Synthesis of thiophenyl thiazole based novel quinoxaline derivatives

Haresh G. Kathrotiya, Yogesh T. Naliapara*

Department of Chemistry, Saurashtra University, Rajkot-360005, Gujarat, India

*E-mail address: naliaparachem@yahoo.co.in

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ABSTRACT A new series of thiophenyl thiazole based novel quinoxaline derivatives **4a-4t** have been synthesized by base catalysed condensation reaction. In which 6-substituted 2,3-dichloroquinoxaline **1a** and 4-(thiophen-2-yl)thiazol-2-amine **2b** reacted in basic condition to afford intermediate **3c** which reacts with various aromatic amine to form final compounds. Easy experimental procedure, high yield, and selectivity are the imperative features of this method. The identity of all the compounds has been established by ^1H NMR, ^{13}C NMR, FT-IR, and elemental analysis.

1. INTRODUCTION

A wide variety of pharmacological properties has been associated with quinoxaline derivatives. Quinoxaline also called benzopyrazine is a heterocyclic compound containing a ring complex made up of benzene ring and a pyrazine ring has been considered as a wonderful nucleus. Quinoxalines have extraordinary potential in pharmacological research [1] and practice. These are important components of several pharmacologically active compounds [2-8] and exhibit special and wider ranges of functions in biologically active compounds [9], electroluminescent materials [10], dyes [11] and anion sensors [12]. Although rarely describe in nature, synthetic quinoxaline derivatives showed variety of pharmaceutical activities encompassed major types of drug target families and effective in many clinical applications such as anti tumor agents [13], kinase inhibitors [14], HIV drugs [15], antibiotics [16], ion channel regulators [17] and anti protozoal agents [18].

Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 1,2-diamines with α -diketones [19, 20], 1,4-addition of 1,2-diamines to diazenylbutenes [21], cyclization-oxidation of phenacyl bromides [22, 23] and oxidative coupling of epoxides with ene-1,2-diamines [24], 2,3-Disubstituted quinoxalines have also been prepared *via* the Suzuki-Miyaura coupling reaction [25], condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation [26] and iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds with substituted *o*-phenylenediamines in DMSO [27] or CH_3CN [28].

A variety of catalysts were tested in these reactions such as acetic acid [29], iodine [30], $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ [31], nickel nanoparticles [32], gallium(III)triflate [33], montmorillonite K-10 [34], ionic liquids [35], Nano- TiO_2 [36], sulfated TiO_2 [37], $\text{Pd}(\text{OAc})_2$ [38], $\text{RuCl}_2(\text{PPh}_3)_3$ -2,2,6,6-tetramethylpiperidine 1-oxyl(TEMPO) [38], MnO_2 [38], Al_2O_3 [39], zirconium(IV)-modified silica gel [40], nanocrystalline CuO [41], cerium(IV) ammonium nitrate [42], iron exchanged molybdophosphoric acid [43], silica-bonded S-sulfonic acid [44], and sulfamic acid/MeOH [45]. Here we report synthesis of novel thiophene thiazole based quinoxaline derivatives by chloro-amine condensation. The constitutions of all the products were confirmed using ^1H NMR, ^{13}C NMR, FTIR, and elemental analysis.

2. EXPERIMENTAL

Required all reagents were obtained commercially. Solvents were purified and dried before being used. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates precoated with silica gel, 60F₂₅₄, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds; eluent-hexane:ethyl acetate: (4:6). UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within $\pm 0.4\%$ of theory specified. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1} . ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-*d*₆ on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as internal standard at 400 MHz and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

2.1 Synthesis of the substituted 2,3-dichloroquinoxaline (1a)

Substituted benzene-1,2-diamine (5 mmol), diethyl oxalate (5 mmol), piperidine (1 ml), and ethanol (10 ml) were charged in a 100 ml round bottom flask with mechanical stirrer and condenser. The reaction mixture refluxed for 4 h. After the completion of reaction (checked by TLC), the separated substituted quinoxaline-2,3(1*H*,4*H*)-dione was filtered and washed with ethanol and dried. Now thionyl chloride (25 mmol) was added to a solution of substituted quinoxaline-2,3(1*H*,4*H*)-dione (10gm) in dry DCM (50 mL). Upon the addition of 1-2 drop of DMF a mixture was heated at reflux for 1 h. After the completion of reaction a mixture was washed with water followed by saturated NaHCO₃ solution. The organic phase was dried over anhydrous Na₂SO₄ and solvent was removed under reduced pressure to afford analytically pure substituted 2,3-dichloroquinoxaline.

2.2 Synthesis of the substituted 3-chloro-*N*-(4-(thiophen-2-yl)thiazol-2-yl)quinoxalin-2-amine (3c)

Substituted 2,3-dichloroquinoxaline **1a** (5 mmol) and 4-(thiophen-2-yl)thiazol-2-amine **2b** (5 mmol) were thoroughly mixed in DMF (10 ml) and then dry K₂CO₃ (5 mmol) was added to it. The mixture was heated at 100 °C 3 h. After the completion of reaction (checked by TLC), the solution was cooled to room temperature. The reaction mixture was poured in to chilled water. The separated precipitates were filtered, thoroughly washed well with water, dried, and recrystallized from ethanol to achieve pure substituted 3-chloro-*N*-(4-(thiophen-2-yl)thiazol-2-yl)quinoxalin-2-amine.

2.3 General procedure for the synthesis of compounds 4(a-t)

Substituted 3-chloro-*N*-(4-(thiophen-2-yl)thiazol-2-yl)quinoxalin-2-amine **3c** (5 mmol) and various aromatic amines (5 mmol) were thoroughly mixed in DMF (10 ml) and then dry K₂CO₃ (5 mmol) was added to it. The mixture was heated at 100 °C for 4-5 h. After the completion of reaction (checked by TLC), the solution was cooled to room temperature. The reaction mixture was poured in to chilled water. The separated precipitates were filtered, thoroughly washed well with water, dried, and recrystallized from chloroform to obtain the pure compounds **4a–4t**. The physicochemical and spectroscopic characterization data of the synthesized compounds **4a–4t** given below.

Scheme 1 Synthetic pathway for synthesis of 1a

Scheme 2 Synthetic pathway for synthesis of 3c

Scheme 3 Synthetic pathway for synthesis of thiophenyl thiazole based quinoxaline derivatives 4a-4t

Scheme 4 Mechanism for the synthesis of thiophenyl thiazole based quinoxaline derivative

Table 1 Synthesis of quinoxaline derivatives 4a-4t

Entry	R	R ₁	RT(h.)	Yield %	mp °C
4a	H	H	4.1	90	180-182
4b	H	4-CH ₃	4	93	186-188
4c	H	4-OCH ₃	4.1	90	173-175
4d	H	4-F	4.3	88	162-164
4e	H	4-Cl	4.4	88	190-192
4f	H	4-Br	4.5	85	161-163
4g	H	4-OH	4.5	84	158-160
4h	H	4-NO ₂	4.1	92	173-175
4i	H	4-NH ₂	4.6	80	166-168
4j	H	3-CH ₃	4.6	70	151-153
4k	CH ₃	H	4.3	89	130-132
4l	CH ₃	4-CH ₃	4.1	90	142-148
4m	CH ₃	4-OCH ₃	4.2	91	136-138
4n	CH ₃	4-F	4.4	85	123-125
4o	CH ₃	4-Cl	4.5	84	120-122
4p	CH ₃	4-Br	4.5	84	136-138
4q	CH ₃	4-OH	4.6	86	127-129
4r	CH ₃	4-NO ₂	4	90	119-121
4s	CH ₃	4-NH ₂	4.7	79	133-135
4t	CH ₃	3-CH ₃	4.8	73	140-142

The required 4-(thiophen-2-yl)thiazol-2-amine **2b** was prepared by solid phase reaction according to literature procedure [46].

In this study, a series of quinoxaline derivatives **4a–4t** have been synthesized by chloro-amine condensation reaction of substituted 3-chloro-*N*-(4-(thiophen-2-yl)thiazol-2-yl)quinoxalin-2-amine and various aromatic amines in DMF at 100 °C using K₂CO₃ as a base (scheme-3). According to the mechanism suggested in (scheme-4), the formation of the quinoxaline derivatives occurs via chloro-amine condensation in presence of K₂CO₃. Reaction of substituted benzene-1,2-diamine and diethyl oxalate gave substituted quinoxaline-2,3(1*H*,4*H*)-dione by removal of two ethanol molecules. Then substituted quinoxaline-2,3(1*H*,4*H*)-dione treated by SOCl₂ to obtain substituted 2,3-dichloroquinoxaline. At last, nucleophilic attack of amine to the substituted 2,3-dichloroquinoxaline moiety took place to afford quinoxaline derivatives **4a–4t** (Scheme 4).

The structures of all the new synthesized compounds were established by ¹H NMR, ¹³C NMR, FTIR, elemental analysis, and molecular weight of some selected compounds were confirmed by mass spectrometry. In ¹H NMR, (DMSO-*d*₆) spectrum of compound **4b** two singlet peak at δ 10.41 ppm and δ 10.62 ppm appeared for two –NH– protons. Aromatic protons of **4b** resonate as multiplets at δ 6.90-8.00 ppm. A singlet at δ 2.80 ppm stands for aromatic methyl protons. ¹³C NMR of **4b** exhibited a distinctive signal at δ 27.12 ppm for aromatic methyl. All the aromatic carbons of **4b** showed signals at δ 107.25-138.39 ppm in the ¹³C NMR spectra. The IR spectrum of compound **4b** exhibited characteristic absorption band at 3,318 and 3,226 cm⁻¹ for two –NH– and 3,026 cm⁻¹ for aromatic C–H stretching. Further, the structures of selected compounds **4b**, **4c**, and **4k** were confirmed by its mass spectral studies. The mass spectra detected the expected molecular ion signals corresponding to respective molecular formula of synthesized compounds. Mass spectra of compound **4b** gave molecular ion peak at 415.0 (M + 1) corresponding to molecular formula C₂₂H₁₇N₅S₂. All spectroscopic data have been given in spectral data.

3. SPECTRAL DATA

***N*²-phenyl-*N*³-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4a)**

yellow solid, yield 90%, m.p. 180-182°C, IR (KBr, ν , cm^{-1}): 3325 (N-H Str.), 3220 (N-H Str.), 3024 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 6.520-8.022 (m, 13H, Ar-H), 10.208 (s, 1H, NH), 10.520 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 107.12, 108.25, 109.00, 110.11, 112.32, 113.00, 114.15, 116.00, 118.32, 119.00, 121.04, 122.32, 123.01, 125.18, 127.93, 128.56, 130.00, 132.35, 134.89, 138.25, 139.28(Ar-C). MS(M⁺): 401.08, Anal. Calcd. for C₂₁H₁₅N₅S₂ (401.51): C 62.82, H 3.77, N 17.44 Found: C 62.70, H 3.45, N 17.52%.

***N*²-(4-(thiophen-2-yl)thiazol-2-yl)-*N*³-p-tolylquinoxaline-2,3-diamine (4b)**

yellow solid, yield 93%, m.p. 186-188°C, IR (KBr, ν , cm^{-1}): 3318 (N-H Str.), 3216 (N-H Str.), 3026 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.800 (s, 3H, CH₃), 6.900-8.003 (m, 12H, Ar-H), 10.412 (s, 1H, NH), 10.620 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 27.12 (Ar-CH₃), 107.25, 108.44, 109.77, 110.59, 111.30, 112.60, 114.60, 115.10, 118.20, 119.18, 121.40, 122.36, 123.22, 124.27, 126.73, 128.42, 130.65, 131.65, 134.50, 137.33, 138.39(Ar-C). MS(M⁺): 415.09, Anal. Calcd. for C₂₂H₁₇N₅S₂ (415.53): C 63.59, H 4.12, N 16.85 Found: C 63.80, H 4.15, N 16.30%.

***N*²-(4-methoxyphenyl)-*N*³-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4c)**

yellow solid, yield 90%, m.p. 173-175°C, IR (KBr, ν , cm^{-1}): 3313 (N-H Str.), 3223 (N-H Str.), 3010 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 3.725 (s, 3H, OCH₃), 7.120-8.321 (m, 12H, Ar-H), 10.133 (s, 1H, NH), 10.236 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 58.00 (OCH₃), 106.13, 107.20, 108.11, 110.54, 112.36, 113.28, 114.20, 116.72, 118.33, 120.00, 121.22, 122.14, 123.31, 124.18, 125.73, 128.64, 130.30, 132.12, 133.56, 136.30, 137.98 (Ar-C). MS(M⁺): 431.09, Anal. Calcd. for C₂₂H₁₇N₅OS₂ (431.53): C 61.23, H 3.97, N 16.23 Found: C 61.12, H 4.02, N 16.70%.

***N*²-(4-fluorophenyl)-*N*³-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4d)**

yellow solid, yield 88%, m.p. 162-164°C, IR (KBr, ν , cm^{-1}): 3318 (N-H Str.), 3216 (N-H Str.), 3028 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 6.998-7.846 (m, 12H, Ar-H), 10.648 (s, 1H, NH), 10.715 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 108.15, 109.16, 110.23, 112.00, 113.66, 114.03, 115.28, 116.30, 118.00, 119.36, 120.22, 122.00, 123.30, 124.21, 126.20, 127.36, 128.00, 129.60, 131.02, 133.06, 135.24(Ar-C). MS(M⁺): 419.07, Anal. Calcd. for C₂₁H₁₄FN₅S₂ (419.5): C 60.13, H 3.36, N 16.69 Found: C 60.35, H 3.42, N 16.77%.

***N*²-(4-chlorophenyl)-*N*³-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4e)**

yellow solid, yield 88%, m.p. 190-192°C, IR (KBr, ν , cm^{-1}): 3344 (N-H Str.), 3248 (N-H Str.), 3001 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 7.120-8.300 (m, 12H, Ar-H), 10.123 (s, 1H, NH), 10.236 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 108.63, 109.56, 111.13, 112.25, 113.78, 114.55, 115.35, 116.65, 118.12, 119.93, 120.88, 122.00, 122.90, 123.11, 125.10, 126.33, 128.01, 129.45, 131.20, 132.15, 134.14 (Ar-C). MS(M⁺): 435.04, Anal. Calcd. for C₂₁H₁₄ClN₅S₂ (435.95): C 57.86, H 3.24, N 16.06 Found: C 57.50, H 3.36, N 16.20%.

***N*²-(4-bromophenyl)-*N*³-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4f)**

yellow solid, yield 85%, m.p. 161-163°C, IR (KBr, ν , cm^{-1}): 3312 (N-H Str.), 3233 (N-H Str.), 3016 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 6.888-7.894 (m, 12H, Ar-H), 10.325 (s, 1H, NH), 10.423 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 106.32, 108.22, 110.21, 111.20, 130.00, 114.65, 115.20, 116.70, 118.01, 119.20, 121.00, 122.36, 1124.77, 125.88, 127.80, 129.36, 132.20, 133.54, 135.10, 137.11, 139.18(Ar-C). MS(M⁺): 478.99, Anal. Calcd. for C₂₁H₁₄BrN₅S₂ (480.40): C 60.29, H 2.94, N 14.58 Found: C 60.43, H 3.03, N 14.70%.

4-(2-(4-(thiophen-2-yl)thiazol-2-ylamino)quinoxalin-3-ylamino)phenol (4g)

yellow solid, yield 84%, m.p. 158-160°C, IR (KBr, ν , cm^{-1}): 3300 (N-H Str.), 3211 (N-H Str.), 3040 (Ar C-H Str.), ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm): δ 4.856 (s, 1H, OH), 7.125-8.136 (m, 12H, Ar-H), 10.236 (s, 1H, NH), 10.312 (s, 1H, NH). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm): 105.32, 107.12, 109.26, 110.32, 112.60, 114.75, 115.50, 116.83, 118.41, 119.33, 121.17, 122.84, 124.37, 125.22, 126.30, 129.39, 131.22, 133.66, 134.12, 135.15, 138.17(Ar-C). MS(M^+): 417.07, Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{N}_5\text{OS}_2$ (417.51): C 60.41, H 3.62, N 16.77 Found: C 60.58, H 3.70, N 16.17%.

 N^2 -(4-nitrophenyl)- N^3 -(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4h)

yellow solid, yield 92%, m.p. 173-175°C, IR (KBr, ν , cm^{-1}): 3327(N-H Str.), 3241 (N-H Str.), 3048 (Ar C-H Str.), ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm): δ 7.201-8.320 (m, 12H, Ar-H), 10.336 (s, 1H, NH), 10.408 (s, 1H, NH). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm): 107.88, 108.90, 110.35, 111.37, 112.98, 114.40, 115.26, 116.78, 118.22, 119.35, 120.45, 122.55, 124.63, 125.72, 128.10, 129.25, 131.40, 132.55, 135.88, 137.20, 138.65(Ar-C). MS(M^+): 446.06, Anal. Calcd. for $\text{C}_{21}\text{H}_{14}\text{N}_6\text{O}_2\text{S}_2$ (446.50): C 56.49, H 3.16, N 18.82 Found: C 56.30, H 3.33, N 18.62%

 N^2 -(4-aminophenyl)- N^3 -(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4i)

yellow solid, yield 80%, m.p. 166-168°C, IR (KBr, ν , cm^{-1}): 3326 (N-H Str.), 3211 (N-H Str.), 3014 (Ar C-H Str.), ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm): δ 7.200-8.365 (m, 12H, Ar-H), 10.123 (s, 1H, NH), 10.220 (s, 1H, NH), 10.700 (s, 2H, NH_2). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm): 109.31, 111.00, 112.48, 113.54, 115.24, 116.44, 117.41, 119.05, 120.33, 122.27, 124.50, 126.40, 128.73, 130.52, 132.33, 135.24, 137.88, 139.61, 142.01, 143.98, 145.00(Ar-C). MS(M^+): 416.09, Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{N}_6\text{S}_2$ (416.52): C 60.55, H 3.87, N 20.18 Found: C 60.43, H 3.70, N 20.50%.

 N^2 -(4-(thiophen-2-yl)thiazol-2-yl)- N^3 -*m*-tolylquinoxaline-2,3-diamine (4j)

yellow solid, yield 70%, m.p. 151-153°C, IR (KBr, ν , cm^{-1}): 3290 (N-H Str.), 3216 (N-H Str.), 3015 (Ar C-H Str.), ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm): δ 2.563 (s, 3H, CH_3), 6.990-7.800 (m, 12H, Ar-H), 10.300 (s, 1H, NH), 10.412 (s, 1H, NH). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm): 26.47 (Ar- CH_3), 109.42, 111.56, 112.53, 114.44, 115.36, 116.28, 117.91, 118.06, 120.13, 122.57, 124.33, 125.30, 128.66, 130.14, 132.20, 135.54, 136.78, 138.71, 141.25, 142.16, 144.01(Ar-C). MS(M^+): 415.09, Anal. Calcd. for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{S}_2$ (415.53): C 63.59, H 4.12, N 16.85 Found: C 63.80, H 4.22, N 16.33%.

6-methyl- N^3 -phenyl- N^2 -(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4k)

yellow solid, yield 89%, m.p. 130-132°C, IR (KBr, ν , cm^{-1}): 3280 (N-H Str.), 3225 (N-H Str.), 3013 (Ar C-H Str.), ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm): δ 2.520 (s, 3H, Ar- CH_3), 6.800-7.920 (m, 12H, Ar-H), 10.302 (s, 1H, NH), 10.613 (s, 1H, NH). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm): 23.16 (Ar- CH_3), 24.99 (Ar- CH_3), 108.20, 109.36, 112.30, 113.00, 114.06, 115.32, 117.18, 119.28, 121.33, 123.96, 126.50, 128.00, 129.23, 132.20, 133.00, 135.60, 137.88, 139.00, 140.12, 142.00, 143.16(Ar-C). MS(M^+): 415.09, Anal. Calcd. for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{S}_2$ (415.53): C 63.59, H 4.12, N 16.85 Found: C 63.44, H 4.17, N 16.52%.

6-methyl- N^2 -(4-(thiophen-2-yl)thiazol-2-yl)- N^3 -*p*-tolylquinoxaline-2,3-diamine (4l)

yellow solid, yield 90%, m.p. 142-148°C, IR (KBr, ν , cm^{-1}): 3318 (N-H Str.), 3250 (N-H Str.), 3030 (Ar C-H Str.), ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm): δ 2.302 (s, 3H, Ar- CH_3), 2.415 (s, 3H, Ar- CH_3), 7.120-8.100 (m, 11H, Ar-H), 10.349 (s, 1H, NH), 10.500 (s, 1H, NH). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm): 26.90 (Ar- CH_3), 57.36 (OCH_3), 107.10, 108.56, 110.20, 112.01, 113.05, 115.36, 117.25, 119.32, 121.44, 123.24, 126.30, 128.19, 129.52, 132.21, 133.36, 134.10, 135.89, 138.60, 140.35, 141.12, 143.96(Ar-C). MS(M^+): 429.11, Anal. Calcd. for $\text{C}_{23}\text{H}_{19}\text{N}_5\text{S}_2$ (429.56): C 64.31, H 4.46, N 16.30 Found: C 64.42, H 4.70, N 16.48%.

***N*³-(4-methoxyphenyl)-6-methyl-*N*²-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4m)**

yellow solid, yield 91%, m.p. 136-138 °C, IR (KBr, ν , cm^{-1}): 3344 (N-H Str.), 3223 (N-H Str.), 3012 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.301 (s, 3H, Ar-CH₃), 3.412 (s, 3H, OCH₃), 6.921-7.900 (m, 11H, Ar-H), 10.256 (s, 1H, NH), 10.562 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 24.40 (Ar-CH₃), 106.22, 109.35, 112.18, 113.23, 114.49, 115.12, 117.33, 119.91, 121.25, 123.62, 126.61, 127.10, 128.20, 131.40, 133.15, 135.45, 137.18, 139.24, 140.16, 141.17, 142.15(Ar-C). MS(M⁺): 445.10, Anal. Calcd. for C₂₃H₁₉N₅OS₂ (445.56): C 62.00, H 4.30, N 15.72 Found: C 62.20, H 4.00, N 15.80%.

***N*³-(4-fluorophenyl)-6-methyl-*N*²-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4n)**

yellow solid, yield 85%, m.p. 123-125 °C, IR (KBr, ν , cm^{-1}): 3298 (N-H Str.), 3314 (N-H Str.), 3001 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.600 (s, 3H, Ar-CH₃), 7.100-8.326 (m, 11H, Ar-H), 10.112 (s, 1H, NH), 10.236 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 27.00 (Ar-CH₃), 110.13, 112.05, 114.31, 115.06, 116.28, 117.00, 119.27, 121.04, 123.25, 125.37, 128.61, 130.66, 132.05, 133.90, 135.22, 137.18, 139.14, 142.21, 143.02, 144.03, 146.10(Ar-C). MS(M⁺): 433.08, Anal. Calcd. for C₂₂H₁₆FN₅S₂ (433.52): C 60.95, H 3.72, N 16.15 Found: C 60.80, H 3.90, N 16.02%.

***N*³-(4-chlorophenyl)-6-methyl-*N*²-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4o)**

yellow solid, yield 84%, m.p. 120-122 °C, IR (KBr, ν , cm^{-1}): 3294 (N-H Str.), 3246 (N-H Str.), 3053 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.315 (s, 3H, Ar-CH₃), 6.895-7.888 (m, 11H, Ar-H), 10.259 (s, 1H, NH), 10.400 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 26.59 (Ar-CH₃), 111.15, 112.35, 114.51, 115.82, 116.34, 117.36, 119.61, 121.32, 123.44, 124.17, 127.51, 130.39, 132.05, 133.10, 135.82, 137.98, 139.22, 142.78, 143.25, 143.90, 145.10(Ar-C). MS(M⁺): 449.05, Anal. Calcd. for C₂₂H₁₆ClN₅S₂ (449.98): C 58.72, H 3.58, N 15.56 Found: C 58.78, H 3.72, N 15.40%.

***N*³-(4-bromophenyl)-6-methyl-*N*²-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4p)**

yellow solid, yield 84%, m.p. 136-138 °C, IR (KBr, ν , cm^{-1}): 3308 (N-H Str.), 3256 (N-H Str.), 3016 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.515 (s, 3H, Ar-CH₃), 7.120-8.000 (m, 11H, Ar-H), 10.369 (s, 1H, NH), 10.546 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 23.96 (Ar-CH₃), 107.43, 108.56, 110.61, 112.34, 114.04, 116.38, 117.20, 119.21, 120.64, 122.07, 124.38, 126.34, 127.09, 129.87, 131.25, 133.44, 135.64, 137.28, 139.24, 141.27, 142.69(Ar-C). MS(M⁺): 493.00, Anal. Calcd. for C₂₂H₁₆BrN₅S₂ (494.43): C 53.44, H 3.26, N 14.16 Found: C 53.20, H 3.35, N 14.33%.

4-(2-(4-(thiophen-2-yl)thiazol-2-ylamino)-6-methylquinoxalin-3-ylamino)phenol (4q)

yellow solid, yield 86%, m.p. 127-129 °C, IR (KBr, ν , cm^{-1}): 3326 (N-H Str.), 3247 (N-H Str.), 3018 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.125 (s, 3H, Ar-CH₃), 4.800 (s, 1H, OH), 7.084-8.125 (m, 11H, Ar-H), 10.365 (s, 1H, NH), 10.654 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 25.64 (Ar-CH₃), 107.66, 109.46, 110.51, 112.24, 113.64, 115.19, 117.21, 118.61, 120.55, 122.97, 124.65, 125.14, 127.98, 129.88, 131.15, 133.24, 135.24, 133.18, 136.04, 139.37, 141.68(Ar-C). MS(M⁺): 431.09, Anal. Calcd. for C₂₂H₁₇N₅OS₂ (431.53): C 61.23, H 3.97, N 16.23 Found: C 61.45, H 4.07, N 16.10%.

6-methyl-*N*³-(4-nitrophenyl)-*N*²-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4r)

yellow solid, yield 90%, m.p. 119-121 °C, IR (KBr, ν , cm^{-1}): 3312 (N-H Str.), 3216 (N-H Str.), 3017 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm): δ 2.312 (s, 3H, Ar-CH₃), 6.985-8.045 (m, 11H, Ar-H), 10.100 (s, 1H, NH), 10.365 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm): 23.17 (Ar-CH₃), 107.55, 108.01, 109.51, 110.34, 113.15, 115.78, 116.90, 119.71, 120.54, 122.08,

124.54, 125.31, 126.01, 128.81, 129.20, 132.41, 135.70, 137.15, 139.22, 140.15, 141.77(Ar-C). MS(M⁺): 460.08, Anal. Calcd. for C₂₂H₁₆N₆O₂S₂ (460.53): C 57.38, H 3.50, N 18.25 Found: C 57.46, H 3.62, N 17.90%.

N³-(4-aminophenyl)-6-methyl-N²-(4-(thiophen-2-yl)thiazol-2-yl)quinoxaline-2,3-diamine (4s)
yellow solid, yield 79%, m.p. 133-135 °C, IR (KBr, ν, cm⁻¹): 3313 (N-H Str.), 3250 (N-H Str.), 3033 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm): δ 2.365 (s, 3H, Ar-CH₃), 7.005-8.100 (m, 11H, Ar-H), 10.125 (s, 1H, NH), 10.200 (s, 1H, NH), 10.600 (s, 1H, NH₂). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm): 26.34 (Ar-CH₃), 113.21, 114.26, 115.67, 117.18, 118.90, 121.40, 123.64, 125.28, 126.40, 128.03, 130.69, 131.15, 132.40, 135.16, 137.14, 138.90, 141.24, 142.33, 144.00, 145.02, 146.21(Ar-C). MS(M⁺): 430.10, Anal. Calcd. for C₂₂H₁₈N₆S₂ (430.55): C 61.37, H 4.21, N 19.52 Found: C 61.48, H 4.55, N 19.20%.

6-methyl-N²-(4-(thiophen-2-yl)thiazol-2-yl)-N³-m-tolylquinoxaline-2,3-diamine (4t)
yellow solid, yield 73%, m.p. 140-142 °C, IR (KBr, ν, cm⁻¹): 3286 (N-H Str.), 3241 (N-H Str.), 3018 (Ar C-H Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm): δ 2.300 (s, 3H, Ar-CH₃), 2.456 (s, 3H, Ar-CH₃), 7.00-8.123 (m, 11H, Ar-H), 10.656 (s, 1H, NH), 10.700 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm): 24.19 (Ar-CH₃), 27.18 (Ar-CH₃), 112.20, 113.21, 114.66, 117.12, 119.10, 122.42, 124.10, 125.66, 126.14, 128.70, 130.1, 131.1, 132.63, 135.34, 137.18, 138.10, 141.39, 142.73, 143.01, 144.01, 145.22(Ar-C). MS(M⁺): 429.11, Anal. Calcd. for C₂₃H₁₉N₅S₂ (429.56): C 64.31, H 4.46, N 16.30 Found: C 64.66, H 4.30, N 16.18%.

4. CONCLUSION

In this article, we report the synthesis of three structurally correlated heterocyclic candidates, i.e., quinoxaline, thiophene and thiazole derivatives. The engaged synthetic strategy allows the construction of relatively complicated nitrogen and oxygen carrying heterocyclic system as well as the introduction of various aromatic substitutions into 3-position of quinoxaline system.

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