The Bioscan
AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES
20(3): S.I (3), 1270-1274, 2025 www.thebioscan.com

A simple synthesis of new quinoxaline-bisquinoline hybrids linked via thiomethyl ether

Banda Padma[1], Praveen Kumar Rathod[1] and Panaganti Leelavathi[1*]

[1]Department of Chemistry, University College of Science, Osmania University

Hyderabad-500 007, India.

Corresponding author E-mail: leelaou@gmail.com

DOI: 10.63001/tbs.2025.v20.i03.S.I(3).pp1270-1274

Received on:

04-08-2025

Accepted on:

08-09-2025

Published on:

10-10-2025

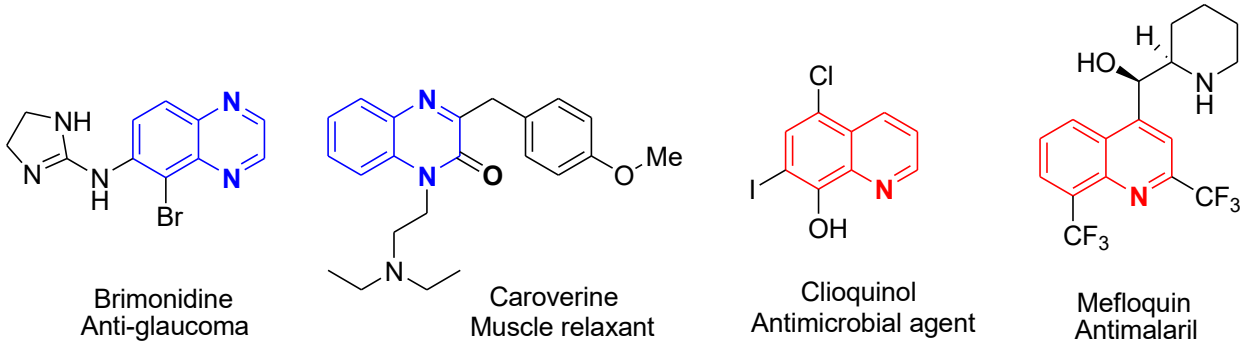
ABSTRACT

A straightforward synthesis of new hybrid molecules comprising two important pharmacophores, quinoline and quinoxaline is presented. The hybrid molecules were synthesized in a convergent manner from S-alkylation of quinoxaline-2,3-dithiol with 2-chloro-3-(chloromethyl) quinolines.

Quinoxaline-2,3-dithiols were accessed from 2,3-dichloroquinoxaline and thiourea. The other component quinolines were obtained from of 2-chloro-3-formyl quinolines by reduction and subsequent chlorination to corresponding chlorides. The designed strategy for target hybrids is simple with broad substrate scope and good yields.

INTRODUCTION

Quinoxalines, a significant class of *N*-heterocycles, have attracted considerable attention due to their importance in medicinal chemistry [1-3]. Quinoxaline derivatives are extensively studied for their wide-ranging biological activities [4-6], including anti-malarial, antibacterial, antiviral, antileprotic, anti-amoebic, anti-TB, anti-inflammatory, anticancer, and antioxidant effects. Few drugs (Fig. 1) having quinoxaline core [7] are talviraline (anti HIV), zonampanel (anti-convulsant), erdafitinib (anticancer), brimonidine (anti-glaucoma). In addition, quinoxalines find applications in areas such as fluorescent materials and semiconductors [8,9]. Quinoline represents other important *N*-heterocycle that appears in various medicinal natural and synthetic products [10-12]. It is one of the most extensively studied heterocycles in the development of biologically active molecules. Several drugs [13-15] featuring the quinoline ring (Fig. 1) include mefloquine (antimalarial), bedaquiline (anti TB), tipifarnib (anticancer), saquinavir (antiviral) etc. Consequently, the quinoxaline and quinoline scaffolds are of great interest owing to their prominent biological activities.



Brimonidine
Anti-glaucoma

Caroverine
Muscle relaxant

Clioquinol
Antimicrobial agent

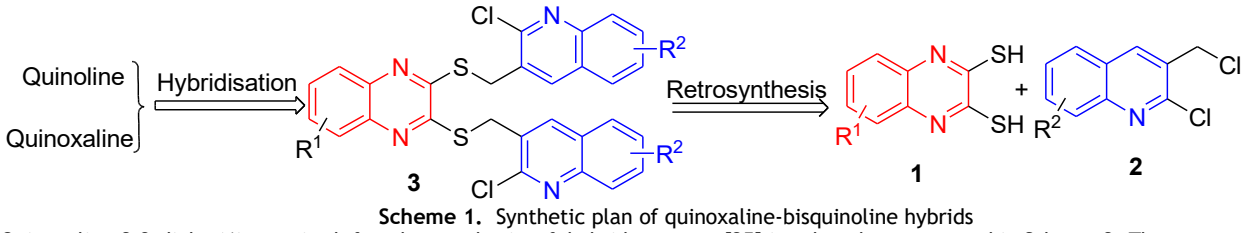
Mefloquin
Antimalaril

Fig. 1. Few examples of drugs containing quinoline and quinoxaline

Molecular hybridization [16-18] is the recently adopted strategy in the drug discovery process, which involves combining two or more pharmacophores of bioactive molecules into a single molecular frame work with an aim to enhance the biological activity. This technique has gained significant attention in developing new bioactive compounds. Thus, it is planned to synthesize hybrid molecules consisting quinoline and quinoxaline in a single molecular frame work. In continuation of our work on synthesis of quinoline derived bioactive molecules [19-23] we report, a simple synthesis of new quinoxaline-bisquinoline hybrids linked via thiomethyl ether

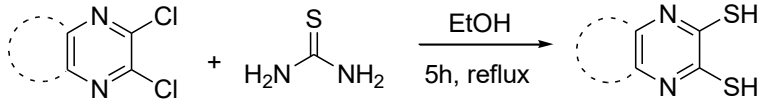
Results and discussion

We planned the synthesis of target hybrid molecules as outlined in scheme 1. The target quinoxaline-bisquinoline hybrids (**3**) could be accessed from quinoxaline-2,3-diol (**1**) and 2-chloro-3-(chloromethyl) quinolines (**2**) involving nucleophilic displacement of C-3 chlorine of quinoline with SH of quinoxaline.



Scheme 1. Synthetic plan of quinoxaline-bisquinoline hybrids

Quinoxaline-2,3-diols (**1**) required for the synthesis of hybrid molecules (**3**) are acquired from quinoxaline2,3-dione by chlorination with $POCl_3$ [24] followed by reaction with thiourea [25] in ethanol as presented in Scheme 2. The structure of dithiol (**2**) is confirmed from its ^1H NMR spectrum which indicated SH protons by the presence of signal at δ 14.26 ppm.

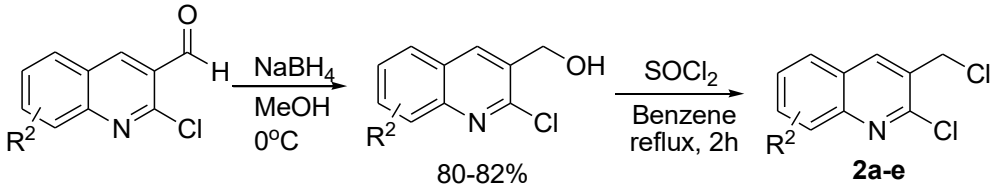


1a: quinoxaline-2,3-dithiol
1b: 6-Methylquinoxaline-2,3-dithiol
1c: 6, 7-Dimethylquinoxaline-2,3-dithiol
1d: Pyrazine-2,3-dithiol

1a-d

Scheme 2. Preparation of quinoxaline/pyrazine-2,3-dithiol (**1a-d**)

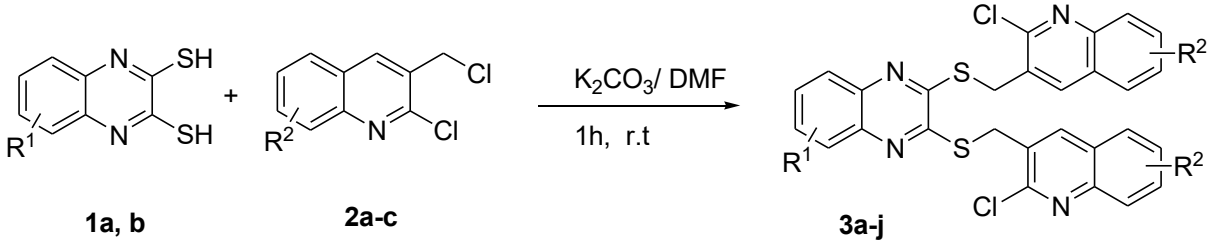
2-Chloro-3-(chloromethyl) quinolines (**2**) are the other starting material required for the synthesis of target hybrids (**3**) and are obtained from 2-chloro-3-formylquinolines by reduction to alcohols followed by chlorination [26] as illustrated in scheme 3.



2a: R^2 = H
2b: R^2 = 6-Me
2c: R^2 = 7-Me
2d: R^2 = 8-Me
2e: R^2 = 6,8-diMe

Scheme 3. Preparation of 2-chloro-3-(chloromethyl) quinolines (**2a-e)**

The final step in synthesis of target molecules is coupling the two precursors i.e. dithiol (**1**) and chloromethyl quinoline (**2**) and this was performed by subjecting them to S-alkylation in the presence of base K_2CO_3 and DMF as solvent at room temperature as depicted in scheme 4. Reaction progress was monitored by TLC and was proceeded smoothly to afford the desired products (**3**). The rection work up without column chromatography purification furnished them in good yields.



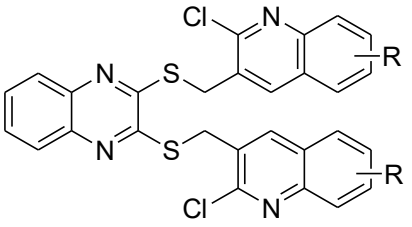
1a, b **2a-c** **3a-j**

Scheme 4. Synthesis of quinoxaline-bisquinoline hybrids (**3a-j**)

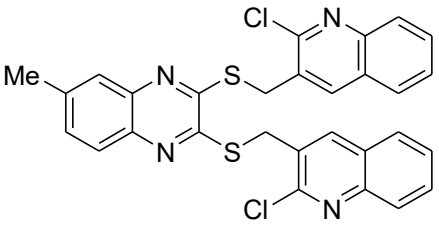
The structure of the compounds (**3**) was confirmed by the absence of SH signal in ^1H NMR at δ 14.26 ppm and presence of SCH_2 signal at δ ~4.8 ppm. The reaction progressed successfully with methyl and dimethyl quinoxaline, pyrazine thiols (**1a-d**) and as well with methyl substituted quinolines (**2a-e**). The synthesized were characterized by ^1H NMR, ^{13}C NMR and MS spectral data. For instance, ^1H NMR spectrum of representative compound **3b** showed singlets for methyl protons at δ 2.46 and SCH_2 signal was displayed at δ 4.82. Broad singlets in the aromatic region at δ7.97, 7.62 for two protons each sis due to quinoxaline ring protons. The rest of the aromatic signals at δ 8.35, 7.85 and 7.49-7.47 are due to quinoline ring protons.

All the synthesized quinoxaline-bisquinoline hybrids (**3a-j**) were presented in table 1.

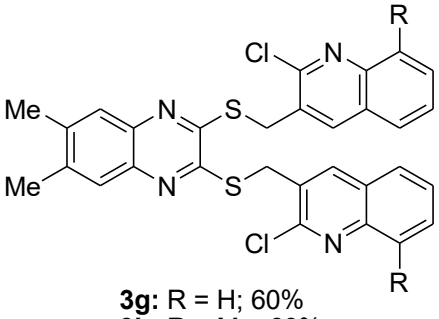
Table 1. The list of synthesized quinoxaline-bisquinoline hybrids (**3a-j**)



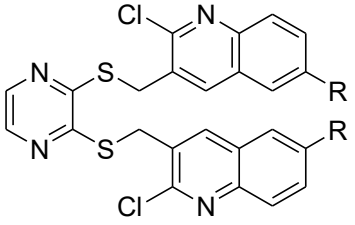
3a: R=H; 61%
3b: R=-6-Me; 62%
3c: R=7--Me; 59%
3d: R=8-Me; 65%
3e: R=6,8-diMe; 61%



3f; 60.6%



3g: R = H; 60%
3h: R = Me; 60%



3i; R = H; 61%
3j; R = Me; 65%

General Experimental

All reagents were purchased from SD Fine, Spectrochem or AVRA and used without further purification unless otherwise stated. Silicon oil baths on stirrer hotplates were employed with temperature control *via* thermometer. Reaction progress was monitored by Thin Layer Chromatography (TLC) using TLC Silica gel 60 F254. Flash column chromatography was performed using silica gel (60-120 or 100-200 mesh) as a stationary phase. Melting points were measured in open capillaries using melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR's were recorded using Varian 400 MHz spectrometer at 300 K. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) are quoted in Hz to one decimal place. For spectra recorded in chloroform-*d* ($CDCl_3$) the 7.26 ppm resonance of residual $CHCl_3$ for proton spectra was used as internal reference. Spectral data for ^{1}H NMR spectroscopy is reported as follows: Chemical shift (multiplicity, coupling constant, number of protons); and for ^{13}C NMR spectroscopy: Chemical shift. The following abbreviations were used for multiplicity in ^{1}H NMR: s (singlet), d (doublet), t (triplet), m (multiplet). All NMR spectra are processed using MestReNova version 6.0.2 (*v*). Mass spectra were analysed by Electrospray Ionization (ESI) method that were obtained on a Shimadzu LCMS-2020 mass spectrometer.

General procedure for the preparation of quinoxaline-2,3 dithiol (1a-d)

A 50 mL RB flask was charged with 2,3-dichloroquinoxaline (1 mmol), thiourea (2 mmol) and 10 mL of ethanol. The reaction mixture was refluxed for 5h and the reaction progress was checked by TLC. After the completion of reaction, contents of the flask were cooled to room temperature. The product precipitated as golden orange colored solid on cooling. Precipitated solid was filtered washed with water thoroughly. The obtained solid was suspended in 5 mL of distilled water. To this suspension, saturated aqueous solution of potassium hydroxide was added slowly till precipitate dissolves completely. The resulting solution pH was adjusted to ~1 by the addition of 1M HCl with continuous stirring which resulted in dark-brown precipitate. The separated solid was filtered, washed with water and dried to obtain quinoxaline-2,3-dithiol (**1**).

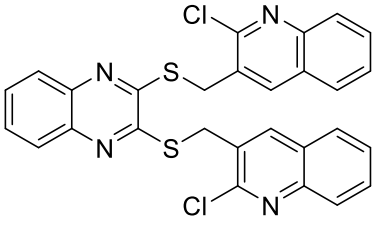
General procedure for the preparation of 2-chloro-3-(chloromethyl) quinoline (2a-e)

2-Chloroquinolin-3-yl-methanol (1 mmol) in benzene (5 mL) was taken in a 25 mL round bottom flask. Thionyl chloride was added then to the reaction mixture and refluxed for 2h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the obtained solid (**2**) was washed, dried and used for the next step.

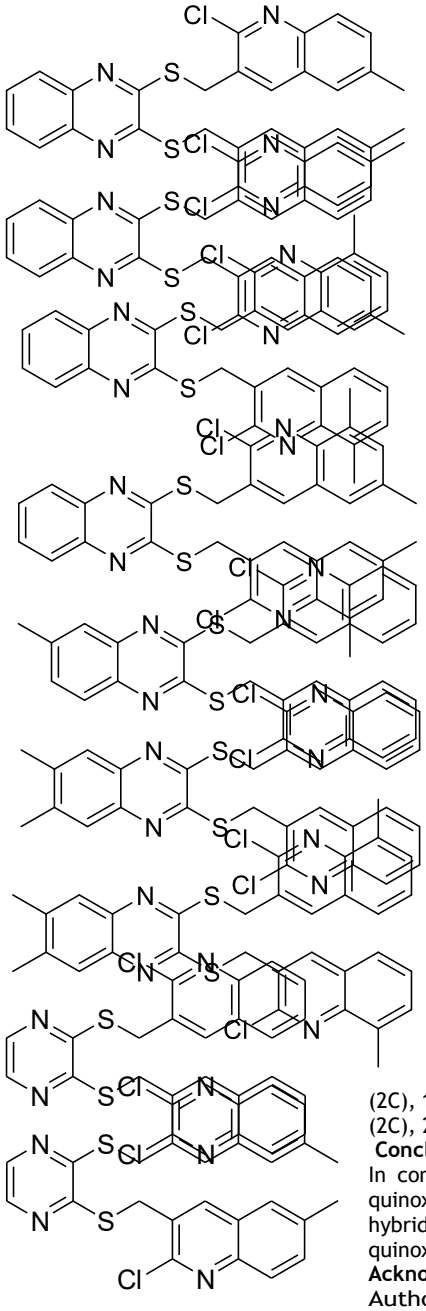
General procedure for the preparation of quinoxaline-bisquinoline hybrids (3a-j)

Quinoxaline-2,3-dithiol (0.225 mmol) was taken in a 25 mL round bottom flask and dissolved in 10 mL of dimethylformamide. 2-Chloro-3-(chloromethyl) quinoline (0.450 mmol) and then anhydrous potassium carbonate (0.675 mmol) were added to the solution. The reaction mixture was stirred at room temperature for two hours. The reaction's progress was monitored by thin-layer chromatography (TLC). After the completion of reaction, contents of the flask were poured into ice-cold water (50 mL). The precipitated crude brownish-yellow solid was collected by vacuum filtration, washed with cold water (3 x 10 mL), and dried.IT was then subjected to column chromatography to furnish final products, quinoxaline-bisquinoline hybrids (**3**).

2, 3-Bis(((2-chloroquinolin-3-yl) methyl) thio) quinoxaline(3a): Pale yellow solid, yield: 75 mg, 61%, **m.p**:190-192^{o} C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.45 (s, 2H), 7.97 (s, 4H), 7.79 – 7.54 (m, 6H), 7.48 (s, 2H), 4.83 (s, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.0 (2C), 151.1 (2C), 147.1(2C), 140.0 (2C), 139.3 (2C), 130.6 (2C), 129.5 (2C), 128.8 (2C), 128.4 (2C), 127.6 (2C), 127.5 (2C), 127.3 (2C), 127.28 (2C) 32.0 (2C); **MS(ESI)m/z**: 545 $[M+H]^{+}$.



2,3-Bis(((2-chloro-6-methylquinolin-3-yl)methyl)thio)quinoxaline(3b): Yellow solid, **yield**: 80 mg, 62%, **m.p**. 208-210° C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (s, 2H), 7.97 (s, 2H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 2.7 Hz, 2H), 7.48 (m, 4H), 4.82 (s, 4H), 2.46 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1(2C), 150.2(2C), 145.6(2C), 140.0(2C), 138.6(2C), 137.4(2C), 132.8(2C), 129.3(2C), 128.7(2C), 128.0(2C), 127.6(2C), 127.3(2C), 126.4(2C), 32.0(2C), 21.7(2C); **MS(ESI)m/z**: 573 $[M+H]^+$.



2,3-Bis(((2-chloro-7-methylquinolin-3-yl)methyl)thio)quinoxaline(3c): Brownish yellow solid, **yield:** 76mg, 59%, **m.p**. 215-217° C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (s, 2H), 7.93 (s, 2H), 7.70 (s, 2H), 7.57 (s, 4H), 7.28 (s, 2H), 4.77 (s, 4H), 2.47 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.1 (2C), 151.0 (2C), 147.3 (2C), 141.1 (2C), 140.0 (2C), 139.0 (2C), 129.5 (2C), 128.7(2C), 128.4 (2C), 127.6 (2C), 127.4 (2C), 127.1 (2C), 125.3 (2C), 32.0 (2C), 22.1(2C); **MS(ESI)m/z:** 573 $[M+H]^+$.

2,3-Bis(((2-chloro-8-methylquinolin-3-yl)methyl)thio)quinoxaline(3d): Light yellow solid, **yield**: 84 mg, 65%, **m.p.** 230-232° C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.97 (s, 2H), 7.62 (s, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.39 – 7.34 (m, 2H), 4.83 (s, 4H), 2.73 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.2 (2C), 150.1 (2C), 146.3 (2C), 140.0 (2C), 139.6 (2C), 136.6 (2C), 130.6 (2C), 129.0 (2C), 128.7 (2C), 127.6 (2C), 127.3 (2C), 127.1 (2C), 125.4 (2C), 32.1 (2C), 18.0 (2C); **MS(ESI) m/z**: 573 $[M+H]^+$.

2,3-Bis(((2-chloro-6,8-dimethylquinolin-3-yl)methyl)thio)quinoxaline(3e): Brown solid, **yield**: 83 mg, 61%, **m.p.**225-227° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 2H), 7.98 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.61 (s, 2H), 7.34 (m, 4H), 4.84 (s, 4H), 2.70 (s, 6H), 2.43 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6 (2C), 149.2 (2C), 140.0 (2C), 138.9 (2C), 137.0 (2C), 133.0 (2C), 128.9 (2C), 128.8 (2C), 128.6 (2C), 127.9 (2C), 127.6 (2C), 127.5 (2C), 124.3 (2C), 32.1 (2C), 18.9 (2C), 17.9 (2C); **MS(ESI) m/z**: 601 $[M+H]^+$.

2,3-Bis(((2-chloroquinolin-3-yl)methyl)thio)-6-methylquinoxaline(3f): Light yellow solid, yield: 78 mg, 60.6% , m.p. 218-220° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.3 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.73(s, 2H), 7.69 (d, *J* =7.3 Hz, 2H), 7.53 – 7.42 (m, 4H), 4.82 (s, 4H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (2C), 150. 0 (2C), 145.4 (2C), 139.8 (2C), 138.4 (2C), 137.2 (2C), 132.6 (2C), 129.1 (2C), 128.5 (2C), 127.8 (2C), 127.4 (2C), 127.1 (2C), 126.2 (2C), 31.8 (2C), 21.5; **MS(ESI) m/z:** 559 $[M+H]^+$.

2,3-Bis(((2-chloroquinolin-3-yl)methyl)thio)-6,7-dimethylquinoxaline (3g): yellow solid, **yield**: 78 mg, 60%, **m.p**: 203-205° C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.42 (s, 2H), 7.97 (d, *J* = 7.0 Hz, 2H), 7.70-7.66(m, 6H), 7.48 (s, 2H), 4.81 (s, 4H), 2.46 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.6 (2C), 151.1 (2C), 147.0 (2C), 139.1 (2C), 139.0 (2C), 138.9 (2C), 130.5 (2C), 129.7 (2C), 128.4 (2C), 127.5 (2C), 127.3 (4C), 127.0 (2C), 31.9 (2C), 20.4 (2C); **MS(ESI) m/z:** 573 $[M+H]^+$

2,3-Bis(((2-chloro-8-methylquinolin-3-yl)methyl)thio)-6,7-dimethylquinoxaline(3h): Brown solid, **yield:** 81 mg, 60%, **m.p.**205-207° C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.38 (s, 2H), 7.71 (s, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.1 Hz, 2H), 7.43 – 7.30 (m, 2H), 4.81 (s, 4H), 2.73 (s, 6H), 2.46 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.8 (2C), 150.1(2C), 146.3 (2C), 139.4 (2C), 138.9 (2C), 136.6 (2C), 130.5 (2C), 129.4 (2C), 129.3 (2C), 128.9 (2C), 127.4; **MS(ESI) m/z**: 601 $[M+H]^+$

2,3-Bis(((2-chloroquinolin-3-yl)methyl)thio)pyrazine (3i): Light yellow solid, **yield :** 68 mg, 61%, **m.p**.185-187° C; **^{1}H NMR (400 MHz, $CDCl_3$):**δ 8.30 (s, 2H), 8.12 (s, 2H), 7.98 (d, *J* = 5.2 Hz, 2H), 7.70 (d, *J* = 9.9 Hz, 4H), 7.52 (d, *J* = 4.4 Hz, 2H), 4.1 (s, 4H); δ 149.9 (2C), 147.5 (2C), 138.9 (3C), 131.2 (3C), 129.3 (2C), 128.5 (3C), 127.8 (3C), 127.7 (2C), 127.3 (2C), 43.3(2C); **MS(ESI) m/z**: 495 $[M+H]^+$

2,3-Bis(((2-chloro-6-methylquinolin-3-yl)methyl)thio)pyrazine(3j): Light yellow solid, **yield:** 73 mg, 62%, **m. p**. 192-194° C**; ^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.19 (s, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 9.9 Hz, 6H), 4.83 (s, 4H), 2.54 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 149.0 (2C), 146.1 (2C), 138.3 (3C), 137.8 (2C), 133.5 (3C), 129.2 (2C), 128.2 (3C), 127.4 (2C), 126.6 (3C), 43.4 (2C), 21.8 (2C); **MS(ESI) m/z**: 523 $[M+H]^+$

Conclusion

In conclusion, synthesis of a new series of molecular hybrids that contain biologically significant quinoxaline and quinoline scaffolds linked by a thiomethyl ether bond is reported. The synthesis of hybrids was achieved through a simple S-alkylation methodology which involves the reaction between quinoxaline-2,3-dithiols and 2-chloro-3-(chloromethyl) quinolines using potassium carbonate.

Acknowledgement

Authors thank the Department of Chemistry, Osmania University, Hyderabad, India, for the infrastructure under SAP(DRS-1) and DST-FIST programs.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

- V. Bala Akash, N. Rama;akshmi, S. Bhuvaneswari, E. Sankari and S. Arunkumar, Russ. J.
- Bioorg. Chem., 48, 657 (2022).
- H. Khatoon and S. M. Mohd Faudzi, Eur. J. Med. Chem., 276, 116675, 2024.
- M. Montana, F. Mathias, T. Terme and P. Vanelle, Eur. J. Med. Chem., 163, 136, 2019.
- S. Suresh Kumar, Ch. Narendra Singh, G. P. Singh, J. M. Padron and J. Yuvraj Kunwar, Eur.
- J. Med. Chem. Rep., 5, 100040,2022.
- V. Montero, M. Montana, M. Carre and P. Venelle, Eur. J. Med. Chem., 271, 116360, 2024.
- S. Tariq, K. Somakala and M. Amir, Eur. J. Med. Chem., 143, 542, 2017.
- A. M. Waseem, R. M. Elmagzoub, M. M. M. Abdelgadir, A. Al Bahir, N. S. Abd EL-Gawaad,
    - S. Abdel-Samea, D. Pratap Rao, K. Kossenas, S. Brase and H. Hashem, Results chem., 13,
- 2025, 101989.
- Z. Abid, L. Ali, S. Gulzar, F. Wahad, R. S. Ashraf and C. B. Nielsen, Beilstein J. Org. Chem.,
- 19, 1694, 2023.
- K. Hyekyoung, R.M. Rajeshkumar, H. Seong-Soo K. Choongik and S. SungYong, J.
- Nanosci., Nanotechnol., 17, 5530, 2017.
- B.S. Matada, R. Pattanashettar and N.G. Yernale, Bioorg. Med. Chem., 32, 115973, 2021.
- O. O. Ajani, K. T. Iyaye and O. T. Ademosun, RSC Adv., 12, 18594, 2022,
- C. W. Wright, J. Addae-Kyereme, A. G. Breen, J. E. Brown, M. F. Cox, S. L. Croft, Y.
- Gokcek, H. Kendrick, R. M. Phillips and P. L. Pollet, J.

Med. Chem., 44, 3187, **2001.**
- V. Yadav, J. Reang, V. Sharma, J. Majeed, P.C. Sharma, K. Sharma, N. Giri, A. Kumar and
- R. K. Tonk, Chem. Biol. Drug Des., 100, 389, 2022.
- P. Kushwaha, Curr. Top. Med. Chem., 24, 2377,2024.
- P. Yadav and K. Shah, Bioorg. Chem., 109, 104639, 2021
- C. Viegas-Junior, A. Danuello, V. da Silva Bolzani, E. J. Barreiro and C. A. M. Fraga, Curr.
- Med. Chem., 14, 1829, 2007.
- V. Ivasiv, C. Albertini, A. E. Goncalves, M. Rossi and M. L. Bolognesi, Curr. Top. Med.
- Chem., 19, 1694, 2019.
- P. de Sena Murteira Pinheiro, L. S. Franco, T. L. Montagnoli and C. A. M. Fraga, Expert
- Opin. Drug Discov., 19, 451, 2024.
- B.K. Reddy, K. Ravi, K. Mahesh and P. Leelavathi, Tetrahedron Lett., 59, 4039, 2018.
- P. K. Rathod, J. Sowmya and P. Leelavathi, Tetrahedron Lett., 66, 12808, 2021.
- P. K. Rathod, K. Krishnaveni and P. Leelavathi, Tetrahedron Lett., 104, 154028, 2022.
- M. K. Arif, R. Praveen Kumar and P. Leelavathi, Asian J. Chem., 37, 473. 202528.
- K. Mahesh, K. Ravi, P. K. Rathod and P. Leelavathi, New J. Chem., 44. 237, 2020.
- P. M. Zhang, Y. W. Li, J. Zhou, L. L. Gan, Y. L. Chen, Z. L. Gan and Y. Yu, J. Het. Chem.,
- 55, 1809,2018.
- D. C. Morrison and A. Frust, J. Org. Chem., 21, 470, 1956.
- J. Sowmya, B. Padma and P. Leelavathi, J. Indian Chem. Soc., 99, 100279, 2022.