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Synthesis of 2-sulfamoylquinoxaline 1,4-dioxide derivatives

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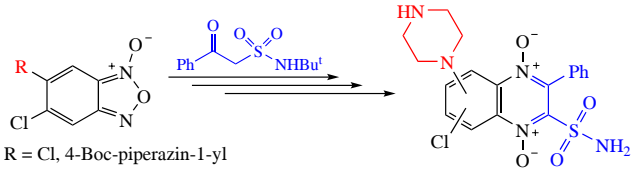
An access to new sulfonamide-containing 3-phenylquinoxaline 1,4-dioxides has been accomplished *via* the Beirut reaction of benzofuroxans with *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide. The reaction of 5-aminobenzofuroxan derivatives afforded 7-amino-2-sulfamoylquinoxaline 1,4-dioxides, whereas nucleophilic substitution of the chlorine atom in 6,7-dichloro-2-sulfamoylquinoxaline 1,4-dioxide gave the corresponding 6-amino-substituted analogs.



Keywords: 2-oxo-2-phenylethane-1-sulfonamide, quinoxaline 1,4-dioxides, sulfonamides, Beirut reaction, nucleophilic substitution.

Quinoxaline 1,4-dioxides exhibit a broad spectrum of biological activities.[1–4] This scaffold is particularly promising for use in the development of new medications for treatment of cancer, malaria, trypanosomiasis, leishmaniasis, and amebiasis.[5–8] For example, compounds with a carboxamide moiety at the C-2 position (*e.g.*, compound **1**, Figure 1) display potent antileishmanial activity with low cytotoxicity for mammalian cells.[9] Water-soluble derivatives have also been identified as hypoxia selective cytotoxins targeting solid tumor cells (*e.g.*, compound **2**).[10–13] Moreover, 3-(trifluoromethyl)quinoxaline 1,4-dioxides (*e.g.*, compound **3**) have demonstrated strong antibacterial activity, including potency against mycobacteria and protozoa.[14,15]

The sulfonamide group, a key pharmacophore in several drug classes, is characterized by a range of unique properties, including strong electron-withdrawing effects, lipophilicity, hydrogen bond-forming ability, acidity, and denticity, all of which are important for ligand binding to intracellular targets.[16] Introduction of a sulfonamide moiety into heterocyclic compounds enhances biological potential, notably through the inhibition of carbonic anhydrases, and confers a multitarget profile that allows interaction with multiple cellular targets.[17] The biological activity of quinoxaline 1,4-dioxide derivatives has been shown to depend significantly on the nature and position of substituents, particularly at C-2 and C-3.[18] This highlights the potential of synthesizing novel quinoxaline 1,4-dioxides bearing pharmacologically relevant sulfonamide group in these positions. Notably, 6(7)-sulfonamide-substituted quinoxaline 1,4-dioxides have demonstrated potent inhibition of the tumor-associated isoform carbonic anhydrase IX (*e.g.*, compound **4**, see Figure 1, K_i = 42.2 nM).[19] Despite ongoing studies on quinoxaline 1,4-dioxides, synthetic methods for their sulfonamide derivatives remain underexplored. Accordingly, the development of efficient strategies for the synthesis and characterization of quinoxaline 1,4-dioxide sulfonamides represents a promising direction in the study of this heterocyclic scaffold.

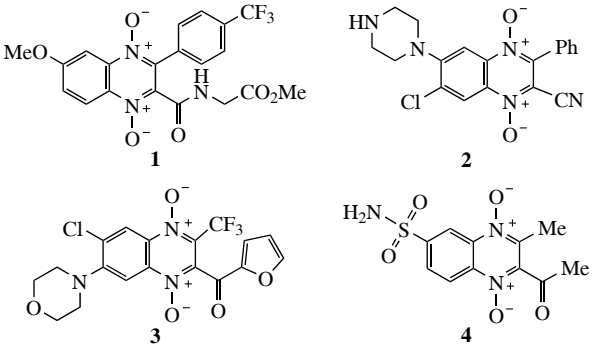
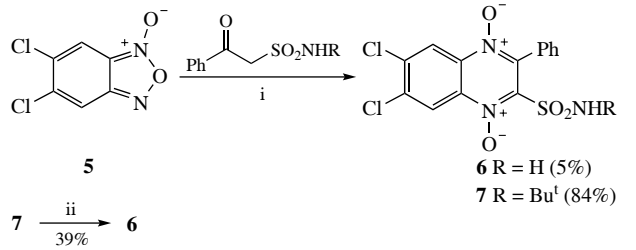


Figure 1 Biologically active derivatives of quinoxaline 1,4-dioxide **1**–**4**.

In continuation of the synthesis of quinoxaline 1,4-dioxide sulfonamides,[19] the preparation of 2-sulfamoylquinoxaline 1,4-dioxides *via* heterocyclization using 2-oxo-2-arylethane-1-sulfonamides, sulfonamide analogs of 1,3-dicarbonyl compounds, as the CH component was investigated. Initially, the Beirut reaction was used to synthesize a 2-sulfamoylquinoxaline 1,4-dioxide derivative from 6,7-dichlorobenzofuroxan **5** and 2-oxo-2-phenylethane-1-sulfonamide (Scheme 1). However, previously optimized conditions for the condensation of benzofuroxans with 1,3-dicarbonyl compounds[20–22] proved to be unsuitable for the reaction of compound **5** with 2-oxo-2-phenylethane-1-sulfonamide. Subsequent optimization revealed that the reaction proceeded in EtOH–THF mixture in the



Scheme 1 *Reagents and conditions*: i, K_2CO_3, $CaCl_2$, THF–EtOH, 50 °C, 8 h; ii, CF_3CO_2H, room temperature, 18 h.

presence of K_2CO_3 and catalytic amounts of $CaCl_2$. However, formation of by-products resulting from reduction of the labile *N*-oxide fragments and resinification of the reaction mixture was the reason of poor yield (~5%) of the target quinoxaline **6**.

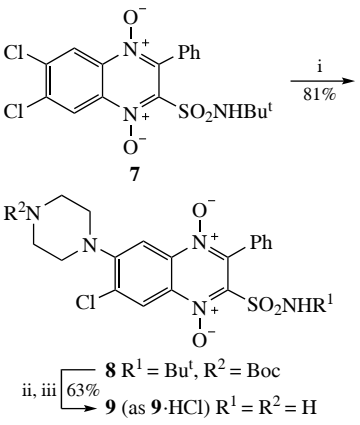
To improve efficiency, an alternative route involving cyclization between 5,6-dichlorobenzofuroxan **5** and *N*-*tert*-butyl-protected form of 2-oxo-2-phenylethane-1-sulfonamide was examined (see Scheme 1). Under optimized conditions (EtOH–THF, K_2CO_3, catalytic $CaCl_2$), this condensation yielded sulfonamide **7**. The comparatively lower yield of 2-sulfamoylquinoxaline **7** than that of analogous reactions with 1,3-dicarbonyl compounds[10,11,19,20] may be attributed to the steric hindrance caused by bulky *tert*-butyl group on the CH component in the Beirut reaction. It is well established that *N*-*tert*-butyl groups can be removed from sulfonamide residues under mild acidic conditions by treatment with trifluoroacetic acid (TFA).[23] This operation was found to be suitable for the preparation of 2-sulfamoylquinoxaline-1,4-dioxide **6** as well. Deprotection of the *N*-*tert*-butyl group in compound **7** using TFA at room temperature afforded the corresponding *N*-unsubstituted sulfonamide **6** in acceptable (39%) yield (see Scheme 1).

The halogen atoms in quinoxaline 1,4-dioxides are activated for nucleophilic aromatic substitution,[10,21,22] enabling the introduction of various amine fragments to obtain water-soluble derivatives. The substitution of the halogen atom in compound **7** (Scheme 2) was investigated to diversify the 2-sulfamoylquinoxaline-1,4-dioxide scaffold. However, first attempts to replace the chlorine atom of quinoxaline **7** with a piperazine moiety under previously reported conditions for 2-cyanoquinoxaline-1,4-dioxides[10,22] resulted in undesired reduction of the *N*-oxide moieties, and only trace amounts of the target compound were obtained. As reported previously, using less reactive *N*-Boc-piperazine and THF as the solvent can reduce side reactions and facilitate chromatographic purification.[21] This procedure turned out to be effective in our case, and the reaction of compound **7** with *N*-Boc-piperazine led to the successful formation of amino derivative **8** (Scheme 2). Notably, in accordance with previous findings for quinoxaline 1,4-dioxides bearing electron-withdrawing substituents at position 2,[10,21,22] the nucleophilic substitution proceeded regioselectively to yield the 6-amino-substituted derivative. Subsequent treatment of compound **8** with TFA at room temperature allowed for the simultaneous removal of both protecting groups (Boc and *tert*-butyl). Final treatment with HCl in methanol afforded water-soluble hydrochloride salt of the target compound, 6-amino-2-sulfamoylquinoxaline 1,4-dioxide derivative **9**·HCl, in good yield (see Scheme 2).

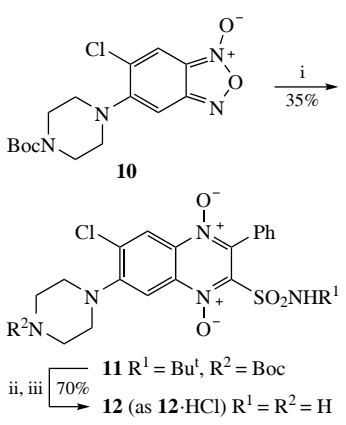
Heterocyclization reaction between 5-aminobenzofuroxan **10** and *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide (Scheme 3) was carried out to explore the feasibility of synthesizing 7-amino derivatives of 2-sulfamoylquinoxaline-1,4-dioxides *via* the Beirut reaction.[20] It was found that, analogously to the formation of 2-sulfamoylquinoxaline **7**, 5-(Boc-piperazinyl)-6-chlorobenzofuroxan **10** reacted efficiently with *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide in dioxane to afford the corresponding 7-amino-substituted 2-sulfamoylquinoxaline 1,4-dioxide **11** in good yield. Usage of dioxane as the solvent for this reaction was preferable as aminobenzofuroxan **10** has limited solubility of in other solvents. Importantly, as observed in previous studies on the regioselective synthesis of 6(7)-isomeric 2-cyano-quinoxaline-1,4-dioxides, as well as 2-acyl and 3-trifluoro-methylquinoxaline-1,4-dioxides,[10,21,22] the condensation of 5-aminobenzofuroxan **10** with the sulfonamide CH-component proceeded with high regioselectivity to yield exclusively the 7-amino-substituted derivative **11**. Subsequent removal of both protective groups (Boc- and *tert*-butyl) by successive treatment with trifluoroacetic acid and hydrogen chloride in methanol, afforded the water-soluble hydrochloride salt of the target compound, 2-sulfamoylquinoxaline 1,4-dioxide **12**·HCl, in good yield (see Scheme 3).

The structures of 2-sulfamoylquinoxaline-1,4-dioxides **6**–**9**, **11**, and **12** were confirmed by NMR spectroscopy and high-resolution mass spectrometry (HRMS). Notably, the obtained regioisomeric derivatives **8**, **11** and **9**, **12** exhibited similar ^{1}H NMR spectra, however altered in their mobility on TLC and showed significant differences in the chemical shifts of some signals observed in the ^{13}C NMR spectra.

In summary, a novel synthetic approach has been developed for the preparation of previously unreported quinoxaline 1,4-dioxide derivatives bearing a sulfonamide group at position 2. This methodology is based on the Beirut reaction of benzofuroxans with the *N*-*tert*-butyl derivative of 2-oxo-2-phenylethane-1-sulfonamide. Additionally, the previously established method for nucleophilic aromatic substitution of activated halogens has been successfully adapted to enable the synthesis of 6-amino-substituted 2-sulfamoylquinoxaline 1,4-dioxides. Meanwhile, the Beirut reaction with 5-aminobenzofuroxan derivatives provides a regioselective route to 7-amino-substituted analogs. This work highlights the effectiveness of using *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide as a CH-component in the Beirut reaction, thereby demonstrating the suitability of sulfonamide analogs of 1,3-dicarbonyl compounds in this transformation. Combined with previously reported methods for amine diversification of the quinoxaline-



Scheme 2 *Reagents and conditions*: i, *N*-Boc-piperazine, THF, room temperature, 14 h; ii, CF_3CO_2H, room temperature, 18 h; iii, HCl, MeOH, room temperature.



Scheme 3 *Reagents and conditions*: i, $PhC(O)CH_2SO_2NHBu^t$, K_2CO_3, $CaCl_2$, EtOH–dioxane, 50 °C, 5–8 h; ii, CF_3CO_2H, room temperature, 18 h; iii, HCl, MeOH, room temperature.

1,4-dioxide scaffold, this strategy offers a universal pattern for the synthesis of structurally diverse and pharmacologically promising 2-sulfamoylquinoxaline 1,4-dioxides.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7868.

References

1 M. González, H. Cerecetto and A. Monge, in *Bioactive Heterocycles V*, ed. M. T. H. Khan (*Topics in Heterocyclic Chemistry*, vol. 11), Springer, Berlin, Heidelberg, 2007, pp. 179–211; https://doi.org/10.1007/7081_2007_066.

2 N. Agrawal and A. Bhardwaj, *Chem. Biol. Drug Des*., 2022, **100**, 346; https://doi.org/10.1111/cbdd.14094.

3 G. Cheng, W. Sa, C. Cao, L. Guo, H. Hao, Z. Liu, X. Wang and Z. Yuan, *Front. Pharmacol*., 2016, **7**, 64; https://doi.org/10.3389/fphar.2016.00064.

4 B. S. Schwartz, J. Pollak, L. Bailey-Davis, A. G. Hirsch, S. E. Cosgrove, C. Nau, A. M. Kress, T. A. Glass and K. Bandeen-Roche, *Int. J. Obes*., 2016, **40**, 615; https://doi.org/10.1038/ijo.2015.218.

5 E. Miller, Q. Xia, M. Cella, A. Nenninger, M. Mruzik, K. Brillos-Monia, Y. Z. Hu, R. Sheng, C. M. Ragain and P. Crawford, *Molecules*, 2017, **22**, 1442; https://doi.org/10.3390/molecules22091442.

6 E. Vicente, L. M. Lima, E. Bongard, S. Charnaud, R. Villar, B. Solano, A. Burguete, S. Perez-Silanes, I. Aldana, L. Vivas and A. Monge, *Eur. J. Med. Chem*., 2008, **43**, 1903; https://doi.org/10.1016/j.ejmech.2007.11.024.

7 G. F. Dos Santos Fernandes, A. R. Pavan and J. L. Dos Santos, *Curr. Pharm. Des*., 2018, **24**, 1325; https://doi.org/10.2174/1381612824666180417122625.

8 M. Montana, V. Montero, O. Khoumeri and P. Vanelle, *Molecules*, 2021, **26**, 4742; https://doi.org/10.3390/molecules26164742.

9 J. F. González, M.-A. Dea-Ayuela, L. Huck, J. M. Orduña, F. Bolás-Fernández, E. de la Cuesta, N. Haseen, A. A. Mohammed and J. C. Menéndez, *Pharmaceuticals*, 2024, **17**, 487; https://doi.org/10.3390/ph17040487.

10 G. I. Buravchenko, A. M. Scherbakov, L. G. Dezhenkova, E. E. Bykov, S. E. Solovieva, A. A. Korlukov, D. N. Sorokin, L. M. Fidalgo and A. E. Shchekotikhin, *Bioorg. Chem*., 2020, **104**, 104324; https://doi.org/10.1016/j.bioorg.2020.104324.

11 Y. Hu, Q. Xia, S. Shangguan, X. Liu, Y. Hu and R. Sheng, *Molecules*, 2012, **17**, 9683; https://doi.org/10.3390/molecules17089683.

12 M. M. F. Ismail, K. M. Amin, E. Noaman, D. H. Soliman and Y. A. Ammar, *Eur. J. Med. Chem*., 2010, **45**, 2733; https://doi.org/10.1016/j.ejmech.2010.02.052.

13 H. U. Gali-Muhtasib, M. J. Haddadin, D. N. Rahhal and I. H. Younes, *Oncol. Rep*., 2001, **8**, 679; https://doi.org/10.3892/or.8.3.679.

14 M. Santivañez-Veliz, S. Pérez-Silanes, E. Torres and E. Moreno-Viguri, *Bioorg. Med. Chem. Lett*., 2016, **26**, 2188; https://doi.org/10.1016/j.bmcl.2016.03.066.

15 S. Pérez-Silanes, E. Torres, L. Arbillaga, J. Varela, H. Cerecetto, M. González, A. Azqueta and E. Moreno-Viguri, *Bioorg. Med. Chem. Lett*., 2016, **26**, 903; https://doi.org/10.1016/j.bmcl.2015.12.070.

16 R. J. Henry, *Bacteriol. Rev*., 1943, **7**, 175; https://doi.org/10.1128/br.7.4.175-262.1943.

17 S. G. Nerella, P. S. Thacker, M. Arifuddin and C. T. Supuran, *Eur. J. Med. Chem. Rep*., 2024, **10**, 100131; https://doi.org/10.1016/j.ejmcr.2024.100131.

18 W. S. Hamama, S. M. Waly, S. B. Said and H. H. Zoorob, *Synth. Commun.*, 2020, **50**, 1737; https://doi.org/10.1080/00397911.2017.1342843.

19 G. I. Buravchenko, A. M. Scherbakov, S. K. Krymov, D. I. Salnikova, G. V. Zatonsky, D. Schols, D. Vullo, C. T. Supuran and A. E. Shchekotikhin, *RSC Adv*., 2024, **14**, 23257; https://doi.org/10.1039/d4ra04548c.

20 G. I. Buravchenko, A. M. Scherbakov, L. G. Dezhenkova, L. Monzote and A. E. Shchekotikhin, *RSC Adv*., 2021, **11**, 38782; https://doi.org/10.1039/D1RA07978F.

21 G. I. Buravchenko, D. A. Maslov, M. S. Alam, N. E. Grammatikova, S. G. Frolova, A. A. Vatlin, X. Tian, I. V. Ivanov, O. B. Bekker, M. A. Kryakvin, O. A. Dontsova, V. N. Danilenko, T. Zhang and A. E. Shchekotikhin, *Pharmaceuticals*, 2022, **15**, 155; https://doi.org/10.3390/ph15020155.

22 J. J. Li, in *Name Reactions: A Collection of Detailed Reaction Mechanisms*, Springer, 2006, pp. 43–44.

23 A. M. Korolev, A. E. Shchekotikhin, L. N. Lysenkova and M. N. Preobrazhenskaya, *Synthesis*, 2003, **3**, 383; https://doi.org/10.1055/s-2003-37354.

24 S. K. Krymov, D. I. Salnikova, L. G. Dezhenkova, F. B. Bogdanov, A. A. Korlyukov, A. M. Scherbakov and A. E. Shchekotikhin, *Pharmaceuticals*, 2024, **17**, 32; https://doi.org/10.3390/ph17010032.

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