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New Quinoxaline-Quinoline-1,2,3-Triazole Hybrids: Design And Synthesis

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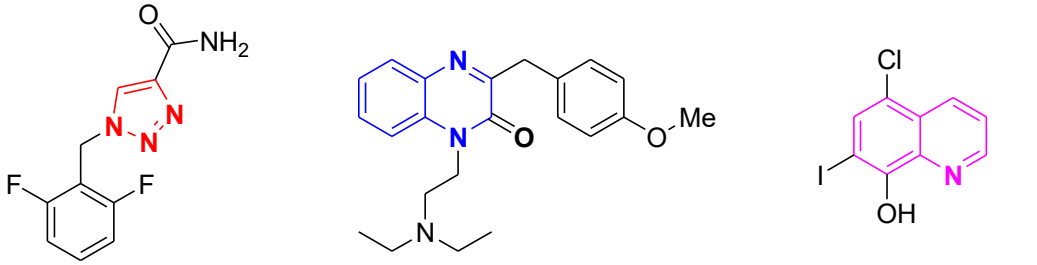
Abstract
We present here, design and synthesis of a new series of hybrid molecules comprising three pharmacologically significant scaffolds viz., quinoxaline, quinoline and 1,2,3-triazole. The hybrid framework was constructed starting from 2,3-dichloroquinoxaline by a three-step sequence. First step involved is conversion of 2,3-dichloroquinoxaline to the corresponding 2,3-dithiol and then a subsequent sequential one pot synthesis of terminal alkyne comprising two successive nucleophilic substitution reactions in which quinoxaline-2,3-dithiol reacted with 2-chloro-3-(chloromethyl) quinolines and then with propargyl bromide. Formation of desired target molecules via copper catalyzed azide-alkyne cycloaddition is the crucial third step. The planned strategy is simple and efficient in affording the desired hybrid molecules in excellent yields.
Keywords: *Quinoxaline-2,3-dithiol, 2-chloro-3-(chloromethyl)quinolines, propargyl bromide, quinoxaline-quinoline-triazole hybrids, click reaction*

INTRODUCTION

Quinoxalines among *N*-heterocycles are of considerable interest owing to their significance in the field of medicinal chemistry [1, 2]. Quinoxaline derivatives are widely described for diverse biological activities [3-6] ranging from antiviral, anti-malarial, antibacterial, anti-amoebic, anti-tubercular, antileprotic, anticancer, anti-inflammatory to antioxidant activity. Further, they are used in [7-9] fluorescent materials, semiconductors, crop protection etc. Quinoline is another important *N*-heterocycle [10- 12] prevalent in several medicinal natural, synthetic products and it is one of the well explored heterocycles for the evolution of biologically active molecules. Some of the drugs [13,14]. containing quinoline ring are clioquinol (antiprotozoal), primaquine (antimalarial), saquinavir (antiviral), ciprofloxacin (antibacterial), bedaquiline (anti TB) montelukast (antihistamine) etc. 1,2,3-triazole constitutes another notable scaffold [15- 17] due to its wide applications in medicinal chemistry and functional materials. Literature reports disclose that triazole derivatives [18-20] act against viruses, protozoa, bacteria, mycobacteria, inflammation, allergy, cancer etc. Thus, the scaffolds, quinoxaline, quinoline and 1,2,3-triazole are of considerable interest due to their significant biological profiles (Fig. 1).



Rufinamide
(Anti-epileptic)

Caroverine
Muscle relaxant

Clioquinol
Antimicrobial agent

Fig. 1. Representative examples of drugs containing quinoline, quinoxaline and 1,2,3-triazole

In drug discovery process, one approach that is used recently is molecular hybridization [21- 23], which comprises combination of two or more pharmacophores of bioactive molecules into a new hybrid molecule with enhanced biological activity. This technique attracted much attention for the development of new bioactive molecules. In consequence, it is considered of interest to incorporate the three biologically significant scaffolds, quinoxaline, quinoline and triazole into a single molecular framework. Following our interest in synthesis of bioactive heterocycles [24-27], we present here a facile and efficient synthesis of quinoxaline-quinoline-1,2,3-triazole hybrids.

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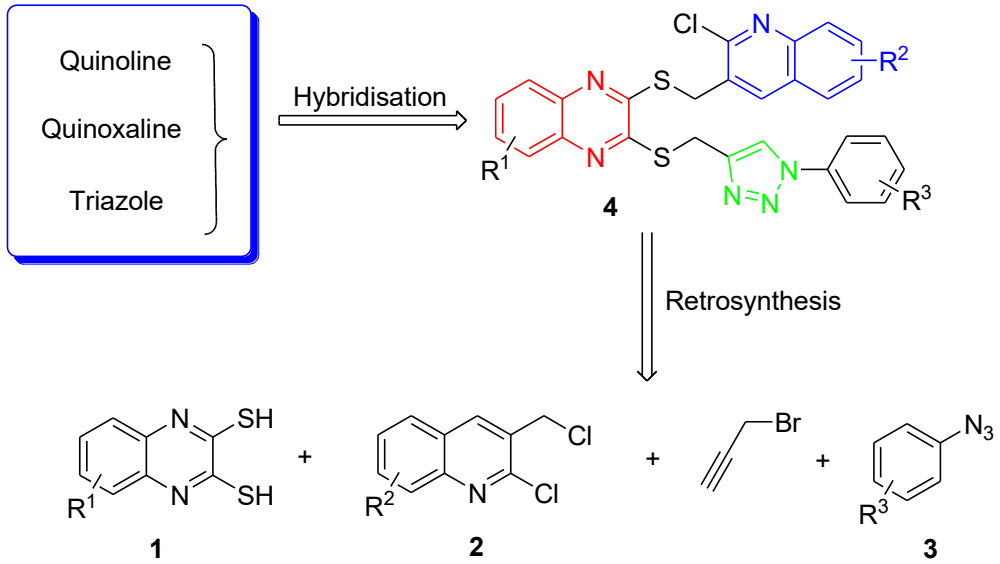
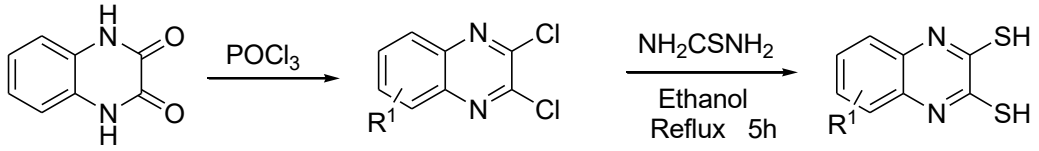
RESULTS AND DISCUSSION

The vast applications of three most important heterocycles, quinoline, quinoxaline, 1,2,3-triazole and molecular hybridization, the recent tool in drug discovery, prompted us to explore the making of hybrid molecules comprising these three heterocycles. We designed the synthesis of target molecules as presented in scheme 1. The hybrid molecules **4** could be accessed from consecutive S-alkylations of quinoxaline 2,3-dithiol (1) with 2-chloro-3-(chloromethyl) quinolines (**2**) and then with propargyl bromide and finally copper catalyzed click reaction with various azides (**3**).



Scheme 1. Design of quinoxaline-quinoline-1,2,3-triazole hybrids

Synthesis of the target hybrid molecules (**4**) was carried out as outlined in scheme 4. The precursors quinoxaline2,3-dithiol is obtained from the reaction of 2,3-dichloroquinoxaline with thiourea [28] in ethanol (scheme 2). 2,3-Dichloroquinoxaline in turn accessed by following literature procedure [29] from quinoxaline-2,3-dione and $POCl_3$. Formation of quinoxaline2,3-dithiol (**1**) is confirmed from its ^1H NMR which displayed characteristic signal for SH protons at δ 14.26 ppm.

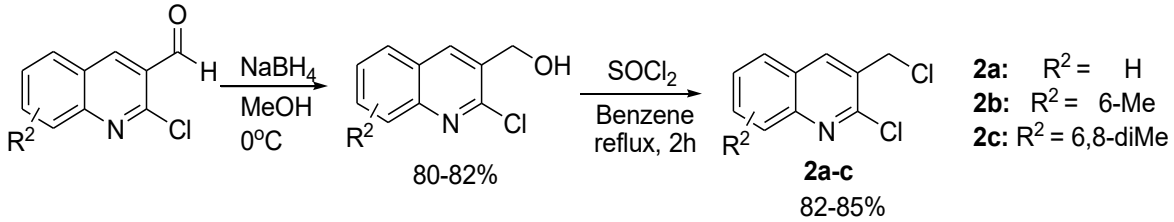


1a, b

1a: R^1= H; **1b:** R^1=6,7-diMe

Scheme 2. Preparation of quinoxaline2,3-dithiol (**1a, b**)

The other precursor required for the synthesis of target molecules (**4**) is quinoline derivative and that was accessed from 2-chloro-3-formyl quinolines [30] as shown in scheme 3. Reduction of 2-chloro-3-formyl quinolines with $NaBH_4$ afforded the corresponding alcohols which were subsequently converted to 2-chloro-3-(chloromethyl) quinolines (**2**) by reaction with thionyl chloride in benzene.



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

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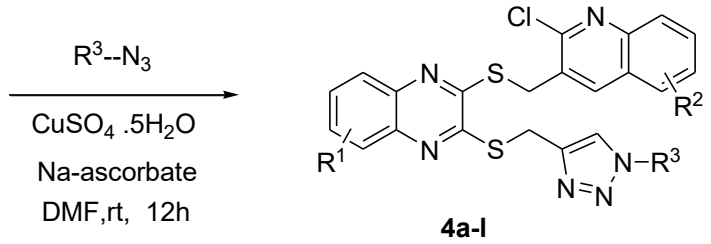
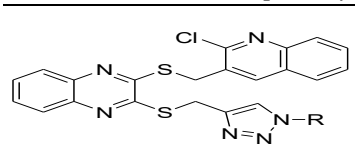
The next step in synthesis of target hybrids is S-alkylation of quinoxaline2,3-dithiol (**1**). This is achieved by a sequential one pot reaction in which both SH groups of (**1**) are alkylated, first with 2-chloro-3-(chloromethyl) quinolines (**2**) in DMF/ K_2CO_3 at room temperature. Reaction progress was checked by TLC, when it indicated the completion of reaction then without isolation of mono S-alkylated product, propargyl bromide was introduced into the reaction mixture and continued for another two hours. The reaction work up yielded crude product, which on purification by column chromatography provided the di-S-alkylated quinoxalines (**3a-e**) in 80-90% yield



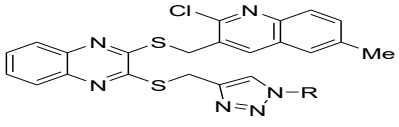
Scheme 4. Synthesis of quinoxaline-quinoline-1,2,3-triazole hybrids (**4a-l**)

Formation of desired di-S-alkylated quinoxalines (**3a-e**), for example 2-(((2-chloroquinolin-3-yl)methyl)thio)-3-(prop-2-yn-1-ylthio)quinoxaline (**3a**) was confirmed from ^{1}H NMR spectrum by the absence of SH signals at ~δ 14 ppm, and presence of propargyl group i.e. signals at δ2.20 (s,1H), 4.12 (s,2H) and -CH_2 attached to quinoline at δ 4.84 as singlet. Similarly, ^{13}C NMR spectrum displayed signals for propargyl group at δ 18.9, 71.5, 79.0 and for methylene carbon bonded to quinolinyl group at δ 32.0. Final step is the click reaction [31] in the synthesis of target hybrid molecules (**4**). The di-S-alkylated quinoxalines (**3**) were subjected to copper catalyzed click reaction with various azides to furnish final triazole hybrids (**4**) and are confirmed from disappearance of propargylic proton at δ ~2 and appearance of triazole proton at δ 7.9 in ^{1}H NMR spectrum. The substrate scope was explored next, and the substitution can be varied in quinoxaline, quinoline and in azides also. By changing the substrates various hybrid that were synthesized are given in Table 1. Thus, the designed route was found to be efficient and afforded desired quinoxaline-quinoline-1,2,3-triazole hybrids (**4a-l**) in good yields with broad substrate scope.

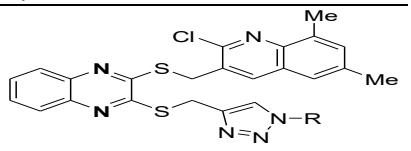
Table 1. Substrate scope of synthesis quinoxaline-quinoline-1,2,3-triazole hybrids (**4a-l**)



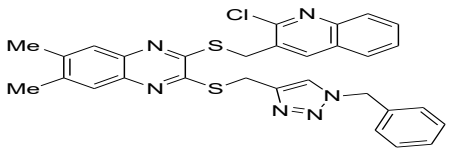
4a: R = $C_6H_5CH_2$; 82%
4b: R = 4-Cl-C_6H_4; 80%
4c: R = 4-OMe-C_6H_4; 88%



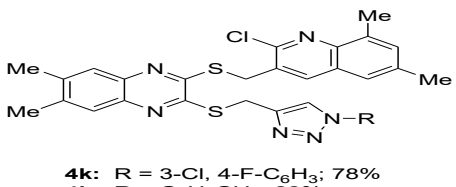
4d: R = $C_6H_5CH_2$; 79%
4e: R = 4-OMe-C_6H_4; 82%



4f: R = 4-Cl-C_6H_4 81%
4g: R = $C_6H_5CH_2$; 83%
4h: R = 4-OMe-C_6H_4; 84%
4i: R = 3-Cl, 4-F-C_6H_3; 73%



4j:78%



4k: R = 3-Cl, 4-F-C_6H_3; 78%
4l: R = $C_6H_5CH_2$; 88%

Reaction conditions: All reactions are carried out on a 0.245 mmol scale of **3,** azide (0.4 mmol), $CuSO_4$. $5H_2O$ (>018 mmol), Sodium ascorbate (0.17 mmol), DMF (15 mL)

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. 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 and 77.16 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. 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), q (quartet), m (multiplet). All NMR spectra are processed using MestReNova version 6.0.2 (*v*). ESI mass spectra were recorded on Micro mass Quattro LC using ESI^{+} software with capillary voltage 3.98 kV and an ESI mode positive ion trap detector.

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

2,3-Dichloroquinoxaline (1 mmol), thiourea (2 mmol) and ethanol 10mL were taken in a 50 mL RB flask. The reaction mixture was refluxed for 5h and after the completion of reaction, it was cooled to room temperature. Upon cooling the product precipitated as golden orange colored solid, which was filtered washed thoroughly with water, and then suspended in 5 mL of distilled water. To this suspension slowly added saturated aqueous solution of potassium hydroxide until precipitate dissolves completely. Then the pH of the resulting solution was adjusted to ~1 by the addition of 1M HCl with continuous stirring that resulted in dark-brown precipitate which was filtered, washed with water and dried to get quinoxaline-2,3-dithiol (**1**).

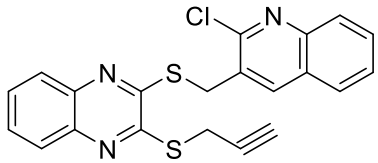
General procedure for the preparation of 2-chloro-3-(chloromethyl) quinoline (2a-c)

A 25 mL round bottom flask was charged with 2-chloroquinolin-3-yl-methanol (1 mmol) and benzene (5 mL). To this thionyl chloride was added and refluxed for 2h. Reaction progress was monitored by TLC. After completion of the reaction, benzene was removed under reduced pressure, the obtained solid (**2**) was washed, dried and used for the next step.

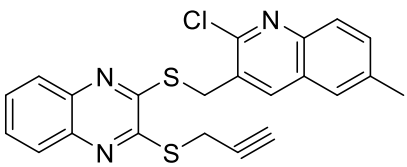
General procedure for the preparation of S- dialkylated quinoxalines(3a-e)

A solution of quinoxaline-2,3-dithiol (**1,** 0.785 mmol) in 10 mL DMF taken in 25mL round bottom flask. To the solution 2-chloro-3-(chloromethyl) quinoline (**2,** 0.785 mmol) and potassium carbonate (325 mg, 2.356 mmol) was added. The reaction mixture was stirred at room temperature for 1h and its progress was monitored by TLC. When it indicated completion, without isolation of product, the next alkylating agent, propargyl bromide (0.1mmol) was added. Stirring of the reaction mixture was continued for another 2h. reaction progress was assessed by TLC. Upon completion, the reaction mixture was poured into ice-cold water, solid separated was filtered, washed with water, dried and purified by column chromatography using hexane + ethyl acetate to furnish the desired propargylated quinoxaline derivatives (**3**).

2-(((2-Chloroquinolin-3-yl)methyl)thio)-3-(prop-2-yn-1- ylthio)quinoxaline (3a): light yellow solid , **yield** : 298 mg , 93% ; **m.p**.124-126°C; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.46 (s, 1H), 7.97 (s, 2H), 7.90 (d, J = 6.2 Hz, 1H) , 7.73 (d, J = 7.0 Hz, 1H), 7.67 (s, 1H), 7.60 (s, 2H), 7.50 (s, 1H), 4.84 (s, 2H), 4.12 (s, 2H), 2.20 (s, 1H) ; **^{13}C NMR** (101 MHz, $CDCl_3$) : δ 152.6 , 152.5 , 151.1 , 147.0 , 140.1 , 139.9 , 139.3 , 130.6 , 129.4 , 128.8 , 128.7, 128.4 , 127.9 , 127.5(2C) , 127.3 (2C) , 79.0 , 71.5 , 32.0 , 18.9 .

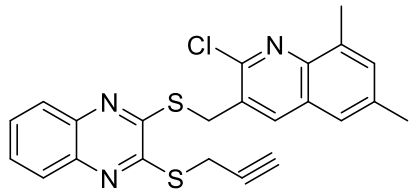


2-(((2-Chloro-6-methylquinolin-3-yl)methyl)thio)-3-(prop-2-yn-1-ylthio)quinoxaline (3b): light yellow solid, **yield** : 292 mg, 88%, **m. p**: 135-137°C; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.37 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.89 (dd, J = 15.0, 8.2 Hz, 2H), 7.67 – 7.56 (m, 2H), 7.50 (d, J = 8.7 Hz, 2H), 4.84 (s, 2H), 4.12 (s, 2H), 2.48 (s, 3H), 2.21 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152. 6, 152.4, 150.0, 145.5, 140.0, 139.8, 138.5, 137.2,

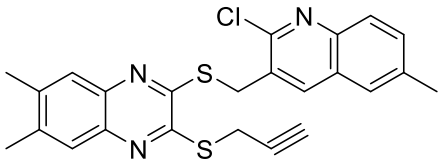


132.7, 129.1, 128.6, 128.5, 127.9, 127.8, 127.3, 127.2, 126.2, 78.9, 71.3, 31.9, 21.5, 18.8.

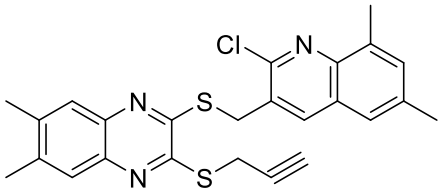
2-(((2-Chloro-6,8-dimethylquinolin-3-yl)methyl)thio)-3-(prop-2-yn-1-ylthio)quinoxaline (3c): Pale yellow solid, **yield**: 286 mg, 83%, **m.p**:128-130°C; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.30 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.55 (m, 2H), 7.33 (d, *J* = 11.8 Hz, 2H), 4.83 (s, 2H), 4.12 (s, 2H), 2.70 (s, 3H), 2.42 (s, 3H), 2.20 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$: δ 152.9, 152.6, 149.1, 145.0, 140.1, 140.0, 138.9, 140.0, 136.2, 132.9, 128.9, 128.8, 128.6, 127.9, 127.5, 127.4, 124.3, 79.1, 71.5, 32.1, 21.7, 18.9, 17.9.



2-(((2-Chloro-6-methylquinolin-3-yl)methyl)thio)-6,7-dimethyl-3-(prop-2-yn-1-ylthio) quinoxaline (3d): yellow solid, **yield**: 280 mg, 79% **,** m. p : 125-128°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.53 – 7.46 (m, 2H), 4.81 (s, 2H), 4.10 (s, 2H), 2.47 (s, 3H), 2.46 (s, 3H), 2.43 (s, 3H), 2.19 (s, 1H)**.** **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.3, 151.2, 150.2, 145.6, 139.0(2C), 138.9 (2C), 138.4, 137.3, 132.7, 129.5, 128.0, 127.4, 127.3, 126.9, 126.4, 79.3, 71.3, 29.9, 21.7, 20.4, 20.3, 18.8.



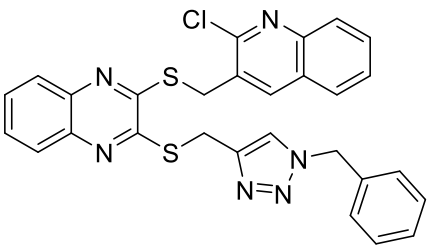
2-(((2-Chloro-6,8-dimethylquinolin-3-yl)methyl)thio)-6,7-dimethyl-3-(prop-2-yn-1-ylthio) quinoxaline (3e):yellow solid , **yield :** 300 mg, 82% , **m. p**. 120-122°C; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 8.28 (s, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 7.34 (s, 1H), 7.31 (s, 1H), 4.82 (s, 2H), 4.09 (s, 2H), 2.70 (s, 3H), 2.46 (s, 3H), 2.43 (s, 6H), 2.19 (s, 1H) **:** **^{13}C NMR** (101 MHz, $CDCl_3$) : δ 151.5, 151.2, 149.2 , 144.9, 139.00, 138.9, 138.8, 138.7, 136.9, 136.1, 132.9, 129.1, 127.5, 127.3, 127.2, 127.0, 124.3, 79.3, 71.3, 29.9, 21.7, 20.4, 20.3, 18.8, 17.9.



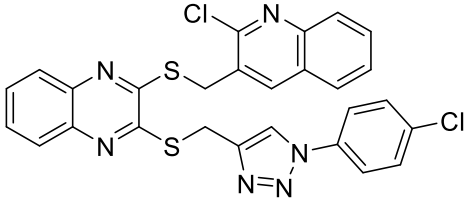
General procedure for the preparation of quinoxaline-quinoline-1,2,3-triazole hybrids (4a-l)

Quinoxaline propargylated derivative (**3**, 0.245 mmol) was taken in a 25 mL round-bottom flask and dissolved in 15 mL DMF and then azide (0.4 mmol) was added. To this solution $CuSO_4.5H_2O$ (0.018 mmol in 2mL of water) and sodium ascorbate (0.17 mmol in 1 mL water) were added. The reaction mixture was stirred at room temperature for 12 h and reaction progress checked by TLC. After the completion of conversion, reaction mixture was poured into crushed ice. The solid separated was filtered, washed with water, dried and purified by column chromatography to afford the quinoxaline-quinoline-1,2,3-triazole hybrids (**4**).

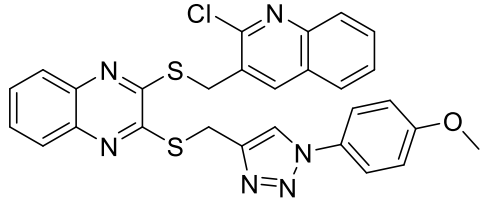
2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(((2-chloroquinolin-3-yl) methyl) thio) quinoxaline (4a) : pale yellow solid, **yield** : 108 mg, 82 % **m.p**.123-125°C ; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.45 (s, 1H), 7.96 (s, 2H), 7.81 – 7.53 (m, 6H), 7.48 (d, *J* = 9.1 Hz, 2H), 7.29 (s, 2H), 7.18 (s, 2H), 5.43 (s, 2H), 4.81 (s, 2H), 4.65 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$)**:** δ 153.5, 153.0, 151.1 (2C), 147.0 (2C), 139.9 (2C), 139.3, 134.6, 130.5, 129.5 (2C), 129.2 (2C), 128.9, 128.6 (2C), 128.4, 128.2, 127.6 (2C), 127.5, 127.3, 122.9, 54.3, 31.2, 25.3; MS(ESI)m/z: 541$[M+H]^+$.



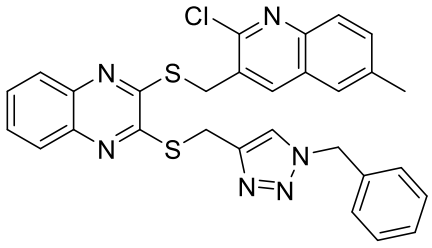
2-(((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(((2-chloroquinolin-3-yl) methyl) thio) quinoxaline (4b): Pale yellow solid, **yield :** 110 mg, 80 % , **m.p**.130-132°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.02 – 7.94 (m, 3H), 7.91 (d, *J* = 7.3 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 18.2, 5.8 Hz, 3H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.83 (s, 2H), 4.75 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.2, 153.1, 151.1 (2C), 147.0 (2C), 139.3, 135.6, 134.6, 130.6, 130.0, 129.4 (2C), 128.8 (2C), 128.4, 127.6, 127.5 (2C), 127.4 (2C), 127.2, 121.8 (2C), 121.0, 29.9, 25.0 ; MS(ESI)m/z: 51$[M+H]^+$.



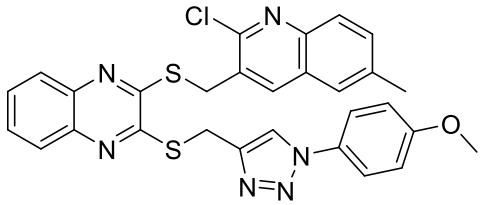
2-(((2-Chloroquinolin-3-yl)methyl)thio)-3-(((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl) thio) quinoxaline (4c): pale yellow solid, yield: 120 mg , 88 %, m.p.110-112^{0}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.97 (t, *J* = 7.98 Hz, 2H), 7.94 – 7.88 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.62 (s, 2H), 7.50 (dd, *J* = 15.3, 7.8 Hz, 3H), 6.94 (d, *J* = 8.2 Hz, 2H), 4.83 (s, 2H), 4.75 (s, 2H), 3.82 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) : δ 159.9 (2C), 153.4, 153.1, 151.1, 147.0 (2C), 140.0, 139.3, 130.6, 129.5 (2C), 128.7 (2C), 128.7, 128.4, 127.6, 127.5(2C), 127.3, 122.3 (2C), 121.3, 114.9 (2C), 55.7, 29.9 (2C) ; MS(ESI)m/z: 557$[M+H]^+$.



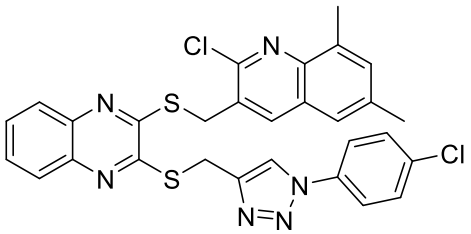
2-(((1-Benzyl-1H-1,2,3-triazol-4-yl) methyl) thio)-3-(((2-chloro-6-methylquinolin-3-yl) methyl) thio) quinoxaline (4d): Pale yellow solid, **yield** : 107 mg, 79% , **m.p**.115-117^0 C ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.04 (s, 1H), 7.90 (d, *J* = 23.8 Hz, 2H), 7.67 (s, 2H), 7.56 (s, 3H), 7.37 (s, 5H), 5.51 (s, 2H), 4.80 (d, *J* = 58.6 Hz, 4H), 2.55 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.4, 153.1 (2C), 150.2, 145.6(2C), 140.0, 139.9, 138.6 (2C), 137.4 (2C), 134.6, 132.8 (2C), 129.3 (2C), 128.9 (2C), 128.6, 128.2, 128.1, 127.6, 127.3 , 126.4, 54.3, 29.9, 25.3, 21.7; MS(ESI)m/z: 555$[M+H]^+$.



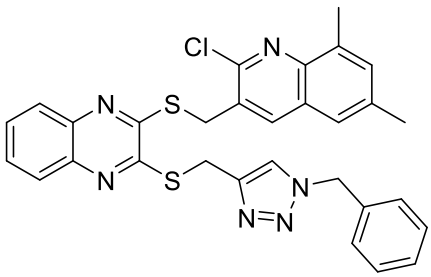
2-(((2-Chloro-6-methylquinolin-3-yl) methyl) thio)-3-(((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl)thio)quinoxaline (4e): pale yellow solid, **yield**: 115 mg, 82% , **m.p**.128-130^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.98 (d, *J* = 6.2 Hz, 1H), 7.89 (s, 2H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.62 (s, 2H), 7.55 – 7.44 (m, 4H), 6.93 (d, *J* = 7.7 Hz, 2H), 4.81 (s, 2H), 4.75 (s, 2H), 3.81 (s, 3H), 2.46 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.9 , 153.4 (2C), 153.1 , 150.2 , 145.6 , 144.9 , 140 (2C) , 138.6, 137.4, 132.8 , 130.6 , 129.3 , 128.7 (2C), 128.0 , 127.6 (2C), 127.3 , 126.3 , 122.3 , 121.3 (2C), 114.8, 55.7, 29.8, 25.1, 21.7; MS(ESI)m/z: 571$[M+H]^+$.



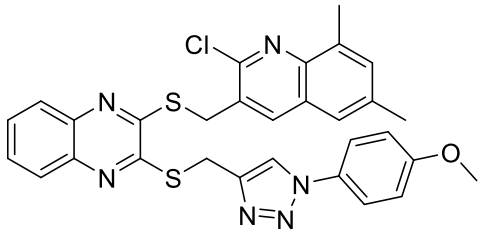
2-(((2-Chloro-6,8-dimethylquinolin-3-yl)methyl)thio)-3-(((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl) methyl)thio)quinoxaline (4f): Brown colour solid, **yield** : 117 mg, 81%, **m.p**.112-115^0 C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.97 (d, *J* = 23.8 Hz, 3H), 7.60 (d, *J* = 17.0 Hz, 4H), 7.42 (s, 2H), 7.32 (d, *J* = 9.8 Hz, 2H), 4.78 (d, *J* = 28.5 Hz, 4H), 2.68 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) : δ 153.3, 149.2(2C), 145.0 (2C), 140.1, 140.0, 138.9, 136.1, 133.0, 132.9, 130.0 (2C), 128.9 (2C), 128.8, 128.6 (2C), 127.7, 127.6, 127.5, 124.2, 121.9 (3C), 32.1, 25.0, 21.7, 17.9; MS(ESI)m/z: 589$[M+H]^+$.



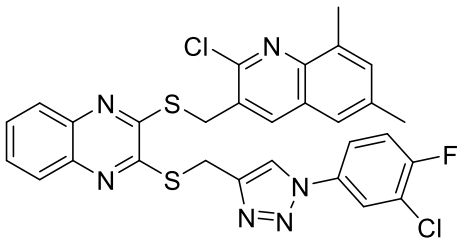
2-(((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)-3-(((2-chloro-6,8-dimethylquinolin-3-yl)methyl) thio) quinoxaline (4g):yellow solid, yield : 116 mg, 83% , m.p : 104-106^0 C; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.30 (s, 1H), 7.97 (d, *J* = 7.0 Hz, 1H), 7.79 (d, *J* = 6.6 Hz, 1H), 7.59 (d, *J* = 20.4 Hz, 2H), 7.46 (s, 1H), 7.38 – 7.24 (m, 5H), 7.18 (s, 2H), 5.43 (s, 2H), 4.81 (s, 2H), 4.65 (s, 2H), 2.69 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.5 , 153.2 , 149.3, 149.1, 144.9, 144.7, 140.0 , 139.9 , 138.8, 137.0, 136.1, 134.7, 132.9, 129.2 (2C), 128.9 (2C), 128.6 (2C), 128.2, 127.6 (2C), 127.4, 124.3 , 122.9, 54.3 , 32.1, 29.9, 21.7, 17.9 ; MS(ESI)m/z: 569$[M+H]^+$.



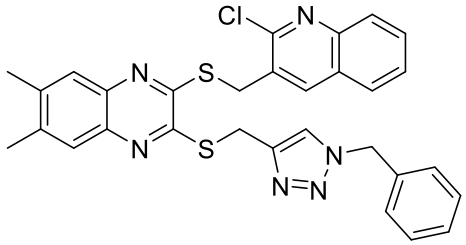
2-(((2-Chloro-6,8-dimethylquinolin-3-yl)methyl)thio)-3-(((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinoxaline (4h): yellow solid, **yield**: 120 mg, 84% , **m.p**.118-120^0 C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (s,1H), 7.99 (s, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.62 (s,2H), 7.52 (d, *J* = 6.7 Hz, 2H), 7.33 (d, *J* = 9.2 Hz, 2H), 6.95 (d, *J* = 7.2 Hz, 2H), 4.83 (s, 2H), 4.75 (s, 2H), 3.82 (s, 3H), 2.69 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.9, 153.4 (2C), 149.1, 145.0 (2C), 144.9, 140.0, 138.9, 137.0, 136.1, 132.9, 128.9 (2C), 128.7 (2C), 127.7, 127.6, 127.4, 124.3, 122.4 (2C), 121.3 114.9 (2C), 55.8, 32.1, 25.1, 21.7, 17.9; MS(ESI)m/z: 585$[M+H]^+$.



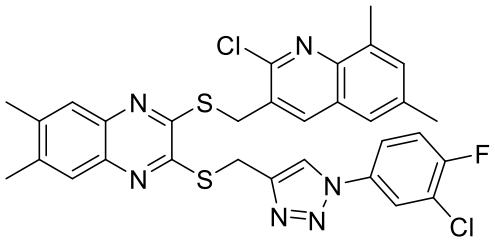
2-(((1-(3-Chloro-4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-3-(((2-chloro-6,8-di methylquinoline-3-yl)methyl)thio)quinoxaline (4i): light yellow solid, **yield**: 108 mg, 73%, **m.p**.135-137^0 C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.91 (s, 2H), 7.74 (d, *J* = 3.7 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.32 (d, *J* = 11.5 Hz, 2H), 7.22 (t, *J* = 8.6 Hz, 1H), 4.82 (s, 2H), 4.74 (s, 2H), 2.68 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.6, 153.1, 153.0, 149.0, 144.8 (2C), 139.9, 139.8, 138.7, 136.9, 136.0, 132.8, 128.7 (2C), 128.6 (2C), 127.6, 127.4, 127.2, 124.0, 123.0, 120.3, 120.2, 117.7, 117.4, 32.0, 24.8, 21.5, 17.7; MS(ESI)m/z: 607$[M+H]^+$.



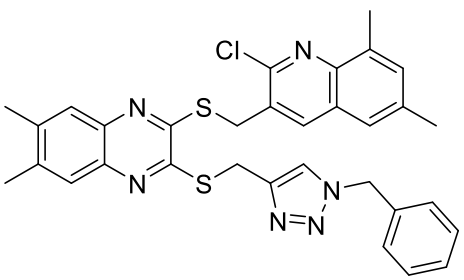
3-(((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)-2-(((2-chloroquinolin-3-yl)methyl)thio)-6,7-di methyl quinoxaline (4j): Pale yellow solid, yield: 108 mg, 78%, m.p.105-107°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.64 (m, 3H), 7.54 (s, 1H), 7.49 (dd, *J* = 15.5, 7.7 Hz, 2H), 7.30 (s, 3H), 7.18 (s, 2H), 5.43 (s, 2H), 4.80 (s, 2H), 4.62 (s, 2H), 2.46 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) : δ 152.1, 151.6 (2C), 151.2 (2C), 147.0 (2C), 139.0 (2C), 138.8, 134.7, 130.5, 129.7 (2C), 129.2 (2C), 128.8 (2C), 128.4, 128.2 , 127.5 (2C), 127.3, 127.0 (2C), 54.3, 31.9, 29.9, 20.4 (2C); MS(ESI)m/z: 569$[M+H]^+$.



2-(((3-(3-Chloro-4-fluorophenyl)-3*H*-pyrazol-5-yl)methyl)thio)-3-(((2-chloro-6,8-dimethylquinolin-3-yl)methyl)thio)-6,7-dimethylquinoxaline (4k): yellow solid , **yield**: 121 mg, 78%, **m.p**.123-125°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.90 (s, 1H), 7.74 (s, 2H), 7.67 (s, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 12.5 Hz, 2H), 7.21 (t, *J* = 8.5 Hz, 1H), 4.80 (s, 2H), 4.72 (s, 2H), 2.68 (s, 3H), 2.46 (d, *J* = 10.7 Hz, 6H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 151.8 (2C), 149.2, 146.2 (2C), 144.9, 139.0 (2C), 138.9 (2C), 138.7 (2C), 137.0, 136.1, 132.9; 127.0 (2C), 124.2, 123.2, 121.0, 120.5, 120.4, 117.8, 117.6, 29.9, 24.8, 21.7, 20.4 (2C), 17.9; MS(ESI)m/z: 635$[M+H]^+$.



2-(((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)-3-(((2-chloro-6,8-dimethylquinolin-3-yl) methyl) thio) -6,7-dimethylquinoxaline (4l): yellow solid, **yield**: 128 mg, 88%, **m.p**.150-153°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.71 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.32 (d, *J* = 14.0 Hz, 5H), 7.18 (s, 2H), 5.42 (s, 2H), 4.78 (s, 2H), 4.62 (s, 2H), 2.69 (s, 3H), 2.46 (s, 3H), 2.42 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.1, 151.8 (2C), 149.1 (2C), 144.9 , 138.9 (2C), 138.8, 138.7 (2C), 136.9, 136.8, 136.1, 134.7, 132.8, 129.2, 129.1, 128.8, 128.2 (2C), 127.5, 127.0, 126.9, 124.3, 54.2, 31.9, 29.9, 25.2, 21.7, 20.4, 17.9 ; MS(ESI)m/z: 597$[M+H]^+$.



Conclusion

In summary, a facile strategy for the construction of library of hybrid molecules having three important heterocyclic scaffolds that is quinoxaline, quinoline and 1,2,3-triazole in a single molecular framework is

disclosed. The synthesis involves click reaction on S-propargyl derivative of quinoxaline as key step. The propargyl intermediate in turn accessed from quinoxaline-2,3-dithiol by two successive nucleophilic substitution reactions in tandem with 2-chloro-3-(chloromethyl) quinolines and propargyl bromide in DMF/potassium carbonate. Notable features of the synthetic plan include convenient and efficient approach combined with broad substrate scope and good yields.

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

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