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AN EFFICIENT SYNTHESIS OF (5-(3-HYDROXYQUINOXALIN-2-YL)-1, 3, 4-THIADIAZOL-2-YL) BENZAMIDES AND (3-(3-HYDROXYQUINOXALIN-2-YL)-5-MERCAPTO-4H-1, 2, 4-TRIAZOL-4-YL) (ARYL) METHANONES

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ABSTRACT

Ethyl-3-hydroxyquinoxaline-2-carboxylate is reacted with hydrazine hydrate to offered 3-hydroxyquinoxaline-2-carbohydrazide (**1**), which on condensation with different isothiocyanates gave (2-(3-hydroxyquinoxaline-2-carbonyl) hydrazine-1-carbonothioyl)benzamides (**2**). Compound **2** is treated with conc. H_2SO_4 and NaOH to offered (5-(3-hydroxyquinoxalin-2-yl)-1,3,4-thiadiazol-2-yl)benzamides (**3**) and (3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1,2,4-triazol-4-yl)(aryl)methanones (**4**), respectively. The structures of all synthesized compounds were confirmed by spectral analyses.

Key words: (5-(3-Hydroxyquinoxalin-2-yl)-1, 3, 4-thiadiazol-2-yl) benzamides, (3-(3-Hydroxyquinoxalin-2-yl)-5-mercapto-4H-1, 2, 4-triazol-4-yl) (aryl) methanones, Spectral analyses.

INTRODUCTION

Quinoxaline derivatives are a very important class of nitrogen-containing heterocycles (containing benzene and pyrazine rings in their structure), as they constitute useful intermediates in organic synthesis. This substructure plays an important role as a basic skeleton for the design of a number of heterocyclic compounds with different biological activities, making this type of compounds important in the fields of (a) medicine: antitumor, anticonvulsant, antimalarial, anti-inflammatory, antiamoebic, antioxidant, antidepressant, antiprotozoal, antibacterial, and anti-HIV agents[1-10] and (b) technology:

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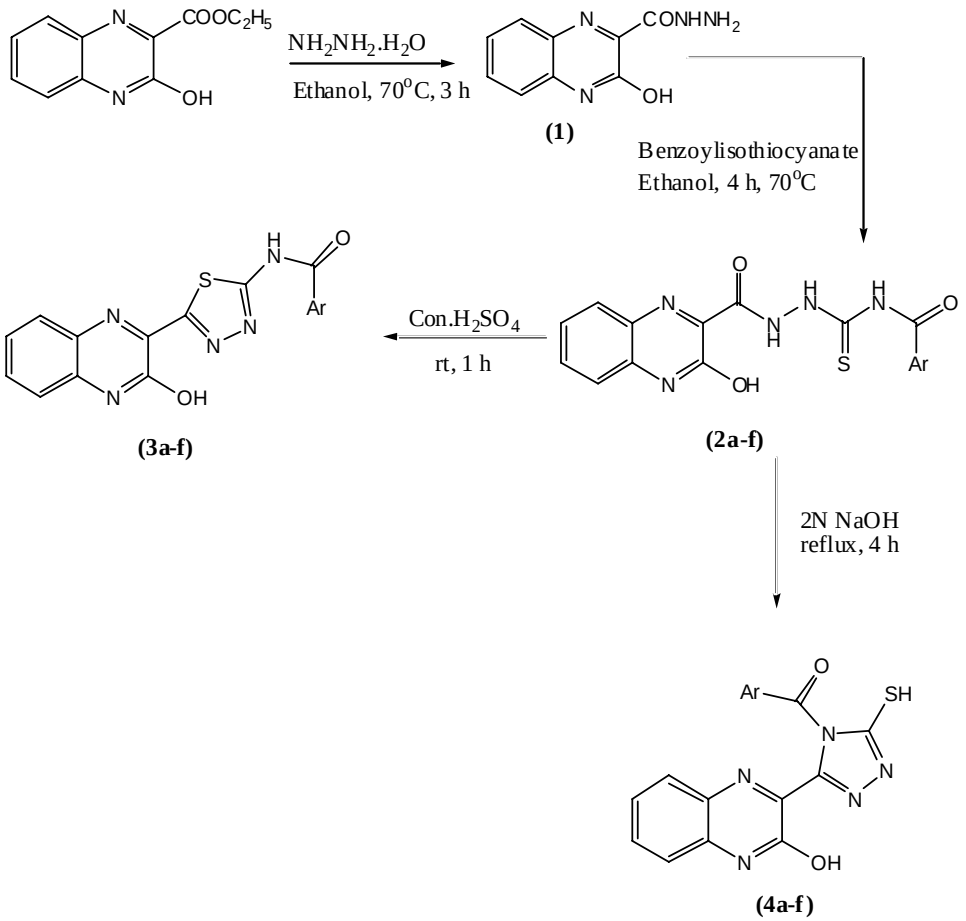
fluorescent dying agents, electroluminescent materials, chemical switches, cavitands, and semiconductors[11-17]. Quinoxalines are important in the pharmaceutical industry, with antibiotics such as echinomycin, levomycin, and actinoleutin having quinoxaline as part of their structure[18].

Derivatives of 1,3,4-thiadiazoles and 1,2,4-triazole are known to exhibit anti-inflammatory, antiviral, analgesic, antimicrobial, anticonvulsant and antidepressant activity, the latter being usually explored by the forced swim test[19-28]. Among the pharmacological profiles of 1,3,4-thiadiazoles and 1,2,4-triazoles, their antimicrobial, anticonvulsant and antidepressant properties seem to be the best documented.



Scheme

Ar = **(a)** Phenyl, **(b)** 4-methoxyphenyl, **(c)** 3,4-dimethoxyphenyl, **(d)** 3,5-bis (trifluoromethyl)phenyl, **(e)** 4- Chloro phenyl, **(f)** Nitro phenyl.

Synthesis of 3-hydroxyquinoxaline-2-carbohydrazide (1)

To a solution of ethyl 3-hydroxyquinoxaline-2-carboxylate (100 mg, 0.45 mmol) in ethanol (5 mL) was added hydrazine hydrate (0.02 mL, 0.45 mmol). Then the reaction mixture was stirred at 70^{o}C for 3 h. Progress of the reaction was monitored by TLC, cooled the mixture to room temperature and the resulting solid was collected by filtration, dried under vacuum pressure to give desired product **(1)** as yellow solid (70 mg, 75%).

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 4.67 (bs, 2H), 7.35-7.39 (m, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 10.04 (bs, 1H), 12.82 (bs, 1H). MS (ESI) 205 m/z $(M + H)^{+}$.

Synthesis of (2-(3-hydroxyquinoxaline-2-carbonyl) hydrazine-1-carbonothioyl) benzamide (2a)

A mixture of 3-hydroxyquinoxaline-2-carbohydrazide (60 mg, 0.29 mmol) and benzoylisothiocyanate (479 mg, 2.9 mmol) in ethanol (25 mL) were stirred at reflux temperature (80^{o}C) for 4 h. After completion of the reaction checked by TLC, the mixture was cooled to room temperature. Then the resulting solid was collected by filtration and dried to furnish compound **(2a)** as a yellow solid (80 mg, 76%).

^{1}H NMR (400 MHz, DMSO-D_6) (2a): (ppm) 7.45-7.48 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.66-7.75 (m, 2H), 7.99-8.02 (m, 3H), 12.0 (bs, 1H), 13.24 (bs, 2H), 13.82 (bs, 1H). MS (ESI) 367.9 m/z $(M + H)^{+}$.

N-(2-(3-hydroxyquinoxaline-2-carbonyl) hydrazine-1-carbonothioyl)-4-methoxy-benzamide (2b)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 3.80 (s, 3H), 7.38 (m, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.60-7.70 (m, 2H), 7.97-8.00 (m, 3H), 12.02 (bs, 1H), 13.22 (bs, 2H), 13.80 (bs, 1H). MS (ESI) 398 m/z $(M + H)^{+}$.

N-(2-(3-hydroxyquinoxaline-2-carbonyl)hydrazine-1-carbonothioyl)-3,4-dimethoxy-benzamide (2c)

^{1}H NMR (400 MHz, DMSO-D_6) (2c): (ppm) 3.82 (s, 3H), 3.85 (s, 3H), 7.38 (m, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.60-7.68 (m, 2H), 7.95-8.00 (m, 3H), 12.00 (bs, 1H), 13.20 (bs, 2H), 13.80 (bs, 1H). MS (ESI) 427.9 m/z $(M + H)^{+}$.

N-(2-(3-hydroxyquinoxaline-2-carbonyl) hydrazine-1-carbonothioyl)-3, 5-bis (trifluoromethyl) benzamide (2d)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.45-7.48 (m, 2H), 7.69-7.78 (m, 2H), 8.02-8.06 (m, 3H), 12.00 (bs, 1H), 13.24 (bs, 2H), 13.82 (bs, 1H). MS (ESI) 504 m/z $(M + H)^+$.

4-chloro-N-(2-(3-hydroxyquinoxaline-2-carbonyl) hydrazine-1-carbonothioyl) benzamide (2e)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.45-7.48 (m, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.64-7.73 (m, 2H), 7.97-8.00 (m, 3H), 12.00 (bs, 1H), 13.23 (bs, 2H), 13.81 (bs, 1H). MS (ESI) 403 m/z $(M + H)^+$.

N-(2-(3-hydroxyquinoxaline-2-carbonyl)hydrazine-1-carbonothioyl)-4-nitrobenzamide (2f)

^{1}H NMR (400 MHz, DMSO-D_6) (2f): (ppm) 7.45-7.48 (m, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.64-7.73 (m, 2H), 7.97-8.00 (m, 1H), 8.20-8.22 (m, 2H), 12.00 (bs, 1H), 13.23 (bs, 2H), 13.81 (bs, 1H). MS (ESI) 412.9 m/z $(M + H)^+$.

Synthesis of (5-(3-hydroxyquinoxalin-2-yl)-1,3,4-thiadiazol-2-yl)benzamide (3a)

To the (2-(3-hydroxyquinoxaline-2-carbonyl)hydrazine-1-carbonothioyl)benzamide (40 mg, 0.10 mmol) was added con. H_2SO_4 (0.02 mL) at room temperature. Then the reaction mixture was stirred at room temperature for 1 h. Progress of the reaction was monitored by TLC, then added ice cold water drop wise and the obtained solid was collected by filtration and dried to give title compound **(3)** as yellow solid (35 mg, 92%).

^{1}H NMR (400 MHz, DMSO-D_6) (3a): (ppm) 7.44 (t, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.64-7.71 (m, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 13.11 (bs, 1H), 13.21 (bs, 1H). MS (ESI) 349.9 m/z $(M+H)^+$.

N-(5-(3-hydroxyquinoxalin-2-yl)-1,3,4-thiadiazol-2-yl)-4-methoxybenzamide (3b)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 3.80 (s, 3H), 7.37 (m, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.62-7.73 (m, 2H), 8.00-8.03 (m, 3H), 13.32 (bs, 1H), 13.86 (bs, 1H). MS (ESI) 380 m/z $(M + H)^+$.

N-(5-(3-hydroxyquinoxalin-2-yl)-1,3,4-thiadiazol-2-yl)-3,4-dimethoxybenzamide (3c)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 3.81 (s, 3H), 3.84 (s, 3H), 7.37 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.62-7.70 (m, 2H), 7.98-8.00 (m, 3H), 13.30 (bs, 2H), 13.86 (bs, 1H). MS (ESI) 409.9 m/z $(M + H)^+$.

N-(5-(3-hydroxyquinoxalin-2-yl)-1, 3, 4-thiadiazol-2-yl)-3, 5-bis (trifluoromethyl) benzamid (3d)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.44-7.48 (m, 2H), 7.73-7.78 (m, 2H), 8.04-8.09 (m, 3H), 13.34 (bs, 2H), 13.88 (bs, 1H). MS (ESI) 486.5 m/z $(M + H)^+$.

4-chloro-N-(5-(3-hydroxyquinoxalin-2-yl)-1, 3, 4-thiadiazol-2-yl)benzamide (3e)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.44-7.48 (m, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.66-7.76 (m, 2H), 7.80-8.00 (m, 3H), 13.33 (bs, 1H), 13.87 (bs, 1H). MS (ESI) 403 m/z $(M+H)^+$.

N-(5-(3-hydroxyquinoxalin-2-yl)-1, 3, 4-thiadiazol-2-yl)-4-nitrobenzamide (3f)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.43-7.48 (m, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.66-7.76 (m, 2H), 7.90-8.00 (m, 1H), 8.20-8.22 (m, 2H), 13.33 (bs, 1H), 13.87 (bs, 1H). MS (ESI) 395 m/z $(M + H)^+$.

Synthesis of (3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1,2,4-triazol-4-yl) (phenyl) methanone (4a)

To the (2-(3-hydroxyquinoxaline-2-carbonyl)hydrazine-1-carbonothioyl)benzamide (40 mg, 0.10 mmol) was added 2N aqs. NaOH solution (1 mL) and the mixture was stirred at 90^Oc for 4 h. After completion of the reaction checked by TLC, the mixture was cooled to 0^OC and added ice cold water. Then adjusted the pH to 4.0 and the resulting solid was collected by filtration, dried to give the title compound **(4a)** as yellow solid (35 mg, 92%).

^{1}H NMR (400 MHz, DMSO-D_6) (4a): (ppm) 7.45-7.48 (m, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.66-7.75 (m, 3H), 8.00-8.02 (m, 3H), 12.02 (s, 1H), 13.42 (bs, 1H). MS (ESI) 349.9 m/z $(M + H)^+$.

(3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1,2,4-triazol-4-yl) (4-methoxyphenyl) methanone (4b)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 3.80 (s, 3H), 7.38 (m, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.60-7.70 (m, 2H), 7.97-8.00 (m, 3H), 12.02 (bs, 1H), 13.98 (bs, 1H). MS (ESI) 380 m/z $(M + H)^+$.

(3,4-dimethoxyphenyl) (3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1, 2, 4-triazol-4-yl) methanone (4c)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 3.82 (s, 3H), 3.85 (s, 3H), 7.38 (m, 1H), 7.42

(t, *J* = 7.2 Hz, 1H), 7.60-7.68 (m, 2H), 7.95-8.00 (m, 3H), 12.00 (bs, 1H), 13.90 (bs, 1H). MS (ESI) 410 m/z $(M + H)^+$.

(3,5-bis(trifluoromethyl)phenyl) (3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1, 2, 4-triazol-4-yl) methanone (4d)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.45-7.48 (m, 2H), 7.69-7.78 (m, 2H), 8.02-8.06 (m, 3H), 12.00 (bs, 1H), 13.92 (bs, 1H). MS (ESI) 485.9 m/z $(M + H)^+$.

(4-chlorophenyl) (3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1, 2, 4-triazol-4-yl) methanone (4e)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.45-7.48 (m, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.64-7.73 (m, 2H), 7.97-8.00 (m, 3H), 12.00 (bs, 1H), 13.92 (bs, 1H). MS (ESI) 384.9 m/z $(M + H)^+$.

(3-(3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1, 2, 4-triazol-4-yl) (4-nitrophenyl) methanone (4f)

^{1}H NMR (400 MHz, DMSO-D_6): (ppm) 7.45-7.48 (m, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.64-7.73 (m, 2H), 7.97-8.00 (m, 1H), 8.20-8.22 (m, 2H), 12.00 (bs, 1H), 13.90 (bs, 1H). MS (ESI) 395 m/z $(M + H)^+$.

RESULTS AND DISCUSSION

The title comopunds of the quinoxalline derivatives are synthesized from introducing the hydrazine group to the ethyl 3-hydroxyquinoxaline-2-carboxylate by the reatcion with hydrazine hydrate in ethanol, yellow solid in the reaction under heating was indicates the formation of carbohydrazide **(1)** and this upon reacts with different substituted isothiocyanate giving desired semithiocarbazides **(2a-f)** which was finally cyclised under acidic condition using con. H_2SO_4 to give substituted thiadiazol ring **(3a-f)** and on treating with 2N NaOH to give substituted triazol ring **(4a-f)** in excellent yield under reflux condition.

All the title molecules and intermediates are synthesized in the scheme shown above are characterised by the ^{1}H NMR and mass spectral analyses.

CONCLUSION

In this study, a series of new triazole and thiadiazole derivatives was synthesized by simple conventional method and the synthesized compounds were confirmed by spectral analysis.

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