Indian Journal of Chemistry
Vol. 61, April 2022, pp. 438-441

Synthesis characterization and docking studies of 1,3,4-thiadiazole and 1,2,4-triazole containing 3-methoxyquinoxalines

Muralidhar Reddy Rachala[a], Laxminarayana Eppakayala[b], Kishre Kumar Ananthoju[c] & Thirumala Chary Maringanti*[c]

[a] Vidya Jyothi Institute of Technology, Aziz Nagar Gate, Hyderabad 500 075, India

[b] Sreenidhi Institute of Science and Technology (Autonomous), Ghatkesar 501 301, India

[c] Jawaharlala Nehru Techological University Hyderabad, Kukatpally, Hyderabad 500 085, India

E-mail: mtcharya@yahoo.com

Received 12 June 2020; accepted (revised) 8 November 2021

A simple method for the syntheses of quinoxalines starting from ethyl 3-methoxyquinoxaline-2-carboxylate using commercially available is described. The synthesized compounds were characterized by spectral analysis. Docking studies for these compounds is also presented.

Keywords: Quinoxaline, spectral analysis, docking studies, synthesis

Nitrogen containing heterocycles are frequently found in privileged structures (pharmacophores)[1-3] but their incorporation sometimes possess special problems (multistep sequences, lack of generality, preparation from acyclic precursors, *etc*.); thus, only a limited number of strategies have been successfully applied in the synthesis of heterocyclic scaffolds.

The chemistry of quinoxalines has attracted considerable attention in the last decade for their chemical reactivity[4,5] biological properties[6,7], and materials applications[8,9]. They exhibit a wide spectrum of biological activities such as antibacterial[10], antifungal[11], and anticancer[12]. Moreover, quinoxaline ring is a part of various antibiotics, such as Echinomycin, Levomycin and Actinoleutin that are known to inhibit growth of gram positive bacteria and to be active against various tumors. Also, thiadiazoline moieties are present in the structure of various bioactive molecules found to act as anti-inflammatory[13], analgesic[14] and allosteric modulator[15].

Experimental Section

Thin layer chromatography was run on silica gel-G and visualization were done using UV light or iodine. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury plus 400 MHz and 100 MHz instruments respectively in DMSO-d_6 solvent using trimethylsilane as internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Jeol-JMS D-300 spectrometer was used to record mass spectra.

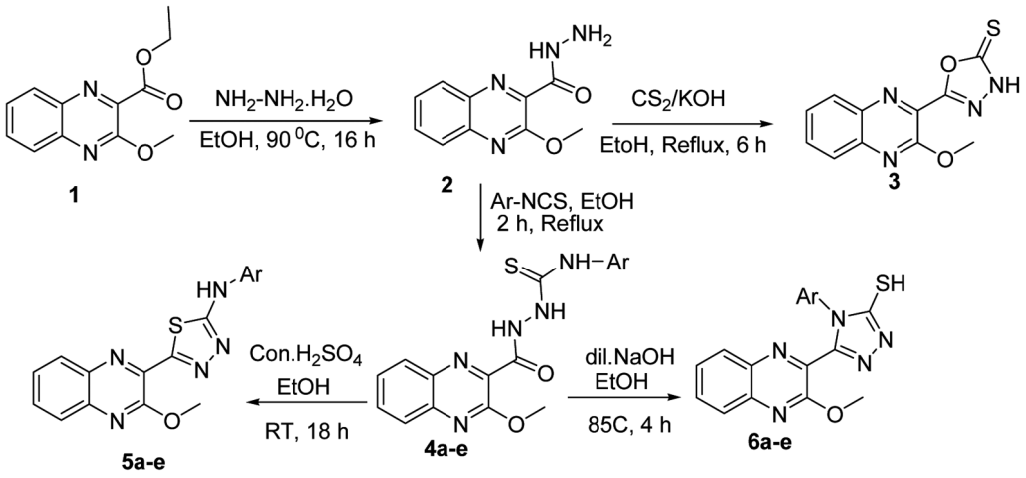
Result and Discussion

Chemistry

The target compounds were prepared as outlined in Scheme I. The compound ethyl 3-methoxy-quinoxaline-2-carboxylate **1** was reacted with hydrazine hydrate in presence EtOH at 90°C for 16 h and afford with 83% yield of compound **2**. Obtained Compound **2** was treated with CS_2 and KOH in EtOH at reflux temperature for 6 h to afford compound **3** with 85% of yield. When compound **2** was reacted with Ar-NCS in EtOH at refux temperature for 2 h compound **4a-e** was formed and yields were 89-94%. This obtained compound **4a-e** was under go cyclisation to get compound **5a-e** in presence of Con. H_2SO_4 in EtOH at RT for 18 h various good yields. In another hand Compound **4a-e** was reacted with dil.NaOH in presence of EtOH at RT and formed corresponding cyclised product **6a-e** with excellent yields.

Docking studies

The protein 1jff (tubulin) was downloaded from RSC PDB and was docked. Compound **5a** was the



Ar= Phenyl, 4-Chlorophenyl, 2-Chlorophenyl, 4-Fluorophenyl, 4-Methoxyphenyl

Scheme I

Table I — Thermodynamic parameters

Rank	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	vdW + Hbond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Frequency	Interact. Surface	Download
1.	−5.33 kcal/mol	123.56 uM	−6.58 kcal/mol	−0.03 kcal/mol	−6.61 kcal/mol	50%	551.867	downloa

most efficient for inhibiting the structural protein. Least inhibition was seen by the compound **5a** as shown in Table I and Table II. The major amino acids which were involved in the binding of the compounds were tyrosine, asparagines, alanine, glutamine, glutamic acid, leucine and serine (Figure 1).

Synthesis of 3-methoxyquinoxaline-2-carbohydrazide, 2

To a stirred solution of ethyl 3-methoxyquinoxaline-2-carboxylate **1** (10 g, 0.0434 mol) in EtOH (100 mL) at RT was added hydrazine hydrate (3.25 g, 0.0651 mol)) and stirred the reaction at 85°C for 18 h. After completion of reaction, cooled the reaction mixture to RT and evaporated the solvent. Residue was poured into water and filtered the formed precipitate to afford 3-methoxyquinoxaline-2-carbohydrazide (**2**) as brown color solid; Yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23(brs, 1H), 8.01(d, 2H, *J*=8.0Hz), 7.70(t, 2H, *J*=8.0Hz, 4.0Hz), 6.61(brs, 2H), 3.72(S, 3H); ESI–MS: *m/z* 218.9 $(M+H)^+$.

Synthesis of 5-(2-alkoxy quinoxalin-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione, 3

To a suspension of KOH(3.85 g, 0.0688 mol) in EtOH (50 mL) was added solution and CS_2 (3.48 g, 0.0458 mol) as added drop wise followed by solution of compound 2a (5 g, 0.0229 mol) and stirred the reaction at reflux temperature for 6 h. After completion of reaction, cooled the reaction mixture to RT and evaporated the solvent. Residue was poured into water and filtered the formed precipitate to afford of 5-(2-alkoxy quinoxalin-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione. Yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11(d, 2H, *J*=8.0Hz), 7.80(t, 2H, *J*=8.2Hz, 4.0Hz), 7.41(brs, 1H), 3.78 (S, 3H); ESI–MS: *m/z* 260.9 $(M+H)^+$.

Synthesis of 3-methoxyquinoxaline-2-yl-4-arylthiosemicarbazides, 4a-e

Solution of aryl isothiocyanate (22.9 mmol) in ethanol (10 mL) was added to a solution of carboxylic acid hydrazide (5 g, 22.9 mmol) in ethanol (40 mL). The mixture was thoroughly mixed, left to stand for 1 h at RT, and heated for 2 h under reflux. After cooling, the precipitate was filtered off, dried, and recrystallized from ethanol or aqueous ethanol.

3-Methoxyquinoxaline-2-yl-4-phenylthiosemicarbazide, 4a: Yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31(brs, 1H), 8.02(d, 2H, *J*=8.01Hz), 7.72 (t, 2H, *J*=8.0Hz), 7.42(m, 3H), 7.10(d, 2H, *J*=7.8Hz), 6.62(brs,1H) 3.75(S, 3H); 2.90(S, 1H); ESI–MS: *m/z* 353.9 $(M+H)^+$.

3-Methoxyquinoxaline-2-yl-4-(4-chlorophenyl) thiosemicarbazide, 4b: Yield: 74%. ^{1}H NMR (400 MHz,

Table II — Molecular interactions

Hydrogen bonds	Polar			pi-pi			Other					
	N2 () [*2.82*]	–	ASP53 (*O*)	H5 () [*2.85*]	–	GLU67 (*OE2*)	C9 () [*3.68*]	–	TYR55 (*CD1*, *CE1*)	N3 () [*3.37*]	–	GLN54 (*CB*)
	N4 () [*2.73*]	–	TYR55 (*CD1*, *CE1*, *O*)				C16 () [*3.90*]	–	TYR55 (*CE2*)	N4 () [*3.67*]	–	GLN54 (*CB*)
	N5 () [*2.87*]	–	GLU67 (*CD*, *OE2*)							N3 () [*3.21*]	–	TYR55 (*CD1*, *CE1*)
										N2 () [*3.68*]	–	TYR55 (*CD1*)
										C14 () [*3.45*]	–	LYS56 (*CD*, *NZ*)
										C13 () [*3.63*]	–	LYS56 (*NZ*)
										C11 () [*3.38*]	–	GLU67 (*CD*, *CG*, *OE2*)
										C15 () [*3.80*]	–	GLU67 (*CG*)
										C16 () [*3.40*]	–	GLU67 (*CG*, *OE2*)
										H5 () [*3.38*]	–	GLU67 (*CD*)
										C10 () [*3.20*]	–	GLU67 (*OE2*)
										S1 () [*3.10*]	–	GLU67 (*OE2*)

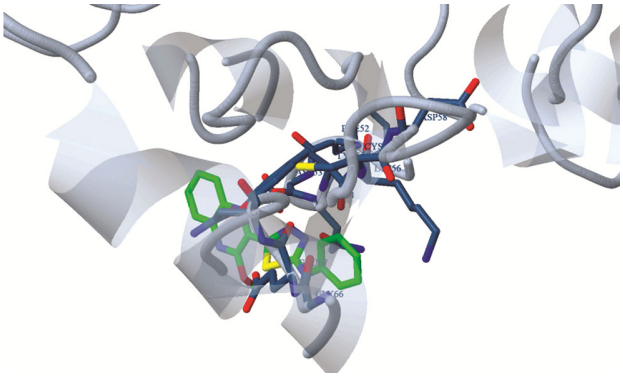


Figure 1 — Bonding involved in the binding of the ligand to the enzyme

DMSO-d_6): δ 8.30 (brs, 1H), 8.01(d, 2H, *J*=8.01Hz), 7.70 (t, 2H, *J*=8.0Hz), 7.40(d, 2H), 7.11 (d, 2H,), 6.60 (brs,1H) 3.73 (S, 3H); 2.91(S, 1H); ESI–MS: *m/z* 360 $(M+H)^+$.

3-Methoxyquinoxaline-2-yl-4-(2-chlorophenyl) thiosemicarbazide, 4c: Yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31(brs, 1H), 8.03 (d, 2H, *J*=8.01Hz), 7.71 (t, 2H, *J*=8.0Hz), 7.41(d, 2H), 7.12 (d, 2H,), 6.61 (brs,1H) 3.72 (S, 3H); 2.90(S, 1H); ESI–MS: *m/z* 360 $(M+H)^+$.

3-Methoxyquinoxaline-2-yl-4-(4-chlorophenyl) thiosemicarbazide, 4d: Yield: 76%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (brs, 1H), 8.03 (d, 2H, *J*=8.01Hz), 7.72 (t, 2H, *J*=8.0Hz), 7.43 (d, 2H), 7.13 (d, 2H,), 6.62 (brs,1H) 3.74 (S, 3H); 2.90(S, 1H); ESI–MS: *m/z* 344 $(M+H)^+$.

3-Methoxyquinoxaline-2-yl-4-(4-methoxyphenyl) thiosemicarbazide, 4e: Yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (brs, 1H), 8.01 (d, 2H, *J*=8.01Hz), 7.72 (t, 2H, *J*=8.0Hz), 7.41 (d, 2H), 7.12 (d, 2H,), 6.61 (brs,1H) 3.72 (S, 3H), 3.06 (S, 3H), 2.91 (S, 1H); ESI–MS: *m/z* 356 $(M+H)^+$.

Synthesis of 5-(2-methoxyquinoxalin-3-yl)-N-aryl-1,3,4-thiadiazol-2-amine, 5a-e

To a suspension of 2-methoxyquinoxaline- aryl thiosemicarbazide (**2** g, 6.3 mmol) in EtOH (20 mL) at 0°C was added solution and Con.H_2SO_4 (2 mL) as added drop wise followed and stirred the reaction at RT for 18 h. After completion of reaction, benzene

was decanted; crude residue was washed with hexane and the formed precipitate filtered to afford 5-(2-alkoxy quinoxalin-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione.

5-(2-Methoxyquinoxalin-3-yl)-N-phenyl-1,3,4-thiadiazol-2-amine, 5a: Yield: 88%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22(d, 2H, *J*=8.0Hz), 8.01(brs, 1H), 7.72(t, 2H), 7.42(m, 3H), 7.05 (d, 2H, *J*=8.2Hz), 3.78(S, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.01, 154.2, 142.1, 140, 138.01, 132.4, 131.5, 128.2, 126.3, 123.01, 120.2, 116.3, 57.5; ESI–MS: *m/z* 335.8 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-N-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine, 5b: Yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 2H, *J*=8.0Hz), 8.02 (brs, 1H), 7.71 (d, 2H), 7.41 (d, 2H), 7.04 (d, 2H, *J*=8.2Hz), 3.77 (S, 3H); ESI–MS: *m/z* 370 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-N-(2-chlorophenyl)-1,3,4-thiadiazol-2-amine, 5c: Yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, 2H, *J*=8.0Hz), 8.01 (brs, 1H), 7.73 (d, 2H), 7.44 (d, 2H), 7.02 (d, 2H, *J*=8.2Hz), 3.74 (S, 3H); ESI–MS: *m/z* 370.3 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-N-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine, 5d: Yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 2H, *J*=8.0Hz), 8.02 (brs, 1H), 7.72 (d, 2H), 7.43 (d, 2H), 7.03 (d, 2H, *J*=8.2Hz), 3.75 (S, 3H); ESI–MS: *m/z* 354.1 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-N-(4-methoxy phenyl)-1,3,4-thiadiazol-2-amine, 5e: Yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (d, 2H, *J*=8.0Hz), 8.03 (brs, 1H), 7.71 (d, 2H), 7.44 (d, 2H), 7.02 (d, 2H, *J*=8.2Hz), 3.11 (S, 3H), 3.73 (S, 3H); ESI–MS: *m/z* 366.2 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-4-aryl-4*H*-1,2,4-triazole-3-thiol, 6a-e

To a stirred solution of ethyl 3-methoxy quinoxaline-2-carboxylate 1 (2 g, 6.32 mmol) in EtOH (20 mL) at RT was added dil.NaOH (2 mL, 50% solution) and the reaction stirred at reflux temperature 85°C for 4 h on a boiling water bath, cooled, and acidified with dil.HCl acid (1:1) to *p*H (2–3), and the precipitate was filtered off, washed with water, dried, and recrystallized from appropriate solvent.

5-(2-Methoxyquinoxalin-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol, 6a: Yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, 2H, *J*=7.8Hz), 7.70 (t, 2H, *J*=7.8Hz, 3.8Hz), 7.42(m, 5H), 3.81(S, 3H), 2.81(S, 1H); ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 169.01, 155.1, 146.01, 144.5, 142.5, 142.1, 138.2, 137.8, 134.4, 132.2, 128.02, 126.2, 55.8; ESI–MS: *m/z* 335.9 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-4-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol, 6b: Yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 2H, *J*=7.8Hz), 7.71 (t, 2H, *J*=7.8Hz, 3.8Hz), 7.61(d, 2H), 7.22 (d, 2H), 3.81 (S, 3H), 2.81 (S, 1H); ESI–MS: *m/z* 370.2 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-4-(2-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol, 6c: Yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 2H, *J*=7.8Hz), 7.71 (t, 2H, *J*=7.8Hz, 3.8Hz), 7.60(d, 2H), 7.21 (d, 2H), 3.81 (S, 3H), 2.81 (S, 1H); ESI–MS: *m/z* 370.4 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-4-(4-fluorophenyl)-4*H*-1,2,4-triazole-3-thiol, 6d: Yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, 2H, *J*=7.8Hz), 7.73 (t, 2H, *J*=7.8Hz, 3.8Hz), 7.62(d, 2H), 7.21 (d, 2H), 3.84 (S, 3H), 2.82 (S, 1H); ESI–MS: *m/z* 354 $(M+H)^+$.

5-(2-Methoxyquinoxalin-3-yl)-4-(4-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol, 6e: Yield: 86%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 2H, *J*=7.8Hz), 7.71 (t, 2H, *J*=7.8Hz, 3.8Hz), 7.62(d, 2H), 7.23 (d, 2H), 3.81 (S, 3H), 2.80 (S, 1H); ESI–MS: *m/z* 366.4 $(M+H)^+$.

References

1 Wess G, Urmann N & Sickenberger B, *Angew Chem Int Ed*, 40 (2001) 3341.
2 Muegge I, *Chem Eur J*, 8 (2002) 1977.
3 Anies C, Pancrazi A & Lallemand J, *Tetrahedron Lett*, 35 (1994) 7771.
4 Diaz F R, del Valle M A, Nunez C, Godoy A, Mondaca J L, Toro-Labbe A & Bernede J C, *Polym Bull*, 56 (2006) 155.
5 De Castro S, Chicharro R & Aran V J, *J Chem Soc*, 1 (2002) 790.
6 Carta A, Piras S, Loriga G & Paglietti G, *Mini-Rev Med Chem*, 6 (2006) 1179.
7 Waring M J, Ben-Hadda T, Kotchevar A T, Ramdani A, Touzani R, Elkadiri S, Hakkou A & Bouakka M & Ellis T, *Molecules*, 7 (2002) 641.
8 Chao W S & Chen C T, *Society Information Display Taipei Chapter*, *Taipei*, (2007) p.802.
9 Chen C T, Lin J S, Moturu M, Lin Y W, Yi W, Tao Y T & Chien C H, *Chem Commun*, 3980 (2005).
10 Badran M M, Moneer A A, Refaat H M & El-Malah A, *J Chin Chem Soc*, 54 (2007) 469.
11 Ganapaty S, Ramalingam P & Rao C B, *Indian J Heterocycl Chem*, 16 (2007) 283.
12 Amin K M, Ismail M M F, Noaman E, Soliman D H & Ammar Y A, *Bioorg Med Chem*, 14 (2006) 6917.
13 Ventatesh P & Pandeya S N, *J Chem*, 6 (2009) 495.
14 Hafez H N, Hegab M I, Ahmed-Farag I S & El-Gazzar A B A, *Bioorg Med Chem Lett*, 18 (2008) 4538.
15 Castro A, Castano T, Encinas A, Porcal W & Gill C, *Bioorg Med Chem*, 14 (2006) 1644.