RESEARCH ARTICLE

A Facile, Efficient and Green Protocol for the Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-octahydroquinazolines and 3,3′-(alkanediyl)bis(1-(2-hydroxyethyl)-5-oxo-octahydroquinazolines)

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Abstract

A facile microwave assisted one-pot synthesis of novel 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines **3a-h** and 3,3'-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines) **4a-d** has been devised by the cyclocondensation of cyclic enaminones **2a-b** with primary amines/diamines and formaldehyde. The structures of the products have been established by spectral and analytical data. The present paper describes a one-pot, efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown octahydroquinazolines and bis-octahydroquinazolines from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

Keywords: Octahydroquinazoline; bis-octahydroquinazolines; enaminones; diamines; cyclocondensation; multi-component reactions.

1. Introduction

Quinazolines are most important class of compounds and have received much attention from synthetic as well as medicinal chemists, because of the diverse range of their pharmacological properties. Keeping in view the biological properties of octahydroquinazolines [1-3], we have recently reported [4-7] the synthesis of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and bis-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines bearing phenyl, benzyl, methyl and phenyl ethyl groups in position 1 of the ring. The biological properties of these molecules are under investigation. Simultaneously, El-Sabbagh *et al.* have reported [8] the synthesis of a few derivatives of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and studied their hypotensive activities.

In continuation of our studies on the synthesis of octahydroquinazolines, we now wish to report herein a short microwave-assisted synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and 3,3'-(alkanediyl)bis(1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines) bearing 2-hydroxyethyl group in position 1 of quinazoline ring to see the impact of this hydrophilic group on the biological properties of these molecules.

2. Methods

All the chemicals used are of commercial grade and were used without further purification. Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-983 spectrometer. ^{1}H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^{1}H NMR and ^{13}C NMR (300MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shift (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to TMS as internal reference. FAB- Mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 using Argon as the FAB gas and m-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a Vario-EL-III instrument. Microwave irradiation was carried out in a CEM Discover Benchmate microwave digester at 180 watt in 2-4 minutes.

Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (3a-d) and 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl--7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (3e-h): General procedure.

Equimolar mixture of 1,3-diketone (**1a,b**) and ethanolamine was irradiated in microwave digester at 180 watt in 2-4 minutes. The reaction gets completed in 2-3 minutes (tlc). The reaction mixture was sucked dry under reduced pressure to give the enaminone **2**. A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone **2** (1 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by column chromatography (silica gel, EtOAc) to isolate **3a-h** in 51-79 % yields.

1-(2-hydroxyethyl)-3-methyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3a. It was obtained as reddish brown gum with 71% yield; IR (KBr): 1530, 1653 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.95-197 (m, 2H), 2.30 (s, 2H), 2.40 (s, 3H), 2.60 (s, 2H), 3.35-3.42 (m, 4H), 3.65-3.70 (m, 2H), 3.90 (s, 2H), 4.60 (s, 1H); MS: m/z 211.2 (MH^+). Anal. Calc. for $C_{11}H_{18}N_2O_2$ (210.14): C, 62.83; H, 8.63; N, 13.32. Found: C, 62.69; H, 8.66; N, 13.28%.

1-(2-hydroxyethyl)-3-phenyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3b. It was obtained as reddish brown gum with 68 % yield; IR (KBr): 1541, 1599 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.96-1.98 (m, 2H), 2.10 (s, 2H), 2.21-2.25 (t, 2H), 2.34 (s, 2H), 3.18 (s, 2H), 3.60 (t, 2H), 4.08 (s, 2H), 4.60 (s, 1H), 6.79-6.94 (m, 3H), 7.18-7.21 (m, 2H); MS: m/z 273 (MH^+). Anal. Calc. for $C_{16}H_{20}N_2O_2$ (272.15): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.70; H, 7.36; N, 10.28%.

1-(2-hydroxyethyl)-3-benzyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3c. It was obtained as reddish brown gum with 59% yield; IR (KBr): 1551, 1603 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.95-1.98 (m, 2H), 2.10 (s, 2H), 2.21-2.25 (t, 2H), 2.34 (s, 2H), 3.18 (s, 2H), 3.57-3.60 (m, 4H), 4.08 (s, 2H), 4.60 (s, 1H), 7.23-7.33 (m, 5H); MS: m/z 287 (MH^+). Anal. Calc. for $C_{17}H_{22}N_2O_2$ (286.17): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.41; H, 7.69; N, 9.83%.

1-(2-hydroxyethyl)-3-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3d. It was obtained as brownish solid in 51% yield, m.p. 90^0C; IR (KBr): 1529, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.94-1.97 (m, 2H), 2.27 (s, 2H), 2.53 (s, 2H), 3.38 (s, 2H), 3.45 (s, 2H), 3.62-3.70 (m, 6H), 4.03 (s, 2H), 5.12 (s, 1H); MS: m/z 241 (MH^+). Anal. Calc. for $C_{12}H_{20}N_2O_3$ (240): C, 59.98; H, 8.39; N, 11.67. Found: C, 59.84; H, 8.45; N, 11.75%.

1-(2-hydroxyethyl)-3,7,7-trimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3e. It was obtained as brown gum with 61 % yield; IR (KBr): 1541, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (s, 6H), 2.16 (s, 2H), 2.34 (s, 2H), 2.40 (s, 3H), 3.37-3.39 (m, 4H), 3.66-3.70 (t, 2H), 3.82 (s, 2H), 4.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 192.85, 156.60, 104.14, 70.33, 59.82, 50.70, 49.76, 46.62, 48.61, 40.48, 36.14, 31.24, 27.59; MS: m/z 239.8 (MH^+). Anal. Calc. for $C_{13}H_{22}N_2O_2$ (238.17): C, 65.51; H, 9.30; N, 11.75. Found: C, 65.66; H, 9.38; N, 11.70%.

1-(2-hydroxyethyl)-3-phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3f. It was obtained as yellow solid in 65% yield, m.p. 68^0C; IR (KBr): 1584, 1599 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (s, 6H), 2.17 (s, 2H), 2.39 (s, 2H), 3.41-3.44 (m, 4H), 3.60-3.63 (t, 2H), 4.13 (s, 1H), 4.61 (s, 2H), 6.95-7.10 (m, 5H); ^{13}C NMR ($CDCl_3$): 192.85, 156.60, 104.14, 70.33, 59.82, 50.70, 49.76, 48.61, 46.62, 40.48, 36,14, 31.24, 27.59; MS: m/z 301.2 (MH^+). Anal. Calc. for $C_{18}H_{24}N_2O_2$ (300.18): C, 71.97; H, 8.05; N, 9.33. Found: C, 72.10; H, 8.00; N, 9.31%.

1-(2-hydroxyethyl)-3-benzyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 3g. It was obtained as yellow solid with 75 % yield, m.p. 95^0C; IR (KBr): 1537, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (s, 6H), 2.15 (s, 2H), 2.35 (s, 2H), 3.29-3.33 (t, 2H), 3.49 (s, 2H), 3.63 (t, 2H), 3.68 (s, 2H), 3.92 (s, 2H), 4.60 (1, 1H), 7.29-7.33 (m, 5H); MS: m/z 315.2 (MH^+). Anal. Calc. for $C_{19}H_{26}N_2O_2$ (314.20): C, 72.58; H, 8.33; N, 8.91. Found: C, 72.51; H, 8.37; N, 8.89%.

1-(2-hydroxyethyl)-3-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline 3h. It was obtained as brown gum with 72 % yield; IR (KBr): 1532, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (s, 6H), 2.36 (s, 2H), 2.65-2.68 (m, 4H), 3.39 (s, 2H), 3.48-3.52 (m, 4H), 3.71 (s, 2H), 4.08 (s, 2H), 4.26 (s, 2H); MS: m/z 269 (MH^+). Anal. Calc. for $C_{14}H_{24}N_2O_3$ (268.12): C, 62.66; H, 9.01; N, 10.44. Found: C, 62.55; H, 9.05; N, 10.40%.

Synthesis of 3,3'-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) (4a-b) and 3,3'-(alkanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) (4c-d): General procedure.

Equimolar mixture of 1,3-diketone (**1a,b**) and ethanolamine was irradiated in microwave at 180 watt. The reaction gets completed in 2-3 minutes (monitored by tlc). The reaction mixture was rendered dry under reduced pressure in hot water-bath to give the enaminone **2**. A mixture of diamine (1mmol) and formaldehyde (4 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone **2** (2 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester at 180 watt in 2-4 minutes. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by column chromatography (silica gel, EtOAc) to isolate **4a-d** in 51-79 % yields.

3,3'-(ethanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) 4a: It was obtained as yellow solid in 65 % yield, m.p. 75^{0}C; IR (KBr): 1533, 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.94-1.97 (m, 4H), 2.28-2.31 (m, 4H), 2.59-2.61 (t, 4H), 2.74 (s, 4H), 3.41-3.44 (t, 4H), 4.14 (s, 4H), 3.90 (s, 2H), 4.60 (s, 2H); MS: m/z 419.2 (MH^+). Anal. Calc. for $C_{22}H_{34}N_4O_4$ (418.53): C, 63.13; H, 8.19; N, 13.39. Found: C, 63.21; H, 8.17; N, 13.32%

3,3'-(butanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) 4b: It was obtained as yellow solid in 79 % yield, m.p. 88^{0}C; IR (KBr): 1531, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.84-1.87 (m, 4H), 2.02-2.04 (m, 4H), 2.84-2.86 (m, 4H), 2.94-2.96 (t, 4H), 3.47 (s, 4H), 3.95-3.97 (t, 4H), 4.06 (s, 4H), 4.60 (s, 4H); MS: m/z 447.2 (MH^+). Anal. Calc. for $C_{24}H_{38}N_4O_4$ (446.29): C, 64.55; H, 8.58; N, 12.55. Found: C, 64.46; H, 8.54; N, 12.60%

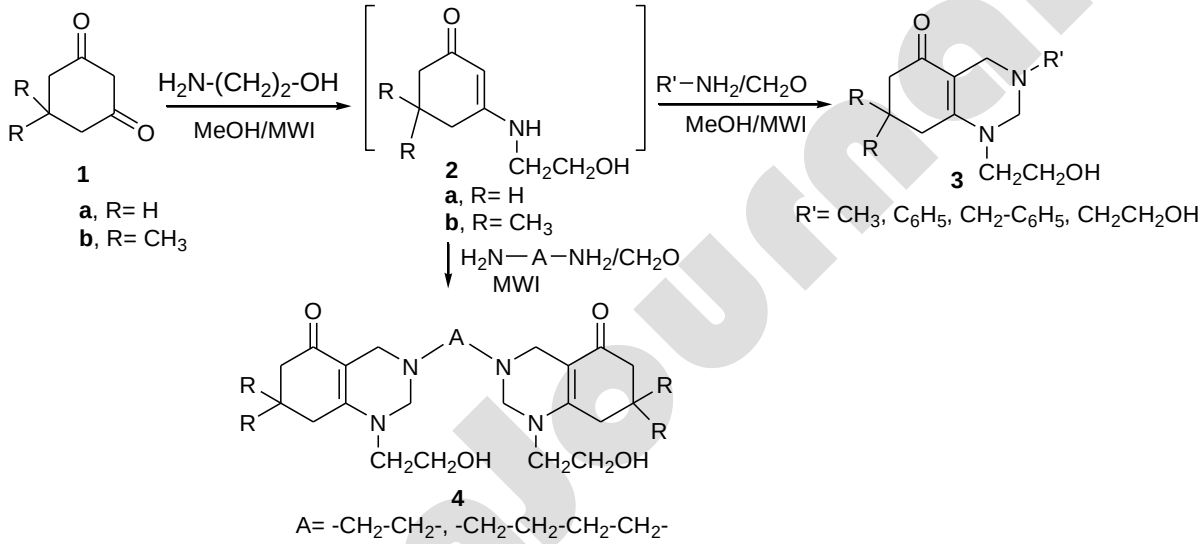
3,3'-(ethanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline) 4c: It was obtained as brown gum in 51 % yield; IR (KBr): 1558, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 12H), 1.90 (s, 4H), 2.65-2.67 (m, 4H), 2.84 (s, 4H), 2.94-2.96 (t, 4H), 3.47 (s, 4H), 4.14 (s, 4H), 3.95-3.97 (t, 4H), 4.06 (s, 4H), 4.60 (s, 2H); MS: m/z 475 (MH^+). Anal. Calc. for $C_{26}H_{42}N_4O_4$ (474.32): C, 65.79; H, 8.92; N, 11.80. Found: C, 65.68; H, 8.95; N, 11.73%.

3,3'-(butanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline) 4d: It was obtained as brown gum in 68 % yield; IR (KBr): 1536, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 12H), 1.63 (s, 4H), 2.12 (s, 4H), 2.28 (s, 4H), 2.54 (s, 4H), 3.30-3.32 (t, 4H), 3.42 (s, 4H), 3.60-3.62 (t, 4H), 3.94 (s, 4H), 4.60 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 193.54, 158.02, 103.73, 69.74, 53.14, 51.13, 49.40, 48.99, 39.34, 32.26, 28.62, 24.02; MS: m/z 503.5(MH^+). Anal. Calc. for $C_{28}H_{46}N_4O_4$ (502.35): C, 66.90; H, 9.22; N, 11.15. Found: C, 66.71; H, 9.17; N, 11.06%.

3. Results and Discussion

When 3-(2-hydroxyethyl)aminocyclohexenone **2a** was treated with methylamine and formaldehyde under the influence of microwaves, a product was obtained in 71% yields which was characterized as 1-(2-hydroxyethyl)-3-methyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline **3a** on the basis of analytical and spectral data. The reaction of **2a** with other primary amines and formaldehyde behaved in a similar manner and octahydroquinazolines **3b-d** were isolated in 51-79% yields. The infrared spectra of **3a-d** showed strong peaks in the region of 1530 to 1653 cm^{-1} due to extensively delocalized double bonds and carbonyl groups [7]. In the ^{1}H NMR spectra of **3a-d**, the methylene protons at C-7 appeared as multiplets in the range of 1.94-1.98 ppm. The methylene proton adjacent to -OH group resonated 3.60 ppm, the methylene protons at C-2 gave sharp singlet 4.12 ppm whereas the CH_2 protons in **3d** appeared around 5.12 may be due to presence of two hydroxyethyl group at 1 and 3 position of quinazoline ring. The hydroxyl group gave broad singlet near 4.60 ppm which disappears with D_2O shake. The methyl protons attached to nitrogen in **3a** gave singlet at 2.40 ppm. The aromatic protons appeared in their usual range. The reactions of **2b** with formaldehyde and primary amines were subsequently examined under similar conditions and the expected 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl--7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline **3e-h** were isolated in 61-75% yields, whose structures could be established with the help of analytical and spectral data. The infrared spectra of **3e-h** showed strong peaks in the region of 1533 to 1600 cm^{-1}. The ^{1}H NMR spectra of tetrahydropyrimidine rings of **3e-h** were found to have a similar pattern as those in **3a-d**. However, the six methyl protons at C-7 appeared as sharp singlets around 1.06 ppm whereas in **3f** it appeared at 1.01 ppm

which may be due to the presence of phenyl group at N-3 position and the CH_2 protons at C-6 and C-8 resonated in ranges of 2.15-2.17 and 2.30-2.40 ppm respectively. Encouraged by the successful synthesis of octahydroquinazolines **3a-h**, we then turned our attention to the synthesis of bis-octahydroquinazolines. Thus, when enaminone **2a** was reacted with 1,2-diaminoethane and formaldehyde under the influence of microwaves in methanol, a product **4a** was isolated in 65 % yield, the structure of which was established to be 3,3'-(ethanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) based on analytical and spectral data. The reaction was found to be general with other diamines and with corresponding **2a-b** to give the respective product **4b-d** in 51-79% overall yields. We were thus able to connect two octahydroquinazoline rings through flexible aliphatic chains **4a-d**, the structures of which could be established with the help of spectral and analytical data. The infrared spectra of **4a-d** showed strong peaks in the range of 1531-1653 cm^{-1} due to extensive delocalization of the enaminone moiety and carbonyl group. The ^1H NMR spectra of these dimers were found to have the same pattern as in the monomeric octahydroquinazolines except that the signals due to NCH_2 protons of ethylene linkers appeared at 2.74-2.84 ppm while those in butylene appeared in the range of 2.54-2.86 ppm. The structure of some monomer and dimer were further supported by their ^{13}C and mass spectra.



Scheme

Synthesis of octahydroquinazolines 3a-h & bis-octahydroquinazolines 4a-d.

Comp.	R	R'/A	Mol. formula	MWI Power/Time	M.P. °C	Yield%
3a	H	$-CH_3$	$C_{11}H_{18}N_2O_2$	180watt/180second	Gum	71
3b	H	$-C_6H_5$	$C_{16}H_{20}N_2O_2$	180watt/210second	Gum	68
3c	H	$-CH_2-C_6H_5$	$C_{17}H_{22}N_2O_2$	180watt/120second	Gum	59
3d	H	$-(CH_2)_2-OH$	$C_{12}H_{20}N_2O_3$	180watt/120second	90	51
3e	$-CH_3$	$-CH_3$	$C_{13}H_{22}N_2O_2$	180watt/150second	Gum	61
3f	$-CH_3$	$-C_6H_5$	$C_{18}H_{24}N_2O_2$	180watt/180second	68	65
3g	$-CH_3$	$-CH_2-C_6H_5$	$C_{19}H_{26}N_2O_2$	180watt/210second	95	75
3h	$-CH_3$	$-(CH_2)_2-OH$	$C_{14}H_{24}N_2O_3$	180watt/180second	Gum	72
4a	H	$-CH_2-CH_2-$	$C_{22}H_{34}N_4O_4$	180watt/180second	79	65
4b	H	$-(CH_2)_4-$	$C_{24}H_{38}N_4O_4$	180watt/180second	88	79
4c	$-CH_3$	$-CH_2-CH_2-$	$C_{26}H_{42}N_4O_4$	180watt/150second	Gum	51
4d	$-CH_3$	$-(CH_2)_4-$	$C_{28}H_{46}N_4O_4$	180watt/150second	Gum	68

4. Conclusion

The present paper describes a one-pot, efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown octahydroquinazolines and bis- octahydroquinazolines from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

Competing Interests

Authors do not have any competing interests.

Authors' Contributions

MS executed the work and RLN was involved in monitoring the progress of the experiments. JNV was responsible for overall planning, execution and writing of this manuscript.

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