

# Microwave-assisted Green Synthesis and Integrated Bioinformatics Study Reveal Curcumin Analogs Dibenzylidene-cyclohexanones as Novel Potential Anti-Tuberculosis Agents



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## General Method

Substituted benzaldehydes (2 molar equivalents) with cyclohexanone (1 molar equivalent) in the presence of an acid catalyst (HCl), sometimes combined with glacial acetic acid, in a suitable organic solvent. Reactions were carried out in a Monowave 400 microwave synthesizer (Anton Paar), where the reaction mixtures were stirred at 600 rpm and irradiated at 80°C for approximately 9 minutes. The crude products were then isolated by washing with appropriate solvent systems (commonly ethanol-water or acetone-water mixtures) and subsequently purified through recrystallization to afford the final yellow crystalline solids.

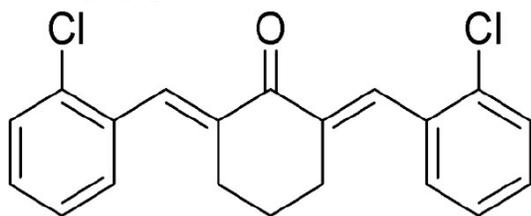
For each derivative, substituted benzaldehydes such as 2-chlorobenzaldehyde, 2-bromobenzaldehyde, 3-bromobenzaldehyde, or 4-chlorobenzaldehyde were employed, tailoring the reaction to produce specific compounds like 2,6-bis(2'-chlorobenzylidene)cyclohexanone (A-125), 2,6-bis(2'-bromobenzylidene)cyclohexanone (A-128), or 2,6-bis(4'-chlorobenzylidene)cyclohexanone (A-144). After microwave irradiation, products were extracted, washed, and recrystallized using solvent combinations optimized for

each compound's solubility and purity. The final products were characterized using Thin-Layer Chromatography (TLC), melting point determination, Infrared (IR) Spectroscopy, Nuclear Magnetic Resonance (NMR) Spectroscopy, and High-Resolution Mass Spectrometry (HRMS), confirming structural identity and purity. For compounds A-143 and A-150, NMRs are not provided because a suitable solvent has not been obtained yet.

## Synthesis of 2,6-bis(2'-chlorobenzylidene)cyclohexanone (A-125)

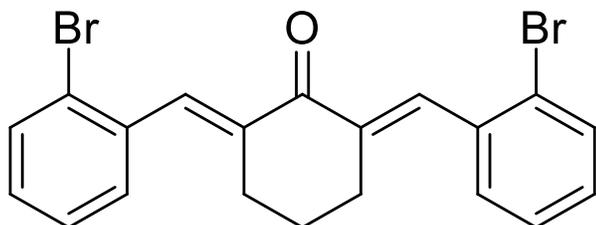
2-Chlorobenzaldehyde (7.11 mmol; 1 g), cyclohexanone (3.56 mmol; 0.368 mL), Glacial acetic acid (0.25 mL), HCl (2 drops); washed with EtOH:H<sub>2</sub>O; recrystallised with MeOH:H<sub>2</sub>O yielded **A-125** as yellow solid in 67%; R<sub>f</sub> = 0.75 (EtOAc:Hex = 1:4); m.p. = 106 - 110°C; IR (neat): ν<sub>max</sub> cm<sup>-1</sup>: 1604.77 (C=O), 1666.50 (C=C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.92 (2H, s, CH=C), 7.39 - 7.42 (2H, m, H-Ph), 7.31- 7.33 (2H, m, H-Ph), 7.23 - 7.27(4H, m, H-Ph), 2.76 (4H, m, CH<sub>2</sub>-cyc), 1.72 (2H, m, CH<sub>2</sub>-cyc); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 23.33, 28.57, 126.56, 129.84, 130.74,

134.19, 134.45, 135.17, 137.88, 189.81; HRMS (ESI):  
calcd. for  $C_{20}H_{16}Cl_2O$  [ $M^+$ ] = 343.2464



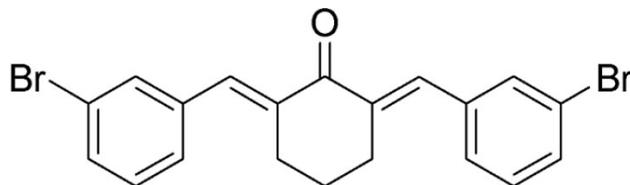
### Synthesis of 2,6-bis(2'-bromobenzylidene)cyclohexanone (A-128)

2-Bromobenzaldehyde (5.40 mmol; 0.63 mL), cyclohexanone (2.70 mmol; 0.265 mL), Glacial acetic acid (0.25 mL), HCl (2 drops); washed with EtOH:H<sub>2</sub>O; recrystallised with Acetone:H<sub>2</sub>O yielded **A-128** as yellow solid in 56%; Rf = 0.625 (EtOAc:Hex = 1:4); m.p. = 133 - 135°C; IR (neat):  $\nu_{max}$  cm<sup>-1</sup> 1566.2(C=O), 1658.78 (C=C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.85 (2H, s, CH=C), 7.63 (2H, dd,  $J_1$  = 7.5 Hz,  $J_2$  = 2.5 Hz, H-Ph), 7.28- 7.34 (4H, m, H-Ph), 7.19 (2H, ddd,  $J_1$  = 9 Hz,  $J_2$  = 6.5 Hz,  $J_3$  = 3 Hz, H-Ph), 2.75 (4H, m, CH<sub>2</sub>-cyc), 1.75 (2H, m, CH<sub>2</sub>-cyc); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  23.08, 28.27, 125.14, 126.87, 127.06, 129.72, 130.52, 132.91, 136.17, 136.35, 137.37, 189.6; HRMS (ESI): calcd. for  $C_{20}H_{16}Br_2O$  [ $M^+$ ] = 432.1484, found [M+Na]<sup>+</sup> = 454.9444



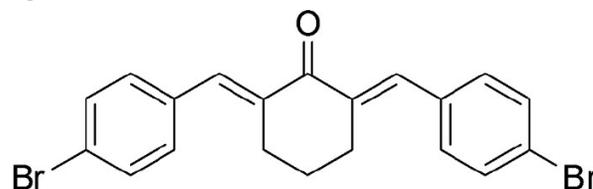
### Synthesis of 2,6-bis(3'- bromobenzylidene)cyclohexanone (A-135)

3-Bromobenzaldehyde (5.234 mmol; 1 g), cyclohexanone (2.62 mmol; 0.271 mL), Glacial acetic acid (0.25 mL), HCl (2 drops); washed with EtOH:H<sub>2</sub>O; recrystallised with DCM:Hex yielded **A-135** as yellow solid in 81%; Rf = 0.7 (EtOAc:Hex = 1:9); m.p. = 112 - 114°C; IR (neat):  $\nu_{max}$  cm<sup>-1</sup> 1604.77 (C=O), 1666.5(C=C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.67 (2H, s, CH=C), 7.56 (2H, s, H-Ph), 7.43 (2H, dd,  $J_1$  = 8 Hz,  $J_2$  = 2 Hz, H-Ph), 7.34 (2H, d,  $J$  = 8 Hz, H-Ph), 7.25 (2H, dd,  $J_1$  = 8 Hz,  $J_2$  = 2 Hz, H-Ph), 2.87 (4H, t,  $J$  = 5.5 Hz, CH<sub>2</sub>-cyc), 1.77 (2H, m, CH<sub>2</sub>-cyc); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  22.9, 28.46, 122.63, 129.09, 130.08, 131.66, 132.95, 135.66, 137.8, 189.77; HRMS (ESI): calcd. for  $C_{20}H_{16}Br_2O$  [ $M^+$ ] = 432.1484



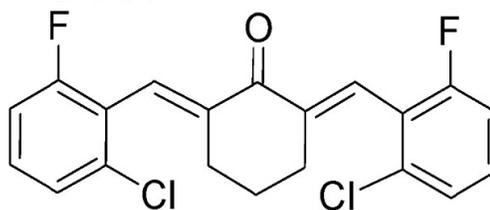
### Synthesis of 2,6-bis(4'-bromobenzylidene)cyclohexanone (A-137)

Bromobenzaldehyde (5.41 mmol; 1 g), cyclohexanone (2.70 mmol; 0.275 mL), Glacial acetic acid (0.25 mL), HCl (2 drops); washed with water; recrystallised with Acetone:water yielded **A-137** as yellow solid in 74%; Rf = 0.45 (EtOAc:Hex = 1:1); m.p. = 166 - 169°C; IR (neat):  $\nu_{max}$  cm<sup>-1</sup> 1606.54 (C=O), 1666.04 (C=C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.70 (2H, s, CH=C), 7.53 (4H, m, H-Ph), 7.31 (4H, m, H-Ph), 2.87 (4H, m, CH<sub>2</sub>-cyc), 1.79 (2H, m, CH<sub>2</sub>-cyc); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  22.77, 28.37, 122.94, 131.64, 131.78, 134.69, 135.82, 136.48, 189.83; HRMS (ESI): calcd. for  $C_{20}H_{16}Br_2O$  [ $M^+$ ] = 432.1484



### Synthesis of 2,6-bis(2'-chloro-6'-fluorobenzylidene)cyclohexanone (A-143)

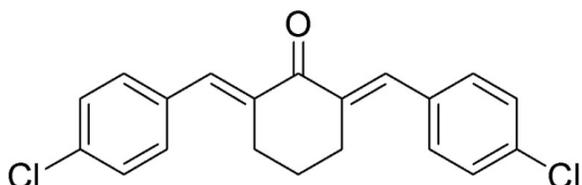
2-Chloro-6-fluorobenzaldehyde (6.31 mmol; 1 g), cyclohexanone (3.15 mmol; 0.326 mL), Glacial acetic acid (0.25 mL), HCl (2 drops); extracted with chloroform and water; recrystallised with EtOH:water yielded **A-143** as a yellow solid in 29%; Rf = 0.8 (EtOAc:Hex = 1:9); m.p. = °C. IR (neat):  $\nu_{max}$  cm<sup>-1</sup>. NMRs are not provided because a suitable solvent has not been obtained yet. HRMS (ESI): calcd. for  $C_{20}H_{14}Cl_2F_2O$  [ $M^+$ ] = 379.2274



### Synthesis of 2,6-bis(4'-chlorobenzylidene)cyclohexanone (A-144)

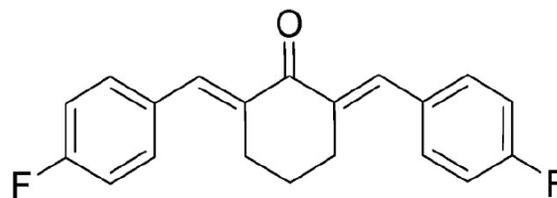
4-Chlorobenzaldehyde (7.11 mmol; 1 g), cyclohexanone (3.56 mmol; 0.368 mL), Glacial acetic acid (0.25 mL), HCl

(2 drops); washed with EtOH and water; recrystallised with Acetone:water yielded **A-144** as yellow solid in 58%; Rf = 0.83 (EtOAc:Hex = 1:3); m.p. = 146 - 148°C; IR (neat):  $\nu_{\text{max}} \text{ cm}^{-1}$  1604.77 (C=O), 1666.5 (C=C);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.71 (2H, s, CH=C), 7.34 - 7.38 (8H, m, H-Ph), 2.86 (4H, t,  $J$  = 6 Hz,  $\text{CH}_2$ -cyc), 1.77 (2H, m,  $\text{CH}_2$ -cyc);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.94, 28.53, 128.79, 128.83, 129.19, 131.39, 131.78, 134.42, 134.74, 135.89, 136.32, 136.53, 189.85; HRMS (ESI): calcd. for calcd. for  $\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{O}$  [ $\text{M}^+$ ] = 343.2464



#### Synthesis of 2,6-bis(4'-fluorobenzylidene)cyclohexanone (A-152)

4-Fluorobenzaldehyde (8.06 mmol; 1 g), cyclohexanone (4.03 mmol; 0.395 mL), Glacial acetic acid (0.25 mL), HCl (2 drops); washed with EtOH and water; recrystallised with Acetone:water yielded **A-152** as yellow solid in 23%; Rf = 0.725 (EtOAc:Hex = 1:4); m.p. = 155 - 157°C; IR (neat):  $\nu_{\text{max}} \text{ cm}^{-1}$  1604.77 (C=O), 1658.78 (C=C);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.75 (2H, s, CH=C), 7.44 (4H, m, H-Ph), 7.09 (4H, m, H-Ph), 2.86 (4H, m,  $\text{CH}_2$ -cyc), 1.79 (2H, m,  $\text{CH}_2$ -cyc);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.88, 28.35, 115.39, 115.47, 115.57, 115.64, 132.28, 132.33, 135.69, 135.86, 189.98; HRMS (ESI): calcd. for  $\text{C}_{20}\text{H}_{16}\text{F}_2\text{O}$  [ $\text{M}^+$ ] = 310.1169



#### Synthesis of 2,6-bis(2',4'-dichlorobenzylidene)cyclohexanone (A-154)

2,6-Dichlorobenzaldehyde (5.71 mmol; 1 g), cyclohexanone (2.86 mmol; 0.295 mL), THF (0.25 mL), HCl (2 drops); washed with water; recrystallised with Acetone: $\text{H}_2\text{O}$  yielded **A-154** as yellow solid in 30%; Rf 0.65= (EtOAc:Hex = 1:9); m.p. = 166 - 167°C; IR (neat):  $\nu_{\text{max}} \text{ cm}^{-1}$  1597.06 (C=O), 1658.78 (C=C);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (2H, s, CH=C), 7.45 (2H, s, H-Ph), 7.26 (4H, m, H-Ph), 2.75 (4H, m,  $\text{CH}_2$ -cyc), 1.76 (2H, m,  $\text{CH}_2$ -cyc);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.02, 28.36, 126.65, 126.70, 129.62, 129.69, 131.13, 131.17, 131.20, 132.77, 132.03, 134.83, 135.80, 137.98, 189.19; HRMS (ESI): calcd. for  $\text{C}_{20}\text{H}_{14}\text{Cl}_4\text{O}$  [ $\text{M}^+$ ] = 412.1366

