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Conventional and Microwave Assisted Synthesis of Quinoxaline Carboxamide Derivatives

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The synthesis of carboxamide derivatives containing quinoxaline scaffold is described. They were prepared from 3-hydroxy quinoxaline-2-carbohydrazide in a series of steps using conventional as well as microwave assisted methods.

Keywords: Carboxamide derivatives, Quinoxaline, Microwave assisted synthesis.

INTRODUCTION

The versatility of the quinoxalines, in addition to its chemical simplicity and accessibility, makes them the most promising sources of bioactive heterocycles.The quinoxaline skeleton is used as an intermediate in designing novel quinoxaline derivatives with potential as anticancer [1-3], antiviral [4], antimicrobial (or antifungal) [3], anticandida [5,6], antithrombotic [7], anxiolytic agents and other activities. Moreover, quinoxaline based drugs have shown to be photochemical DNA cleaving agents making them highly promising scaffolds for anticancer therapeutics.

Especially tetracyclic quinoxaline carboxamides showed cytotoxic activity which is helpful in treating cancers. Cisplatin is a platinum containing anticancer drug, used to treat various types of cancers, including sarcomas, some carcinomas, bladder cancer, lymphomas and cervical cancer. The synthesis of new platinum compounds using quinoxaline-2-carboxamide as a ligand would reveal the significance of quinoxaline derivatives [8]. They show cytotoxic activity, though displaying poor activity, compared to cisplatin [9]. Quinoxaline 2-carboxamides are efficient 5-HT_3 receptor antagonists, which reduce the side effects of cancer treatment like nausea and vomiting [10].

High blood pressure is the main cause of sudden cardiac arrest. Some of the quinoxaline derivatives are antagonists of bradykinin, which is a peptide responsible for the dilatation of blood vessels, thus leading to the lowering of blood pressure [11].

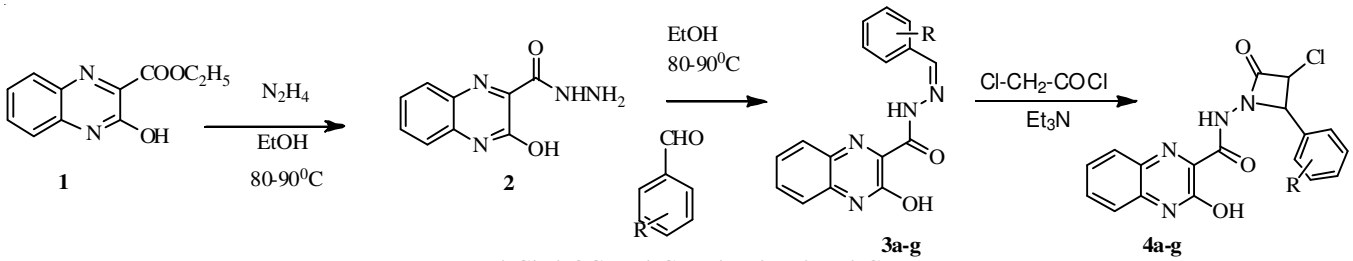
It is found that microwave enhances the rate of chemical reaction, thereby reducing reaction time, improving yields, purity and suppressing the formation of side products. Considering the significance of microwave assisted synthesis, we planned to synthesize some of the quinoxaline compounds through microwave.

EXPERIMENTAL

Chemicals and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Microwave assisted synthesis was carried out in BP090 Laboratory grade microwave oven. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellet with a Perkin-Elmer spectrum gx FTIR instrument and only diagnostic and/or intense peaks are reported. ^{1}H NMR spectra were recorded in DMSO-d_6 with a Varian Mercury plus 400 MHz instrument. All the chemical shifts were reported in δ (ppm) where TMS is used as an internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under argon atmosphere.

RESULTS AND DISCUSSION

All the quinoxaline derivatives were synthesized by both conventional and microwave-assisted synthetic methods. Synthesis of N-[3-chloro-2-(aryl)-4-oxoazetidin-1-yl]-3-hydroxy-quinoxaline-2-carboxamides were carried out according to **Scheme-I**. The condensation of 3-hydroxyquinoxaline-2-carbohydrazide (**2**) and aldehyde in ethanol was carried out under reflux conditions for 1 h. The yields ranging from 55 to 65 % when synthesized by conven-tional method. The yield



R = 4-Cl, 4-OCH_3, 4-CH_3, 4-F, 3-F, 2-F, 4-CF_3

Reagents and conditions: (a) N_2H_4, EtOH, reflux, 10 h; (b) benzaldehydes **a-j**, ethanol, reflux, 1 h; c) $ClCH_2COCl$, Et_3N, DMF

Scheme-I: Synthesis of N-[3-chloro-2-(aryl)-4-oxoazetidin-1-yl]-3-hydroxyquinoxaline-2-carboxamide (**4a-j**)

may vary (65-73 %) when synthesized by using microwave irradiation. After the completion of the reaction (monitored by TLC), reaction mixture was poured on to crushed ice, solid product (**3**) thus obtained was filtered, washed with water and recrystallized from ethanol.

N-Arylidene-3-hydroxyquinoxaline-2-carbohydrazide (**3a-g**) was treated with chloroacetyl chloride and Et_3N in DMF at 0 °C and the reaction mixture was stirred at room temperature for 2 h to obtain N-[3-chloro-2-(aryl)-4-oxoazetidin-1-yl[-3-hydroxyquinoxaline-2-carboxamide. The products can also be obtained by microwave irradiation under solvent free conditions (**4a-g**).

The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Synthesis of N-arylidene-3-hydroxyquinoxaline-2-carbohydrazides (3a-g)

Method A: A mixture of 3-hydroxyquinoxaline-2-carbohydrazide (**2**) (0.01 mmol) and aldehyde (0.01 mmol) were dissolved in ethanol and the mixture was refluxed for 1 h. After the completion of the reaction (monitored by TLC), reaction mixture was poured on to crushed ice, solid product (**3**) thus obtained was filtered, washed with water and recrystallized from ethanol.

Method B: A mixture of 3-hydroxyquinoxaline-2-carbohydrazide (**2**) (0.01 mmol) and aldehyde (0.01 mmol) were taken in pyrex glass vessel and added few drops of ethanol to make the mixture into a paste. Then it is treated in microwave (360 Watt) to 125 °C for 2-4 min. Solid product (**3**) thus obtained was filtered, washed with water and recrystallized from ethanol.

N'-(4-Chlorobenzylidene)-3-hydroxyquinoxaline-2-carbohydrazide (3a, $C_{16}H_{11}N_4O_2Cl$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.86 (brs, 2H), 8.74 (brs, 1H), 8.74 (brs, 1H), 7.98 (d, 1H, *J* = 7.8 Hz), 7.82 (d, 2H), 7.64 (d, 1H, *J* = 7.8 Hz), 7.58 (d, 2H, *J* = 8.0 Hz); MS (70 eV): *m/z* 327 (M^+).

N'-(4-Methoxy benzylidene)-3-hydroxyquinoxaline-2-carbohydrazide (3b, $C_{17}H_{14}N_4O_3$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.88 (brs, 2H), 8.74 (S, 1H), 8.33 (S, 1H), 8.01 (d, 1H, *J* = 7.8 Hz), 7.80 (d, 2H, *J* = 8.0 Hz), 7.42 (m, 1H), 3.78 (S, 3H); MS (70 eV): *m/z* 323 (M^+).

N'-(4-Methylbenzylidene)-3-hydroxyquinoxaline-2-carbohydrazide (3c, $C_{17}H_{14}N_4O_2$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.90 (brs, 2H), 8.77 (S, 1H), 8.34 (S, 1H), 8.02 (d, 1H, *J* = 7.8 Hz), 7.82 (d, 2H, *J* = 8.0 Hz), 7.43 (m, 1H), 2.36 (S, 3H); MS (70 eV): *m/z* 307 (M^+).

N'-(4-Fluorobenzylidene)-3-hydroxyquinoxaline-2-carbohydrazide (3d, $C_{16}H_{11}N_4O_2F$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.91 (brs, 2H), 8.76 (S, 1H), 8.32 (S, 1H), 8.00 (d, 1H, *J* = 7.8 Hz), 7.80 (d, 2H, *J* = 8.0 Hz), 7.64 (m, 1H), 7.55 (m, 2H), 7.44 (m, 1H); MS (70 eV): *m/z* 311 (M^+)

N'-(3-Fluorobenzylidene)-3-hydroxyquinoxaline-2-carbohydrazide (3e, $C_{16}H_{11}N_4O_2F$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.92 (brs, 1H), 9.75 (brs, 1H), 8.70 (s, 1H), 8.31 (s, 1H), 7.99 (m, 2H), 7.88 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 1H, *J* = 8.0 Hz), 7.44 (m, 1H). MS (70 eV): *m/z* 311 (M^+).

N'-(2-Fluorobenzylidene)-3-hydroxyquinoxaline-2-carbo-hydrazide (3f, $C_{16}H_{11}N_4O_2F$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.90 (brs, 2H), 8.74 (S, 1H), 8.29 (S, 1H), 8.03

TABLE-1
YIELDS & TOTAL REACTION TIME FOR SYNTHESIZED QUINOXALINE DERIVATIVES

Compound	m.f.	Conventional time (min)	Microwave assisted time (min)	m.p. (°C)	Yield (%)
3a	$C_{16}H_{11}N_4O_2Cl$	60	3	198	75
3b	$C_{17}H_{14}N_4O_3$	65	4	200	65
3c	$C_{17}H_{14}N_4O_2$	59	2	202	86
3d	$C_{16}H_{11}N_4O_2F$	57	2	200	50
3e	$C_{16}H_{11}N_4O_2F$	60	3	198	65
3f	$C_{16}H_{11}N_4O_2F$	62	3	206	70
3g	$C_{17}H_{11}N_4O_2F_3$	70	4	208	64
4a	$C_{18}H_{12}N_4O_3Cl_2$	60	2	206	72
4b	$C_{19}H_{15}N_4O_4Cl$	68	4	210	80
4c	$C_{19}H_{15}N_4O_3Cl$	56	3	212	86
4d	$C_{18}H_{12}N_4O_3ClF$	65	4	210	75
4e	$C_{18}H_{12}N_4O_3ClF$	35	3	208	65
4f	$C_{18}H_{12}N_4O_3ClF$	56	3	206	76
4g	$C_{19}H_{12}N_4O_3ClF_3$	58	2	204	78

(d, 1H, *J* = 7.8 Hz), 7.79 (d, 2H, *J* = 8.0 Hz), 7.62 (m, 1H), 7.56 (m, 2H), 7.41 (m, 1H); MS (70 eV): *m/z* 311 (M^+).

N'-(4-Triflouromethylbenzylidene)-3-hydroxyquinoxaline-2-carbohydrazide (3g, $C_{17}H_{11}N_4O_2F_3$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.89 (brs, 2H), 8.78 (S, 1H), 8.32 (S, 1H), 8.03 (d, 1H, *J* = 7.8 Hz), 7.79 (d, 2H, *J* = 8.0 Hz), 7.39 (m, 1H); MS (70 eV): *m/z* 361 (M^+)

Synthesis of N-[3-chloro-2-(aryl)-4-oxoazetidin-1-yl]-3-hydroxyquinoxaline-2-carboxamides (4a-g)

Method A: To a stirred solution of N-arylidene-3-hydroxyquinoxaline-2-carbohydrazide (**3**) (0.01 mmol) in DMF (5 mL) and Et_3N (0.001 mmol), chloro acetyl chloride (0.01 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction (monitored by TLC), reaction mixture was poured on to crushed ice, solid product thus obtained was filtered, washed with water and recrystallized from ethanol.

Method B: To N-arylidene-3-hydroxyquinoxaline-2-carbohydrazide (0.01 mmol) (**3**) Et_3N (0.001 mmol), chloro acetyl chloride (0.01 mmol) was added at 0 °C and the reaction mixture was heated to 40 °C in microwave for 2-5 min. After the completion of the reaction (monitored by TLC), solid product thus obtained was filtered, washed with water and recrystallized from ethanol.

N-(3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4a, $C_{18}H_{12}N_4O_3Cl_2$): Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.81 (s, 1H), 7.81 (d, 1H, *J* = 8.0 Hz), 7.66 (m, 1H), 7.60 (m, 1H), 7.40 (m, 3H), 7.25 (s, 1H), 7.10 (d, 1H, *J* = 8.0 Hz), 6.98 (t, 1H), 4.72 (d, 1H, *J* = 5.2 Hz), 4.60 (d, 1H, *J* = 5.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 163.06, 163.02, 158.02, 154.43, 152.35, 142.39, 133.34, 132.26, 131.77, 129.96, 129.88, 128.70, 124.59, 123.19, 120.95, 115.97, 112.36, 39.01; MS (70 eV): *m/z* 403 (M^+).

N-(3-Chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4b, $C_{19}H_{15}N_4O_4Cl$): Light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.80 (s, 1H), 7.80 (d, 1H, *J* = 8.0 Hz), 7.65 (m, 1H), 7.59 (m, 1H), 7.39 (m, 3H), 7.26 (s, 1H), 7.11 (d, 1H, *J* = 8.0 Hz), 6.99 (t, 1H), 4.73 (d, 1H, *J* = 5.2 Hz), 4.60 (d, 1H, *J* = 5.2 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 163.14, 162.95, 158.14, 154.20, 152.11, 142.10, 133.15, 132.16, 131.62, 128.95, 128.01, 127.10, 124.59, 123.10, 120.16, 115.37, 112.17, 89.02, 56.27; MS (70 eV): *m/z* 399 (M^+).

N-(3-Chloro-2-(*p*-tolyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4c, $C_{19}H_{15}N_4O_3Cl$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.83 (s, 1H), 7.82 (d, 1H, *J* = 8.0 Hz), 7.65 (m, 1H), 7.45 (t, 1H), 7.38 (m, 3H), 7.29 (s, 1H), 7.12 (d, 1H, *J* = 8.0 Hz), 6.98 (t, 1H), 4.76 (d, 1H, *J* = 5.2 Hz), 4.54 (d, 1H, *J* = 5.2 Hz), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 162.75, 162.16, 158.10, 154.20, 152.12, 142.05, 133.65, 132.17, 131.17, 131.63, 128.55, 128.00, 122.17, 124.10, 123.75, 120.10, 115.75, 112.05, 89.02, 28.36; MS (70 eV): *m/z* 383 (M^+).

N-(3-Chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4d, $C_{18}H_{12}N_4O_3ClF$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.70 (s, 1H), 7.80 (d, 1H, *J* = 8.0 Hz), 7.64 (m, 1H), 7.44 (t, 1H), 7.39 (m, 3H), 7.25 (s, 1H), 7.14 (d, 1H, *J* = 8.0 Hz), 6.99 (t, 1H), 4.75 (d, 1H, *J* = 5.2 Hz), 4.55 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 164.03, 163.15, 162.95, 159.15, 152.12, 142.15, 133.80, 132.17, 131.75, 128.95, 128.15, 127.15, 124.60, 124.10, 120.80, 115.37, 112.85, 89.04; MS (70 eV): *m/z*387 (M^+).

N-(3-Chloro-2-(3-fluorophenyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4e, $C_{18}H_{12}N_4O_3ClF$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.72 (s, 1H), 7.79 (d, 1H, *J* = 8.0 Hz), 7.64 (m, 1H), 7.45 (t, 1H), 7.39 (m, 3H), 7.24 (s, 1H), 7.14 (d, 1H, *J* = 8.0 Hz), 6.98 (t, 1H), 4.75 (d, 1H, *J* = 5.2 Hz), 4.56 (d, 1H, *J* = 5.2 Hz; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 163.85, 163.02, 161.15, 158.00, 152.85, 142.65, 133.85, 132.80, 131.76, 128.66, 128.10, 128.00, 124.75, 124.70, 120.81, 115.38, 112.16, 89.02; MS (70 eV): *m/z* 387 (M^+).

N-(3-Chloro-2-(2-fluorophenyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4f, $C_{18}H_{12}N_4O_3ClF$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.65 (s, 1H), 7.82 (d, 1H, *J* = 8.0 Hz), 7.62 (m, 1H), 7.46 (t, 1H), 7.41 (m, 3H), 7.23 (s, 1H), 7.12 (d, 1H, *J* = 8.0 Hz), 7.00 (t, 1H), 4.74 (d, 1H, *J* = 5.2 Hz), 4.65 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 164.03, 163.15, 162.95, 152.12, 142.15, 133.80, 131.95, 128.95, 128.15, 127.15, 124.60, 124.10, 120.80, 115.37, 112.85, 89.04; MS (70 eV): *m/z* 387 (M^+).

N-(3-Chloro-2-(4-(trifluoromethyl)phenyl)-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide (4g, $C_{19}H_{12}N_4O_3ClF_3$): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.82 (s, 1H), 7.81 (d, 1H, *J* = 8.0 Hz), 7.66 (m, 1H), 7.44 (t, 1H), 7.35 (m, 3H), 7.30 (s, 1H), 7.10 (d, 1H, *J* = 8.0 Hz), 6.97 (t, 1H), 4.73 (d, 1H, *J* = 5.2 Hz), 4.51 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 162.75, 162.16, 158.10, 154.20, 152.12, 142.05, 133.65, 132.17, 131.63, 128.55, 128.00, 127.14, 124.10, 123.73, 120.10, 115.75, 112.05, 89.02; MS (70 eV): *m/z* 437 (M^+).

Conclusion

N-(3-Chloro-2-aryl-4-oxoazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamideswere prepared from 3-hydroxy quinoxaline-2-carbohydrazide in a series of steps using conventional as well as microwave assisted methods and analyzed by IR, ^{13}C and ^{1}H NMR spectroscopy.

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REFERENCES

1. A. Carta, P. Sanna, L. Gherardini, D. Usai and S. Zanetti, *IL Farmaco*, **56**, 933 (2001); https://doi.org/10.1016/S0014-827X(01)01161-2.
2. J.J. Cai, J.P. Zou, X.Q. Pan and W. Zhang, *Tetrahedron Lett.*, **49**, 7386 (2008); https://doi.org/10.1016/j.tetlet.2008.10.058.
3. P. Sanna, A. Carta, M. Loriga, S. Zanetti and L. Sechi, *IL Farmaco*, **54**, 1169 (1999).
4. Y.A. Ammar, M.M.F. Ismail, M.S.A. El-Gaby and M.A. Zahran, *Indian J. Chem.*, **41B**, 1486 (2002).

5. V.K. Tandon, D.B. Yadav, H.K. Maurya, A.K. Chaturvedi and P.K. Shukla, *Bioorg. Med. Chem.*, **14**, 6120 (2006); https://doi.org/10.1016/j.bmc.2006.04.029.
6. H.M. Refaat, A.A. Moneer and O.M. Khalil, *Arch. Pharm. Res.*, **27**, 1093 (2004); https://doi.org/10.1007/BF02975110.
7. U.J. Ries, H.W.M. Priepke, N.H. Hauel, S. Handschuh, G. Mihm, J.M. Stassen, W. Wienen and H. Nar, *Bioorg. Med. Chem. Lett.*, **13**, 2297 (2003); https://doi.org/10.1016/S0960-894X(03)00443-8.
8. L.W. Deady, A.J. Kaye, G.J. Finlay, B.C. Baguley and W.A. Denny, *J. Med. Chem.*, **40**, 2040 (1997); https://doi.org/10.1021/jm970044r.
9. P. Marqués-Gallego, M.A. Gamiz-Gonzalez, F.R. Fortea-Pérez, M. Lutz, A.L. Spek, A. Pevec, B. Kozlevcar and J. Reedijk, *Dalton Trans.*, **39**, 5152 (2010); https://doi.org/10.1039/C001158D.
10. R. Mahesh, T. Devadoss, D.K. Pandey and S.K. Yadav, *J. Enzyme Inhib. Med. Chem.*, **26**, 610 (2011); https://doi.org/10.3109/14756366.2010.543419.
11. D.S. Su and M.G. Bock, 2-Quinoxalinone Derivatives as Bradykinin Antagonists and Novel Compounds, US Patent 20050020591 (2005).