RESEARCH ARTICLE

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Microwave-Assisted One-Pot Synthesis of Novel 1-Phenylethylhexahydroquinazolin-5(6H)-ones and Bis-1-Phenylethylhexahydroquinazolin-5(6H)-ones

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Abstract

A facile microwave-assisted one-pot synthesis of novel 1-phenylethylhexahydro quinazolin-5 (6H)-ones **3a–j** and bis-1-phenylethylhexahydro quinazolin-5 (6H)-ones **4a–f** and **5a–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 with the help of spectral and analytical data.

Keywords: 1-Phenylethylhexahydroquinazolin-5(6H)-ones; bis-1-phenylethylhexahydroquinazolin-5(6H)-ones; enaminones; diamines; cyclocondensation.

1. Introduction

Quinazolines have attracted considerable attention because of their great pharmacological importance and biological activities. Keeping in view the biological properties of octahydroquinazolines [1–3], we have recently reported [4–6] the synthesis of hexahydroquinazolin-5(6H)-ones bearing phenyl, benzyl and methyl groups in position 1 of the ring and bis-hexahydroquinazolin-5(6H)-ones bearing phenyl, benzyl and methyl group in position 1 of the ring. The biological properties of these molecules are under investigation. We now report herein a short microwave-assisted synthesis of hexahydroquinazolin-5(6H)-ones and bis-hexahydroquinazolin-5(6H)-ones bearing phenylethyl group in position 1 of quinazoline ring to see the impact of this group incorporated in position 1 on biological properties of these molecules.

2. Methods

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer (Perkin-Elmer). ^{1}H NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard pattern with reference to TMS as internal reference. Fast atom bombardment (FAB)-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument. Microwave irradiation was carried out in CEM Discover Benchmate microwave digester. Enaminones **2a** and **2b** were synthesized by reported procedure [7].

Synthesis of 1,3-substituted-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-ones (3a–e) and 1,3-substituted-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-ones (3f–j). General procedure. A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 min 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 min at 180 W at 60°C. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to produce a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate **3a–j** in 55–85% yields.

1-Phenylethyl-3-methyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3a**). It was obtained as grey solid in 78% yield, mp 53°C; IR (KBr): 1557, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ1.52–1.58 (m, 2H), 1.83 (s, 2H), 2.08 (s, 2H), 2.24 (s, 2H), 2.40 (s, 2H), 2.84 (s, 3H), 3.43 (s, 2H), 3.85 (s, 2H), 7.19–7.31 (m, 5H)); ^{13}C NMR ($CDCl_3$): δ 21.40, 25.35, 35.62, 35.73, 41.60, 50.09, 70.89, 103.88, 126.93, 128.78, 128.82, 137.95, 158.27, 193.62; MS: *m/z* 271.9 (MH^+). Anal. Calcd. for $C_{17}H_{22}N_2O$ (270.17): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.71; H, 8.15; N, 10.39%.

1-Phenylethyl-3-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3b**). It was obtained as pale yellow gum in 75% yield: IR (KBr): 1557, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.69–1.75 (m, 2H), 2.04–2.07 (m, 2H), 2.22–2.25 (m, 2H), 2.91–2.95 (m, 2H), 3.40–3.48 (m, 2H), 4.14 (s, 2H), 4.57 (s, 2H), 6.88–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$): 21.29, 25.44, 35.66, 36.61, 45.26, 45.49, 50.75, 67.54, 104.44, 117.67, 120.86, 126.88, 128.78, 128.78, 128.84, 128.96, 137.99, 159.71, 193.41; MS: *m/z* 332.8 (MH^+). Anal. Calcd. for $C_{22}H_{24}N_2O$ (332.19): C, 79.48; H, 7.28; N, 8.43. Found: C, 79.33; H, 7.32; N, 8.37%.

1-Phenylethyl-3-tolyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3c**). It was obtained as pale yellow gum in 55% yield: IR (KBr): 1559, 1603 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.64–1.67 (m, 2H), 1.86 (s, 2H), 2.04–2.06 (m, 2H), 2.15 (s, 3H), 2.67–2.72 (s, 2H), 3.36–3.39 (m, 2H), 3.99 (s, 2H), 4.47 (s, 2H), 6.79–7.18 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 20.50, 21.29, 25.43, 30.94, 35.55, 35.64, 36.61, 45.26, 45.71, 50.77, 67.97, 104.47, 125.09, 126.87, 128.50, 129.78, 159.67, 193.40; MS: *m/z* 347.8 (MH^+). Anal. Calcd. for $C_{23}H_{26}N_2O$ (346.2): C, 79.73; H, 7.56; N, 8.09. Found: C, 79.82; H, 7.52; N, 8.13%.

1-Phenylethyl-3-(4-chlorophenyl)-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3d**). It was obtained as grey solid in 58% yield, mp 158°C; IR (KBr): 1563, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.71–1.77 (m, 2H), 2.17 (s, 2H), 2.26 (s, 4H), 2.93–2.96 (m, 4H), 3.45–3.48 (m, 2H), 7.20–7.30 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 17.73, 21.36, 25.44, 30.94, 35.63, 36.64, 45.26, 108.01, 126.44, 128.50, 128.88, 138.92, 166.34, 194.07; MS: *m/z* 366.40 (M^+). Anal. Calcd. for $C_{22}H_{23}ClN_2O$ (366.15): C, 72.02; H, 6.32; N, 7.64. Found: C, 72.17; H, 6.28; N, 7.70%.

1-Phenylethyl-3-benzyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3e**). It was obtained as brown gum in 75% yield: IR (KBr): 1553, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80–1.83 (m, 2H), 2.20–2.26 (m, 4H), 2.72–2.75 (m, 2H), 3.36–3.39 (m, 2H), 3.55 (s, 2H), 3.64 (s, 2H), 3.86 (s, 2H), 7.12–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$): 21.39, 25.36, 35.69, 48.72, 50.88, 57.93, 68.32, 104.00, 126.88, 127.44, 128.46, 128.78, 128.98, 137.80, 138.02, 158.74, 193.63 MS: *m/z* 347.1 (MH^+). Anal. Calcd. for $C_{23}H_{26}N_2O$ (346.2): C, 79.73; H, 7.56; N, 8.09. Found: C, 79.91; H, 7.53; N, 8.15%.

1-Phenylethyl-3,7,7-trimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3f**). It was obtained as pale yellow solid in 73% yield, m.p 75°C IR (KBr): 1559, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (s, 6H), 1.99 (s, 2H), 2.06 (s, 2H), 2.33 (s, 2H), 2.74–2.78 (t, 2H, J = 5.4Hz), 3.38–3.41 (m, 5H,), 3.81 (s, 2H), 7.11–7.28 (m, 5H); MS: *m/z* 299.1 (MH^+). Anal. Calcd. for $C_{19}H_{26}N_2O$ (298.2): C, 76.47; H, 8.78; N, 9.39. Found: C, 76.35; H, 8.73; N, 9.45%.

1-Phenylethyl-3-phenyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3g**). It was obtained as pale yellow solid in 69% yield, mp 85°C; IR (KBr): 1559, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (s, 6H), 1.90 (s, 2H), 2.14 (s, 2H), 2.70–2.75 (t, 2H, J=6.3 Hz), 3.44–3.49 (t, 2H, J = 6.3 Hz), 4.19 (s, 2H), 4.63 (s, 2H), 6.93–7.32 (m, 10H); MS: *m/z* 361.2 (MH^+). Anal. Calcd. for $C_{24}H_{28}N_2O$ (360.22): C, 79.96; H, 7.83; N, 7.77. Found: C, 79.85; H, 7.87; N, 7.74%.

1-Phenylethyl-3-tolyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3h**). It was obtained as pale yellow solid in 85% yield, mp 89°C; IR (KBr): 1526, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.84 (s, 6H), 2.07 (s, 3H), 2.17 (s, 2H), 2.25 (s, 2H), 2.68–2.71 (t, 2H, J = 5.1 Hz), 3.41–3.44 (t, 2H, J = 5.1Hz), 4.13 (s, 2H), 4.57 (s, 2H), 6.87–7.27 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 20.48, 28.65, 30.92, 31.90, 32.00, 35.65, 39.11, 45.24, 49.28, 50.27, 68.29, 118.16, 126.80, 128.71, 128.93, 130.46, 138.05, 146.40, 157.94, 192.88; MS: *m/z* 375.1 (MH^+). Anal. Calcd. for $C_{25}H_{30}N_2O$ (374.24): C, 80.17; H, 8.07; N, 7.48. Found: C, 80.02; H, 8.11; N, 7.51%.

1-Phenylethyl-3-(4-chlorophenyl)-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3i**). It was obtained as pale yellow solid in 62% yield, mp 95°C; IR (KBr): 1530, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.96 (s, 6H), 2.05 (s, 2H), 2.14 (s, 2H), 2.77–2.81 (t, 2H, J = 5.1 Hz), 3.42–3.51 (t, 2H, J = 5.1 Hz), 3.60 (s, 2H), 3.95 (s, 2H), 7.06–7.30 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 28.66, 32.00,32.47, 35.96, 39.13, 47.37, 49.24, 50.72, 55.72, 69.83, 102.21, 126.22, 126.95, 128.46, 128.71, 137.94, 139.84, 157.14, 193.21; MS: *m/z* 395.6 (MH^+). Anal. Calcd. for $C_{24}H_{27}ClN_2O$ (394.18): C, 72.99; H, 6.89; N, 7.09. Found: C, 73.15; H, 6.84; N, 7.05%.

1-Phenylethyl-3-benzyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**3j**). It was obtained as brown gum in 76% yield; IR (KBr): 1559, 1602 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (s, 6H), 2.09 (s, 2H), 2.15 (s, 2H), 2.74–2.78 (t, 2H, J = 7.2 Hz), 3.37–3.39 (t, 2H, J = 7.2 Hz), 3.60 (s, 2H), 3.66 (s, 2H), 3.93 (s, 2H), 7.15–7.36 (m, 10H); MS: *m/z* 375.2 (MH^+). Anal. Calcd. for $C_{25}H_{30}N_2O$ (374.24): C, 80.17; H, 8.07; N, 7.48. Found: C, 80.03; H, 8.05; N, 7.51%.

Synthesis of bis-quinazolines 4a–f & 5a–d. General procedure. A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1.5 mL methanol was shaken at room temperature for 5 min. To this mixture, a solution of enaminone **2** (1 mmol) in 5 mL methanol was added in one lot and the resulting mixture was irradiated in a microwave digester for 2–4 min at 180 W at 60°C. At the end of the reaction (monitored by tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) yielding **4a–f and 5a–d** in 51–79% yields.

3,3′-(Ethane-1,2-diyl) bis (1-Phenylethyl -1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**4a**). It was obtained as brown gum in 71% yield; IR (KBr): 1597, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.73–1.94 (m, 4H), 2.16–2.29 (m, 8H), 2.54 (s, 4H), 2.73 (s, 4H), 3.36 (s, 4H), 3.44 (s, 4H), 3.93 (s, 4H), 7.09–7.26 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.36, 25.32, 35.56, 35.75, 47.31, 50.97, 51.28, 70.41, 103.05, 126.95, 128.72, 128.77, 128.84, 137.91, 159.91,159.06,193.74; MS: *m/z* 539.7 (MH^+). Anal. Calcd. for $C_{34}H_{42}N_4O_2$ (538.33): C, 75.80; H, 7.86; N, 10.40. Found: C, 75.96; H, 7.81; N, 10.46%.

3,3′-(Propane-1,3-diyl) bis (1-phenylethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**4b**). It was obtained as brown gum in 68% yield; IR (KBr): 1560, 1659 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66–1.75 (m, 2H), 1.75–1.77 (m, 4H), 2.06–2.10 (m, 8H), 2.44–2.47 (m, 4H), 2.73–2.76 (m, 4H), 3.37–3.40 (m, 8H), 3.81 (s, 4H), 7.09–7.26 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.34, 25.33, 25.77, 29.69, 35.61, 35.72, 48.18, 51.00, 51.56, 69.57, 103.80, 126.92, 128.82, 137.98, 158.82, 193.61; MS: *m/z* 553.7 (MH^+). Anal. Calcd. for $C_{35}H_{44}N_4O_2$ (552.35): C, 76.05; H, 8.02; N, 10.14. Found: C, 76.20; H, 8.09; N, 10.08%.

3,3′-(Butane-1,4-diyl) bis (1-phenylethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**4c**). It was obtained as brown gum in 59% yield; IR (KBr): 1587, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (s, 4H), 1.73–1.76 (m, 4H), 2.10–2.19 (m, 8H), 2.34 (s, 4H), 2.73–2.77 (m, 4H), 3.37 (s, 8H), 4.19 (s, 4H), 7.12–7.26 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.37, 25.34, 25.46, 30.94, 35.63, 35.73, 47.84, 50.97, 53.50, 69.84, 103.84, 126.91, 128.79, 128.81, 137.99, 158.77, 193.61; MS: *m/z* 567.8 (MH^+). Anal. Calcd. for $C_{36}H_{46}N_4O_2$ (566.36): C, 76.29; H, 8.18; N, 9.89. Found: C, 76.50; H, 8.24; N, 9.86%.

3,3′-(Ethane-1,2-diyl) bis (1-phenylethyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**4d**). It was obtained as yellow solid in 65% yield, mp 90°C; IR (KBr): 1547, 1669 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (s, 12H), 2.08 (s, 4H), 2.14 (s, 4H), 2.61 (s, 4H), 2.80–2.85 (t, 4H, J = 6.9Hz), 3.47–3.94 (t, 4H, J = 6.9Hz), 3.55 (s, 4H), 4.03 (s, 4H), 7.18–7.36 (m, 10H); MS: m/z 595.8 (MH^+). Anal. Calcd for $C_{38}H_{50}N_4O_2$ (594.39): C, 76.73; H, 8.47; N, 9.42. Found: C, 76.52; H, 8.51; N, 9.47%.

3,3′-(Propane-1,3-diyl) bis(1-phenylethyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**4e**). It was obtained as brown gum in 75% yield; IR (KBr): 1556, 1651cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (s, 12H), 1.74–1.78 (m, 2H), 2.04 (s, 4H), 2.12 (s, 4H), 2.50–2.55 (t, 4H, J = 7.2Hz), 2.80–2.84 (t, 4H, J = 7.2Hz), 3.44 (s, 4H), 3.59 (s, 4H), 3.95 (s, 4H), 7.18–7.35 (m, 10H); MS: *m/z* 609.4 (MH^+). Anal. Calcd. for $C_{39}H_{52}N_4O_2$ (608.41): C, 76.93; H, 8.61; N, 9.20. Found: C, 76.76; H, 8.65; N, 9.16%.

3,3-(Butane-1,4-diyl) bis (1-phenylethyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**4f**). It was obtained as brown solid in 72% yield, mp 68°C; IR (KBr): 1557, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (s, 12H), 1.58 (s, 4H), 1.98 (s, 4H), 2.14 (s, 4H), 2.47 (s, 4H), 2.81–2.85 (t, 4H, J = 6.9Hz), 3.45–3.50 (m, 8H), 3.94 (s, 4H), 7.18–7.37 (m, 10H); MS: *m/z* 623.4 (MH^+). Anal. Calcd. for $C_{40}H_{54}N_4O_2$ (622.42): C, 77.13; H, 8.74; N, 8.99. Found: C, 77.01; H, 8.78; N, 8.96%.

3,3-(1,4-Phenylene) bis (1-phenylethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**5a**). It was obtained as brown solid in 51% yield, mp 95°C; IR (KBr): 1557,1632 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25–1.28 (m, 4H), 2.06 (s, 4H), 2.26 (s, 4H), 2.69 (s, 4H), 3.42–3.45 (m, 4H), 3.92 (s, 4H), 4.17 (s, 4H), 6.93–7.26 (m, 14H); MS: *m/z* 587.8 (MH^+). Anal. Calcd. for $C_{38}H_{42}N_4O_2$ (586.33): C, 77.78; H, 7.21; N, 9.55. Found: C, 77.97; H, 7.24; N, 9.50%.

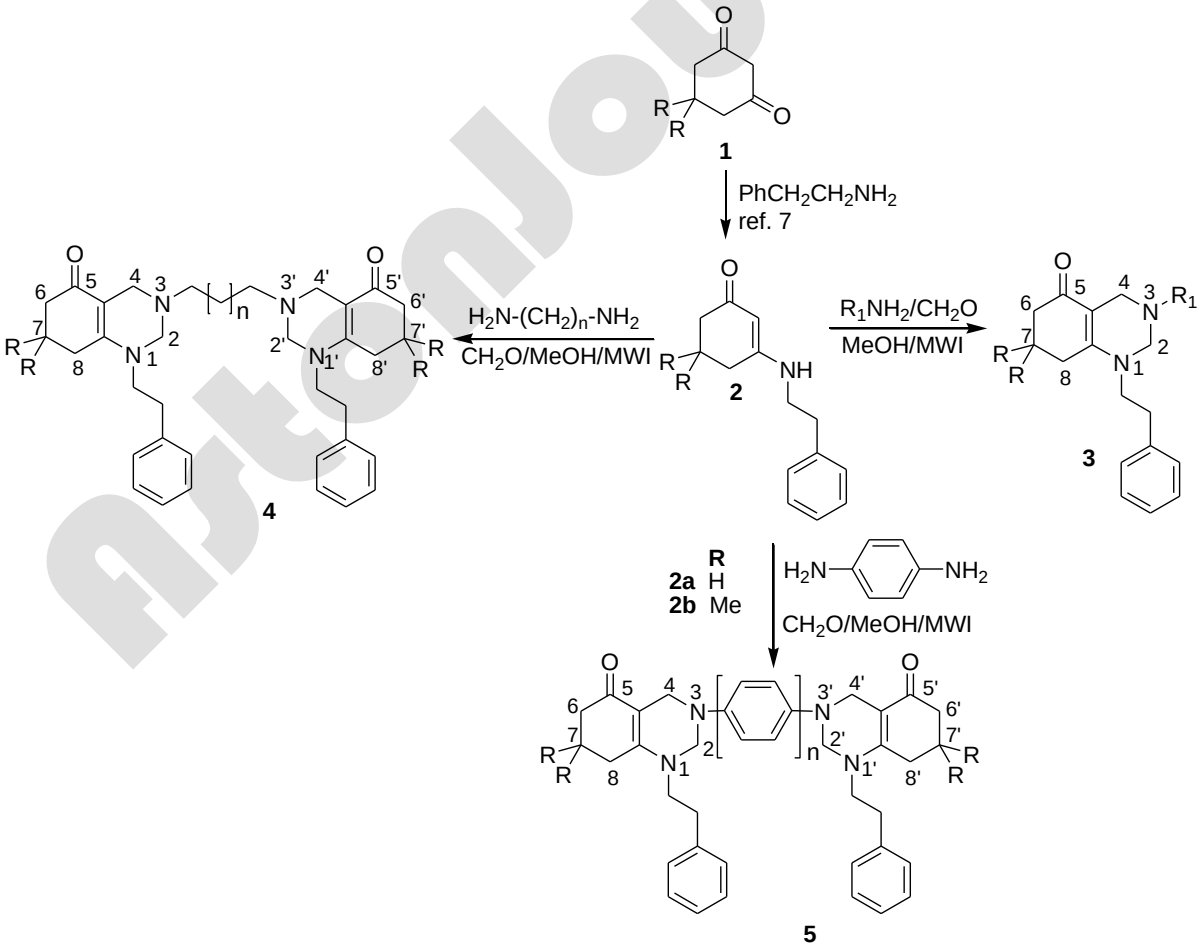
3,3-(Biphenyl-4,4′-diyl) bis (1-phenylethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**5b**). It was obtained as brown gum in 61% yield; IR (KBr): 1545, 1659 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25–1.28 (m, 4H), 1.79 (s, 4H), 2.26 (s, 4H), 2.92–2.96 (m, 8H), 3.30 (s, 4H), 3.49 (s, 4H), 7.20–7.28 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 17.17, 21.35, 25.44, 29.70, 35.57, 36.62, 45.27, 107.99, 126.45, 128.50, 128.63, 128.88, 138.90, 166.46, 194.04; MS: *m/z* 661.8 (M^+). Anal. Calcd. for $C_{44}H_{46}N_4O_2$ (662.36): C, 79.73; H, 6.99; N, 8.45. Found: C, 79.55; H, 7.02; N, 8.40%.

3,3′-(1,4-Phenylene) bis (1-phenylethyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**5c**). It was obtained as brown solid in 65% yield, mp 88°C; IR (KBr): 1549, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (s, 12H), 1.88 (s, 4H), 2.11 (s, 4H), 2.65–2.69 (t, 4H, J = 7.8 Hz), 3.39–3.43 (t, 4H, J = 6.4 Hz), 4.09 (s, 4H), 4.59 (s, 4H) 7.21–7.27 (m, 14H); MS: *m/z* 643.3 (MH^+). Anal. Calcd. for $C_{42}H_{50}N_4O_2$ (642.39): C, 78.47; H, 7.84; N, 8.72. Found: C, 78.61; H, 7.89; N, 8.75%.

3,3′-(Biphenyl-4,4′-diyl) bis (1-phenylethyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one) (**5d**). It was obtained as brown solid in 79% yield, mp 96^{0}C; IR (KBr): 1538, 1609 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (s, 12H), 2.11 (s, 4H), 2.37 (s, 4H), 3.25–3.29 (t, 4H, J = 7.2Hz), 3.41–3.46 (m, 4H), 4.17 (s, 4H), 4.62 (s, 4H), 6.91–7.48 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 13.64, 22.20, 28.02, 28.28, 28.87, 29.20, 31.43, 31.75, 38.89, 41.17, 45.73, 48.78, 49.52, 70.49, 103.24, 128.29, 128.44, 155.35, 192.80; MS: *m/z* 719.7 (MH^+). Anal. Calcd. for $C_{48}H_{54}N_4O_2$ (718.42): C, 80.19; H, 7.57; N, 7.79. Found: C, 80.05; H, 7.54; N, 7.82%.

3. Results and Discussion

When 3-phenylethylaminocyclohexenone **2a** was treated with a mixture of methylamine and formaldehyde (1 : 2) under the influence of microwaves, a product was obtained in 78% yields which was characterized as 1-phenylethyl-3-methyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **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–e** were isolated in 55–78% yields. The infrared spectra of **3a–e** showed strong peaks in the region of 1553–1615 cm^{-1} due to extensively delocalized double bonds and carbonyl groups. In the ^{1}H NMR spectra of **3a–e**, the methylene protons at C-2 resonated near 3.85 ppm except in **3b** where they appeared in the vicinity of 4.57 ppm but in **3d** it appeared near 3.45 ppm. This increment in chemical shift could be attributed to the presence of delocalization of N-3 lone pair of electrons with phenyl ring. Methylene protons at C-2 for **3f–j** resonated at higher δ value than the corresponding **3a–e** which may be due to presence of electronic donating methyl groups at C-7 in **3f–j**. Probably a similar explanation could be extended for the appearance of CH_2 protons at C-4 close to 3.43 ppm except in **3b** and **3d** where they were found to resonate near 4.14 ppm and 2.96 ppm respectively. While CH_2 protons at C-7 in **3a–e** appeared as multiplets in the range of 1.52–1.83 ppm, those at C-6 and C-8 resonated close to 2.40 and 2.30 ppm respectively. The methylene protons at N-1 gave multiplets close to 2.84–3.36 ppm whereas the adjacent methylene protons gave multiplets close to 2.40–2.69 ppm. The reactions of **2b** with formaldehyde and primary amines were subsequently examined under similar conditions and the expected 1-phenylethyl-3-alkyl/aralkyl/aryl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **3f–j** were isolated in 62–85% yields, and their structures could be established with the help of analytical and spectral data. The infrared spectra of **3f–j** showed strong peaks in the region of 1526–1623 cm^{-1}. The ^{1}H NMR spectra of quinazoline rings of **3f–j** were found to have a similar pattern as those of **3a–e.** However, the six methyl protons at C-7 appeared as sharp singlets around 0.90 ppm and the CH_2 protons at C-6 and C-8 resonated in ranges of 1.99–2.17 and 2.10–2.25 ppm respectively. The structures of the molecules were well supported by their $^{13}CNMR$ spectra.



Scheme

Encouraged by the successful synthesis of octahydroquinazolines **3a–j**, 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 71% yield, the structure of which was established to be 3,3'-(Ethane-1,2-diyl)bis(1-phenylethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 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–f** in 51–68% overall yields (Table 1). We were thus able to connect two octahydroquinazoline rings through flexible aliphatic chains **4a–f** and through aromatic linkers **5a–d (Scheme)**. The structures of which could be established with the help of spectral and analytical data. The infrared spectra of **4a–f** and **5a–d** showed strong peaks in the range of 1538–1669 cm^{-1} due to extensive delocalization of the enaminone moiety and carbonyl group. The ^{1}H 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 2.61–2.73 ppm while those in propylene resonated in the range of 2.04–2.47 ppm and in butylene appeared in the ranges of 2.14–2.34 ppm. The dimeric structures of **4a–d** and **5a–d** were further supported by their ^{13}C and mass spectra.

Table 1: Synthesis of quinazolines **3a–j**, **4a–d** and **5a–d**.

Compound	R	R_1	n	Microwave Irradiation (W/min)
3a	H	$-CH_3$	–	180/2
3b	H	$-C_6H_5$	–	180/3
3c	H	$-C_6H_4-CH_3$	–	180/2.5
3d	H	$-C_6H_4-Cl$	–	180/3
3e	H	$-CH_2-C_6H_5$	–	180/2.5
3f	$-CH_3$	$-CH_3$	–	180/2
3g	$-CH_3$	$-C_6H_5$	–	180/1.5
3h	$-CH_3$	$-C_6H_4-CH_3$	–	180/1.5
3i	$-CH_3$	$-C_6H_4$-Cl	–	180/2
3j	$-CH_3$	$-CH_2-C_6H_5$	–	180/1.5
4a	H	–	0	180/3
4b	H	–	1	180/3.5
4c	H	–	2	180/2
4d	$-CH_3$	–	0	180/2
4e	$-CH_3$	–	1	180/2.5
4f	$-CH_3$	–	2	180/3
5a	H	–	1	180/3.5
5b	H	–	2	180/3
5c	$-CH_3$	-	1	180/3
5d	$-CH_3$	–	2	180/3

4. Conclusion

The present paper describes an 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 was responsible for execution of the work. EK were involved in monitoring the progress of the work and in the interpretation of spectral and analytical data. JNV was involved in designing, planning and literature survey of the work.

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