}$); 1143 (m, $\nu_{arC-CF3}$); 1111 (m, $\nu_{arC-CF3}$); 1085 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.52 (t, 1H, N**H**, $J_{NH-CH2} = 5.5$ Hz); 8.76 (s, 1H, **H$_8$**); 8.70 (d, 1H, **H$_5$**, $J_{5-6} = 9.0$ Hz); 8.29 (dd, 1H, **H$_6$**, $J_{6-8} = 1.7$ Hz); 7.78 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.1$ Hz); 7.70 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.68 (d, 2H, C**H$_2$**); 2.47 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{19}H_{13}F_6N_3O_3$: C, 51.25%; H, 2.94%; N, 9.44%. Found: C, 51.26%; H, 2.74%; N, 9.34%.

*6.1.5.21. 3,7-dimethylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4e**).* Yield: 28%. IR (KBr): 3199 (w, ν_{N-H}); 3032 (w, ν_{arC-H}); 1669 (s, $\nu_{C=O}$); 1325 (s, ν_{N+O-}); 1165 (m, $\nu_{arC-CF3}$); 1100 (m, $\nu_{arC-CF3}$); 1167 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.49 (t, 1H, N**H**, $J_{NH-CH2} = 5.5$ Hz); 8.40 (d, 1H, **H$_5$**, $J_{5-6} = 8.8$ Hz); 8.31 (s, 1H, **H$_8$**); 7.84 (d, 1H, **H$_6$**); 7.76 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.2$ Hz); 7.70 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.66 (d, 2H, C**H$_2$**); 2,59 (s, 3H, C**H$_3$**–C$_7$); 2.42 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{19}H_{16}F_3N_3O_3$: C, 58.31%; H, 4.12%; N, 10.74%. Found: C, 58.05%; H, 4.09%; N, 10.48%.

*6.1.5.22. 7-methoxy-3-methylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4f**).* Yield: 29%. IR (KBr): 3212 (w, ν_{N-H}); 3040 (w, ν_{arC-H}); 1679 (m, $\nu_{C=O}$); 1325 (s, ν_{N+O-}); 1169 (m, $\nu_{arC-CF3}$); 1118 (m, $\nu_{arC-CF3}$); 1066 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.51 (t, 1H, N**H**, $J_{NH-CH2} = 5.6$ Hz); 8.42 (d, 1H, **H$_5$**, $J_{5-6} = 9.5$ Hz); 7.81 (d, 1H, **H$_8$**, $J_{8-6} = 2.60$ Hz); 7.77 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.1$ Hz); 7.71 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 7.61 (dd, 1H, **H$_6$**); 4.66 (d, 2H, C**H$_2$**); 4.00 (s, 3H, OC**H$_3$**); 2,41 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{19}H_{16}F_3N_3O_4$: C, 56.02%; H, 3.96%; N, 10.32%. Found: C, 55.90%; H, 3.84%; N, 10.14%.

*6.1.5.23. 6,7-dichloro-3-methylquinoxaline-2-carboxylic acid p-trifluoromethylbenzylamide 1,4-di-N-oxide (**4g**).* Yield: 12%. IR (KBr): 3237 (w, ν_{N-H}); 3071 (w, ν_{arC-H}); 1670 (m, $\nu_{C=O}$); 1323 (s, ν_{N+O-}); 1169 (m, $\nu_{arC-CF3}$); 1109 (m, $\nu_{arC-CF3}$); 1069 (m, $\nu_{arC-CF3}$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.51 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 8.69 (s, 1H, **H$_5$**); 8.68 (s, 1H, **H$_8$**); 7.76 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.4$ Hz); 7.68 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.66 (d, 2H, C**H$_2$**); 2.43 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{18}H_{12}Cl_2F_3N_3O_3$: C, 48.45%; H, 2.71%; N, 9.42%. Found: C, 48.75%; H, 2.82%; N, 9.44%.

*6.1.5.24. 3-methylquinoxaline-2-carboxylic acid p-chlorobenzylamide 1,4-di-N-oxide (**5a**).* Yield: 47%. IR (KBr): 3192 (w, ν_{N-H}); 3071 (w, ν_{arC-H}); 1675 (s, $\nu_{C=O}$); 1327 (s, ν_{N+O-}); 1082 (m, ν_{arC-Cl}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.40 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 8.53–8.49 (m, 2H, $\mathbf{H_5} + \mathbf{H_8}$); 8.01–7.97 (m, 2H, $\mathbf{H_6} + \mathbf{H_7}$); 7.49 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.5$ Hz); 7.45 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.56 (d, 2H, C**H$_2$**); 2.42 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$: C, 59.40%; H, 4.10%; N, 12.22%. Found: C, 59.14%; H, 4.10%; N, 12.58%.

*6.1.5.25. 7-chloro-3-methylquinoxaline-2-carboxylic acid p-chlorobenzylamide 1,4-di-N-oxide (**5b**).* Yield: 37%. IR (KBr): 3271 (w, ν_{N-H}); 3103 (w, ν_{arC-H}); 1650 (s, $\nu_{C=O}$); 1326 (s, ν_{N+O-}); 1073 (m, ν_{arC-Cl}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.40 (t, 1H, N**H**, $J_{NH-CH2} = 5.7$ Hz); 8.50 (d, 1H, **H$_5$**, $J_{5-6} = 9.3$ Hz); 8.49 (d, 1H, **H$_8$**, $J_{8-6} = 2.0$ Hz); 8.04 (dd, 1H, **H$_6$**); 7.48 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.6$ Hz); 7.45 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.55 (d, 2H, C**H$_2$**); 2.41 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{17}H_{13}Cl_2N_3O_3$: C, 53.99%; H, 3.46%; N, 11.11%. Found: C, 54.03%; H, 3.53%; N, 11.05%.

*6.1.5.26. 3,7-dimethylquinoxaline-2-carboxylic acid p-chlorobenzylamide 1,4-di-N-oxide (**5e**).* Yield: 21%. IR (KBr): 3250 (w, ν_{N-H}); 3064 (w, ν_{arC-H}); 1670 (s, $\nu_{C=O}$); 1322 (s, ν_{N+O-}); 1068 (m, ν_{arC-Cl}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.40 (t, 1H, N**H**, $J_{NH-CH2} = 5.5$ Hz); 8.40 (d, **H$_5$**, $J_{5-6} = 8.8$ Hz); 8.31 (s, 1H, **H$_8$**); 7.83 (dd, 1H, **H$_6$**, $J_{6-8} = 1.5$ Hz); 7.49 (dd, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.5$ Hz, $J_{3'-Cl} = 1.3$ Hz); 7.45 (dd, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$, $J_{2'-Cl} = 1.1$ Hz); 4.55 (d, 2H, C**H$_2$**); 2.59 (s, 3H, C**H$_3$**–C$_7$); 2.40 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{18}H_{16}ClN_3O_3$: C, 60.43%; H, 4.51%; N, 11.74%. Found: C, 60.08%; H, 4.46%; N, 11.51%.

*6.1.5.27. 6,7-dichloro-3-methylquinoxaline-2-carboxylic acid p-chlorobenzylamide 1,4-di-N-oxide (**5g**).* Yield: 11%. IR (KBr): 3243 (w, ν_{N-H}); 3071 (w, ν_{arC-H}); 1671 (s, $\nu_{C=O}$); 1321 (s, ν_{N+O-}); 1066 (m, ν_{arC-Cl}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.43 (t, 1H, N**H**, $J_{NH-CH2} = 5.9$ Hz); 8.69 (d, 1H, **H$_5$**, $J_{5-8} = 0.5$ Hz); 8.68 (d, 1H, **H$_8$**); 7.48 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.8$ Hz); 7.45 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.55 (d, C**H$_2$**); 2.41 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{17}H_{12}Cl_3N_3O_3$: C, 49.48%; H, 2.93%; N, 10.18%. Found: C, 49.76%; H, 2.98%; N, 10.12%.

*6.1.5.28. 3-methylquinoxaline-2-carboxylic acid p-bromobenzylamide 1,4-di-N-oxide (**6a**).* Yield: 7%. IR (KBr): 3271 (w, ν_{N-H}); 3090 (w, ν_{arC-H}); 1677 (s, $\nu_{C=O}$); 1331 (s, ν_{N+O-}); 1073 (m, ν_{arC-Br}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.40 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 8.52–8.49 (m, 2H, $\mathbf{H_5} + \mathbf{H_8}$); 8.03–7.96 (m, 2H, $\mathbf{H_6} + \mathbf{H_7}$); 7.59 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{H3'-H2'} = 8.3$ Hz); 7.43 (d, 2H, $\mathbf{H_{2'}} + \mathbf{H_{6'}}$); 4.54 (d, 2H, C**H$_2$**); 2.42(s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{17}H_{14}BrN_3O_3$: C, 52.60%; H, 3.63%; N, 10.82%. Found: C, 52.23%; H, 3.55%; N, 10.43%.

*6.1.5.29. 7-chloro-3-methylquinoxaline-2-carboxylic acid p-bromobenzylamide 1,4-di-N-oxide (**6b**).* Yield: 14%. IR (KBr): 3237 (w, ν_{N-H}); 3064 (w, ν_{arC-H}); 1670 (s, $\nu_{C=O}$); 1325 (s, ν_{N+O-}); 1071 (m, ν_{arC-Br}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.40 (bs, 1H, N**H**); 8.50 (d, 1H, **H$_5$**, $J_{5-6} = 9.3$ Hz); 8.49 (d, 1H, **H$_8$**, $J_{8-6} = 2.4$ Hz); 8.04 (dd, 1H, **H$_6$**); 7.59 (d, 2H, $\mathbf{H_{3'}} + \mathbf{H_{5'}}$, $J_{3'-2'} = 8.4$ Hz); 7.42 (d, 2H,

H2′ + H6′); 4.53 (d, 2H, C**H2**, J_{CH2-NH} = 5.8 Hz); 2.41 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{17}H_{13}BrClN_3O_3$: C, 48.31%; H, 3.10%; N, 9.94%. Found: C, 48.30%; H, 3.00%; N, 9.64%.

*6.1.5.30. 3,7-dimethylquinoxaline-2-carboxylic acid p-bromobenzylamide 1,4-di-N-oxide (**6e**).* Yield: 27%. IR (KBr): 3205 (w, ν_{N-H}); 3058 (w, ν_{arC-H}); 1667 (s, $\nu_{C=O}$); 1327 (s, ν_{N+O-}); 1068 (m, ν_{arC-Br}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.40 (bs, 1H, N**H**); 8.40 (d, 1H, **H5**, J_{5-6} = 8.8 Hz); 8.31 (s, 1H, **H8**); 7.83 (dd, 1H, **H6**, J_{6-8} = 1.3 Hz); 7.58 (d, 2H, **H3′ + H5′**, $J_{3'-2'}$ = 8.5 Hz); 7.43 (d, 2H, **H2′ + H6′**); 4.53 (d, 2H, C**H2**, J_{CH2-NH} = 5.9 Hz); 2.59 (s, 3H, C**H3**–C_7); 2.40 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{18}H_{16}BrN_3O_3$: C, 53.75%; H, 4.01%; N, 10.45%. Found: C, 53.41%; H, 3.86%; N, 10.07%.

*6.1.5.31. 6,7-dichloro-3-methylquinoxaline-2-carboxylic acid p-bromobenzylamide 1,4-di-N-oxide (**6g**).* Yield: 14%. IR (KBr): 3237 (w, ν_{N-H}); 3066 (w, ν_{arC-H}); 1670 (s, $\nu_{C=O}$); 1320 (s, ν_{N+O-}); 1067 (m, ν_{arC-Br}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.43 (t, 1H, N**H**, J_{NH-CH2} = 5.9 Hz); 8.69 (s, 1H, **H5**); 8.68 (s, 1H, **H8**); 7.58 (d, 2H, **H3′ + H5′**, $J_{3'-2'}$ = 8.3 Hz); 7.41 (d, 2H, **H2′ + H6′**); 4.53 (d, 2H, C**H2**); 2.41 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{17}H_{12}BrCl_2N_3O_3$: C, 44.67%; H, 2.65%; N, 9.19%. Found: C, 44.33%; H, 2.56%; N, 8.92%.

*6.1.5.32. 3-methylquinoxaline-2-carboxylic acid p-methylbenzylamide 1,4-di-N-oxide (**7a**).* Yield: 61%. IR (KBr): 3224 (w, ν_{N-H}); 3045 (w, ν_{arC-H}); 1671 (s, $\nu_{C=O}$); 1336 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.30 (t, 1H, N**H**, J_{NH-CH2} = 5.8 Hz); 8.52–8.49 (m, 2H, **H5 + H8**); 8.02–7.97 (m, 2H, **H6 + H7**); 7.33 (d, 2H, **H2′ + H6′**, $J_{2'-3'}$ = 7.8 Hz); 7.19 (d, 2H, **H3′ + H5′**); 4.51 (d, 2H, C**H2**); 2.42 (s, 3H, C**H3**–C_3); 2.30 (s, 3H, C**H3**–ph). Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86%; H, 5.30%; N, 13.00%. Found: C, 66.62%; H, 5.28%; N, 12.78%.

*6.1.5.33. 7-chloro-3-methylquinoxaline-2-carboxylic acid p-methylbenzylamide 1,4-di-N-oxide (**7b**).* Yield: 35%. IR (KBr): 3259 (w, ν_{N-H}); 3077 (w, ν_{arC-H}); 1671 (s, $\nu_{C=O}$); 1325 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.30 (t, 1H, N**H**, J_{NH-CH2} = 5.9 Hz); 8.50 (d, 1H, **H5**, J_{5-6} = 9.1 Hz); 8.48 (s, 1H, **H8**); 8.03 (dd, 1H, **H6**, J_{6-8} = 2.3 Hz); 7.32 (d, 2H, **H2′ + H6′**, $J_{2'-3'}$ = 7.9 Hz); 7.19 (d, 2H, **H3′ + H5′**); 4.51 (d, 2H, C**H2**); 2.40 (s, 3H, C**H3**–C_3); 2.30 (s, 3H, C**H3**–ph). Anal. Calcd. for $C_{18}H_{16}ClN_3O_3$: C, 60.43%; H, 4.51%; N, 11.74%. Found: C, 60.41%; H, 4.57%; N, 11.71%.

*6.1.5.34. 3,7-dimethylquinoxaline-2-carboxylic acid p-methylbenzylamide 1,4-di-N-oxide (**7e**).* Yield: 10%. IR (KBr): 3281 (m, ν_{N-H}); 3065 (w, ν_{arC-H}); 1650 (s, $\nu_{C=O}$); 1325 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.31 (bs, 1H, N**H**); 8.39 (d, 1H, **H5**, J_{5-6} = 8.8 Hz); 8.30 (s, 1H, **H8**); 7.83 (dd, 1H, **H6**, J_{6-8} = 1.8 Hz); 7.33 (d, 2H, **H2′ + H6′**, $J_{2'-3'}$ = 8.1 Hz); 7.19 (d, 2H, **H3′ + H5′**); 4.50 (d, 2H, C**H2**, J_{CH2-NH} = 5.8 Hz); 2.60 (s, 3H, C**H3**–C_7); 2.40 (s, 3H, C**H3**–C_3); 2.30 (s, 3H, C**H3**–ph). Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64%; H, 5.68%; N, 12.45%. Found: C, 67.27%; H, 5.70%; N, 12.25%.

*6.1.5.35. 6,7-dichloro-3-methylquinoxaline-2-carboxylic acid p-methylbenzylamide 1,4-di-N-oxide (**7g**).* Yield: 12%. IR (KBr): 3270(m, ν_{N-H}); 3045 (w, ν_{arC-H}); 1649 (s, $\nu_{C=O}$); 1359 (m, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.35 (t, 1H, N**H**, J_{NH-CH2} = 5.3 Hz); 8.62 (s, 1H, **H5**); 8.45 (s, 1H, **H8**); 7.32 (d, 2H, **H2′ + H6′**, $J_{2'-3'}$ = 7.3 Hz); 7.19 (d, 2H, **H3′ + H5′**); 4.51 (d, 2H, C**H2**); 2.55(s, 3H, C**H3**–C_3); 2.30 (s, 3H, C**H3**–ph). Anal. Calcd. for $C_{18}H_{15}Cl_2N_3O_3$: C, 55.12%; H, 3.85%; N, 10.71%. Found: C, 55.37%; H, 4.17%; N, 10.45%.

*6.1.5.36. 3-methylquinoxaline-2-carboxylic acid 2,2-diphenylethylamide 1,4-di-N-oxide (**8a**).* Yield: 8%. IR (KBr): 3237 (w, ν_{N-H}); 3064 (w, ν_{arC-H}); 1681 (s, $\nu_{C=O}$); 1339 (m, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.90 (t, 1H, N**H**, J_{NH-CH2} = 5.7 Hz); 8.47–8.42 (m, 2H, **H5 + H8**); 7.99–7.92 (m, 2H, **H6 + H7**); 7.41 (dd, 4H, 2**H2′**+2**H6′**, $J_{2'-3'}$ = 7.2 Hz, $J_{2'-4'}$ = 1.3 Hz); 7.35–7.31 (m, 4H, 2**H3′**+2**H5′**); 7.20 (tt, 2H, 2**H4′**, $J_{4'-3'}$ = 7.3 Hz); 4.32 (t, 1H, C**H**, J_{CH-CH2} = 8.0 Hz); 4.02 (dd, 2H, C**H2**); 1.97 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{24}H_{21}N_3O_3$: C, 72.17%; H, 5.30%; N, 10.52%. Found: C, 72.02%; H, 5.34%; N, 10.29%.

*6.1.5.37. 7-chloro-3-methylquinoxaline-2-carboxylic acid 2,2-diphenylethylamide 1,4-di-N-oxide (**8b**).* Yield: 17%. IR (KBr): 3231 (w, ν_{N-H}); 3058 (w, ν_{arC-H}); 1679 (s, $\nu_{C=O}$); 1326 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.88 (bs, 1H, N**H**); 8.45 (d, 1H, **H5**, J_{5-6} = 9.2 Hz); 8.41 (d, 1H, **H8**, J_{8-6} = 2.1 Hz); 8.00 (dd, 1H, **H6**); 7.40 (dd, 4H, 2**H2′**+2**H6′**, $J_{2'-3'}$ = 7.8 Hz, $J_{2'-4'}$ = 1.2 Hz); 7.35–7.30 (m, 4H, 2**H3′**+2**H5′**); 7.22 (tt, 2H, 2**H4′**, $J_{4'-3'}$ = 7.3 Hz); 4.32 (t, 1H, C**H**, J_{CH-CH2} = 7.9 Hz); 4.03 (dd, 2H, C**H2**); 1.98 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{24}H_{20}ClN_3O_3$: C, 66.44%; H, 4.65%; N, 9.68%. Found: C, 66.53%; H, 5.03%; N, 9.31%.

*6.1.5.38. 3,7-dimethylquinoxaline-2-carboxylic acid 2,2-diphenylethylamide 1,4-di-N-oxide (**8e**).* Yield: 11%. IR (KBr): 3223 (w, ν_{N-H}); 3057 (w, ν_{arC-H}); 1678 (s, $\nu_{C=O}$); 1328 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.90 (bs, 1H, N**H**); 8.34 (d, 1H, **H5**, J_{5-6} = 8.5 Hz); 8.23 (s, 1H, **H8**); 7.79 (dd, 1H, **H6**, J_{6-8} = 1.2 Hz); 7.40 (d, 4H, 2**H2′**+2**H6′**, $J_{2'-3'}$ = 7.5 Hz); 7.32 (t, 4H, 2**H3′**+2**H5′**, $J_{3'-4'}$ = 7.5 Hz); 7.24–7.20 (m, 2H, 2**H4′**); 4.31 (t, 1H, C**H**, J_{CH-CH2} = 7.9 Hz); 4.02 (dd, 2H, C**H2**, J_{CH2-NH} = 5.8 Hz); 2.57 (s, 3H, C**H3**–C_7); 1.95 (m, 3H, C**H3**–C_3). Anal. Calcd. for $C_{25}H_{23}N_3O_3$: C, 72.62%; H, 5.61%; N, 10.16%. Found: C, 72.26%; H, 5.84%; N, 9.77%.

*6.1.5.39. 6,7-dichloro-3-methylquinoxaline-2-carboxylic acid 2,2-diphenylethylamide 1,4-di-N-oxide (**8g**).* Yield: 15%. IR (KBr): 3212 (w, ν_{N-H}); 3083 (w, ν_{arC-H}); 1676 (s, $\nu_{C=O}$); 1321 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.91 (t, 1H, N**H**, J_{NH-CH2} = 5.8 Hz); 8.63 (s, 1H, **H5**); 8.60 (s, 1H, **H8**); 7.40 (dd, 4H, 2**H2′**+2**H6′**, $J_{2'-3'}$ = 7.8 Hz, $J_{2'-4'}$ = 1.3 Hz); 7.32 (dd, 4H, 2**H3′**+2**H5′**, $J_{3'-4'}$ = 7.4 Hz); 7.24 (tt, 2H, 2**H4′**); 4.32 (t, 1H, C**H**, J_{CH-CH2} = 8.1 Hz); 4.02 (dd, 2H, C**H2**); 1.07 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{24}H_{19}Cl_2N_3O_3.1/2H_2O$: C, 60.33%; H, 4.22%; N, 8.79%. Found: C, 60.10%; H, 4.25%; N, 8.60%.

*6.1.5.40. 3-methylquinoxaline-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide 1,4-di-N-oxide (**9a**).* Yield: 25%. IR (KBr): 3261 (m, ν_{N-H}); 3077 (w, ν_{arC-H}); 1642 (s, $\nu_{C=O}$); 1329 (m, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.29 (t, 1H, N**H**, J_{NH-CH2} = 5.8 Hz); 8.52–8.38 (m, 2H, **H5 + H8**); 8.02–7.95 (m, 2H, **H6 + H7**); 7.03 (bs, 1H, **H2′**); 6.91 (bs, 2H, **H5′ + H6′**); 6.01 (s, 2H, O–C**H2**–O); 4.47 (d, 2H, C**H2**); 2.42 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{18}H_{15}N_3O_5.1/2H_2O$: C, 59.61%; H, 4.41%; N, 11.59%. Found: C, 59.72%; H, 4.32%; N, 11.56%.

*6.1.5.41. 7-chloro-3-methylquinoxaline-2-carboxylic acid (benzo[1,3] dioxol-5-yl methyl)amide 1,4-di-N-oxide (**9b**).* Yield: 18%. IR (KBr): 3276 (w, ν_{N-H}); 3090 (w, ν_{arC-H}); 1649 (s, $\nu_{C=O}$); 1326 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.29 (t, 1H, N**H**, J_{NH-CH2} = 5.6 Hz); 8.51–8.49 (m, 2H, **H5 + H8**); 8.05–8.02 (m, 1H, **H6**); 7.02 (bs, 1H, **H2′**); 6.91 (bs, 2H, **H5′ + H6′**); 6.01 (s, 2H, O–C**H2**–O); 4.46 (d, 2H, C**H2**); 2.40 (s, 3H, C**H3**–C_3). Anal. Calcd. for $C_{18}H_{14}ClN_3O_5$: C, 55.75%; H, 3.64%; N, 10.84%. Found: C, 55.50%; H, 3.46%; N, 10.68%.

*6.1.5.42. 3,7-dimethylquinoxaline-2-carboxylic acid (benzo[1,3] dioxol-5-ylmethyl) amide 1,4-di-N-oxide (**9e**).* Yield: 21%. IR (KBr): 3266 (w, ν_{N-H}); 3071 (w, ν_{arC-H}); 1649 (s, $\nu_{C=O}$); 1325 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.29 (t, 1H, N**H**, J_{NH-CH2} = 5.8 Hz); 8.39 (d, 1H, **H5**, J_{5-6} = 8.8 Hz); 8.31 (s, 1H, **H8**); 7.83 (d, 1H, **H6**); 7.04 (bs, 1H, **H2′**); 6.91 (bs, 2H, **H5′ + H6′**); 6.02 (s,

2H, O–C**H$_2$**–O); 4.47 (d, 2H, C**H$_2$**); 2.59 (s, 3H, C**H$_3$**–C$_7$); 2.40 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{19}H_{17}N_3O_5$: C, 62.12%; H, 4.66%; N, 11.44%. Found: C, 61.74%; H, 4.80%; N, 11.68%.

*6.1.5.43. 6,7-dichloro-3-methylquinoxaline-2-carboxylic acid (benzo [1,3]dioxol-5-ylmethyl) amide 1,4-di-N-oxide (**9g**).* Yield: 22%. IR (KBr): 3273 (w, ν_{N-H}); 3058 (w, ν_{arC-H}); 1647 (s, $\nu_{C=O}$); 1326 (s, ν_{N+O-}). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.31 (t, 1H, N**H**, $J_{NH-CH2} = 5.8$ Hz); 8.69 (s, 1H, **H$_5$**); 8.67 (s, 1H, **H$_8$**); 7.02 (bs, 1H, **H$_{2'}$**); 6.90 (bs, 2H, **H$_{5'}$** + **H$_{6'}$**); 6.02 (bs, 2H, O–C**H$_2$**–O); 4.46 (d, 2H, C**H$_2$**); 2.50 (s, 3H, C**H$_3$**–C$_3$). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_5$: C, 51.20%; H, 3.10%; N, 9.95%. Found: C, 51.22%; H, 3.07%; N, 9.62%.

6.2. Pharmacology [31]

6.2.1. Primary screening (Dose–Response): determination of a 90% inhibitory concentration (IC_{90})

The initial screening is conducted against *M.Tbc.* H$_{37}$Rv (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA) [32]. Compounds are tested in ten 2-fold dilutions, typically from 100 μg/mL to 0.19 μg/mL. The IC_{90} is defined as the concentration effecting a reduction in fluorescence of 90% relative to controls. This value is determined from the dose–response curve using a curve-fitting program. Any IC_{90} value of $\leq$10 μg/mL is considered "Active" for anti-tubercular activity.

6.2.2. Secondary screening: determination of mammalian cell cytotoxicity (CC_{50})

The VERO cell cytotoxicity assay is carried out in parallel with the TB Dose–Response assay. After 72 h exposure, viability is assessed using Promega's Cell Titer Glo Luminescent Cell Viability Assay, a homogeneous method for determining the number of viable cells in culture based on quantitation of the ATP present. Cytotoxicity is determined from the dose–response curve as the CC_{50} using a curve-fitting program. Then the CC_{50} is divided by the IC_{90} for calculating a Selectivity Index (SI) value. SI values of $\geq$10 are considered for further testing.

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