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# A facile and one-pot synthesis of new tetrahydrobenzo[b]pyrans in water under microwave irradiation

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## Abstract

Eleven new tetrahydrobenzo[b]pyran derivatives were synthesized via a three component reaction of different aromatic aldehydes, methyl cyanoacetate and 1,3-cyclohexadione, with water as solvent under catalyst-free microwave irradiation. The structures of all the new molecules were well analysed and their structures established by using various spectral techniques ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{15}\text{N}$  NMR and HRMS). Various advantages of reported protocol are the ease of preparation, short reaction times (10 min), aqueous solvent and excellent yields (89–98%). Additionally, this method provides a clean access to the desired products by simple workup.

**Keywords:** Microwave irradiation, Multicomponent reactions, One-pot synthesis, Green synthesis, Benzopyrans

## Introduction

Multi component reaction (MCR) is an important technique for the effective and swift synthesis of a wide range of composite heterocyclic frameworks [1–3]. MCR is a distinctly focused approach for organic synthesis, because of their ability to make composite molecular functionality from the three or more starting materials through one-pot reaction [3–5] and for the creation of new C–C and C–O bonds [6]. Improvement in new multicomponent reactions with an environmentally benign perception has received ample attention due to the prospect of compliance with green chemistry principles [6, 7].

Reactions facilitated by microwave irradiation (MWI) have attracted significant attention, owing to the environmental benign operational simplicity and higher selectivity [8, 9]. MWI enhances the reaction rate by providing more energy to the reacting molecules and in many cases the reaction rate is 10- to 1000-fold faster than conventional heating [10, 11]. With advent of MWI, catalyst-free and solvent-free reactions have increased as they provide an opportunity to work with open vessels

[12]. Furthermore, it circumvents the problems associated with higher-pressure conditions and offers a possibility for scaling-up the reaction under a moisture free environment [13]. Moreover, MWI offers other benefits including reduced reaction time, fast reaction optimization, mild reaction conditions, higher yields, reproducibility, lower solvent consumption and ease of synthesis of difficult compounds [14].

Heterocyclic frameworks have always presented an opportunity for the preparation of numerous privileged scaffolds with diverse biological activity [15–17]. Ease of MCR assembly and many sites for diversification helped mapping bioactive chemical space [7, 15–19]. Furthermore, new innovative and workable procedures for the synthesis of different heterocyclic molecules are always attractive. Benzopyran and its derivatives have appealed to the researchers from medicinal, organic, industrial and other chemical fields, due to their useful pharmacological or medicinal applications, such as anticancer [20], anti-HIV [21], antifungal [22], antiviral [23], anti-inflammatory [24], antimalarial [25] antioxidant [26] and antimicrobial [27] activities. They are also broadly used in perfumes, cosmetics, agrochemicals and in food as additives [28, 29]. Literature reveals reports for synthesis of benzopyrans using with various catalysts like hexamethylenetetraminebromine [30],

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magnetite-dihydrogen phosphate [31], Bmim[BF<sub>4</sub>] [32], PPA-SiO<sub>2</sub> [33], Ca(OTf)<sub>2</sub>:Bu<sub>4</sub>NPF<sub>6</sub> [34], phenylboronic acid [35] and H<sub>6</sub>P<sub>2</sub>W<sub>12</sub>O<sub>62</sub>·H<sub>2</sub>O [36], MWI/PEG [37] etc. Previously reported procedures come with various limitations, like use of expensive reagents/catalysts, toxic solvents, strict reaction conditions, low product yields, long reaction times and nonrecyclability of catalysts, which confine their scope in practical applications (details in Additional file 1: Table S1).

In our continuous quest for evolving facile and efficient approaches for the synthesis of diverse heterocycles via MCR methodologies [38–40], we have earlier reported the protocols for the synthesis of several heterocyclic biological active molecules [41–44]. The current work focus on the microwave irradiation approach for the first time, for the synthesis of a new series of benzopyran derivatives, through one-pot reaction of aromatic aldehyde, methyl cyanoacetate and 1,3-cyclohexadione using water as solvent.

## Experimental procedure

### General procedure for synthesis of tetrahydrobenzo[*b*]pyrans (4a–k)

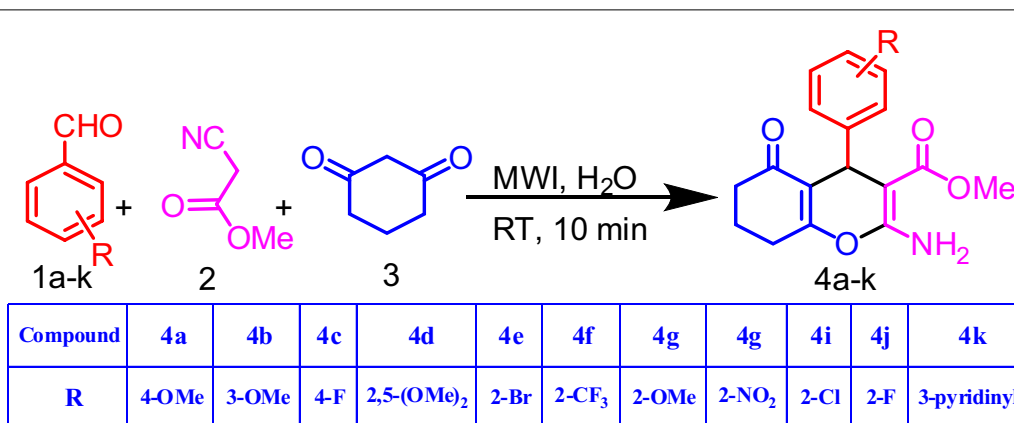
A mixture of aromatic aldehyde (1 mmol), methyl cyanoacetate (1.1 mmol) and 1,3-cyclohexadione (1 mmol) were dissolved in water (5.0 mL) in a microwave vessel. Then, the mixture was microwave irradiated at 150 W for 10 min (Fig. 1). Thin layer chromatography (TLC) analysis was used to monitor the reaction progress. After completion of the reaction, the reaction mixture was cooled, filtered and washed with cold ice water. Further, the crude product was recrystallized by using ethanol to obtain pure product. Structures of all products were confirmed based on the spectral analysis with <sup>1</sup>H NMR, <sup>15</sup>N NMR (GHSQC), <sup>13</sup>C NMR, <sup>19</sup>F NMR, FTIR, and HRMS (instrumentation details in Additional file 1).

### Spectral data of representative compounds

*Methyl 2-amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4a)* Mp.: 193–195 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 1.80–1.82 (m, 1H, CH<sub>2</sub>), 1.91–1.96 (m, 1H, CH<sub>2</sub>), 2.21–2.30 (m, 2H, CH<sub>2</sub>), 2.60–2.63 (m, 2H, CH<sub>2</sub>), 3.67 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.48 (s, 1H, CH), 6.75 (d, *J* = 8.64 Hz, 2H, ArH), 7.09 (d, *J* = 8.64 Hz, 2H, ArH), 7.50 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 19.85, 26.23, 30.62, 32.02, 36.29, 50.44, 53.09, 54.85, 55.73, 77.82, 79.11, 98.23, 113.22, 141.95, 123.91, 128.33, 133.51, 138.58, 154.55, 157.33, 159.23, 162.87, 163.57, 168.34, 196.02; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ = 7.50 (s, 2H, NH<sub>2</sub>); FT-IR: 3397, 3302, 2944, 2843, 1725, 1689, 1583, 1509, 1429; HRMS of [C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub> + Na]<sup>+</sup> (*m/z*): 352.1161; Calcd.: 352.1161.

*Methyl 2-amino-4-(3-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4b)* Mp.: 209–210 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 1.85–1.90 (m, 1H, CH<sub>2</sub>), 1.99–2.03 (m, 1H, CH<sub>2</sub>), 2.30–2.36 (m, 2H, CH<sub>2</sub>), 2.64–2.68 (m, 2H, CH<sub>2</sub>), 3.58 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 4.59 (s, 1H, CH), 6.73–6.78 (m, 3H, ArH), 7.18 (t, *J* = 8.68 Hz, 1H, ArH), 7.60 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 19.82, 26.24, 32.77, 36.25, 50.49, 54.76, 77.40, 110.60, 113.73, 116.78, 119.51, 128.93, 147.95, 158.80, 159.37, 164.15, 168.26, 196.03; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ = 7.60 (s, 2H, NH<sub>2</sub>); FT-IR: 3404, 3280, 2946, 2836, 1682, 1665, 1594, 1510; HRMS of [C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub> + H]<sup>+</sup> (*m/z*): 330.1763; Calcd.: 330.1766.

*Methyl 2-amino-4-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4c)* Mp.: 188–189 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 1.79–1.85 (m, 1H, CH<sub>2</sub>), 1.92–1.98 (m, 1H, CH<sub>2</sub>), 2.23–2.30 (m, 2H, CH<sub>2</sub>),



**Fig. 1** Three-component synthetic route for tetrahydrobenzo[*b*]pyran derivatives

2.59–2.61 (m, 2H, CH<sub>2</sub>), 3.50 (s, 3H, OCH<sub>3</sub>), 4.53 (s, 1H, CH), 7.01 (d, *J*=15.72 Hz, 2H, ArH), 7.15 (d, *J*=3.08 Hz, 2H, ArH), 7.56 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 19.80, 26.25, 30.65, 32.40, 36.23, 50.48, 53.33, 77.38, 101.91, 115.55, 116.73, 128.04, 128.08, 133.65, 133.75, 153.88, 159.23, 162.28, 163.40, 164.06, 168.17, 196.01; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=7.56 (s, 2H, NH<sub>2</sub>); <sup>19</sup>F NMR (376.58 MHz, DMSO): –104.15; FT-IR: 3420, 3309, 2949, 1691, 1648, 1520, 1487; HRMS of [C<sub>17</sub>H<sub>16</sub>NO<sub>4</sub>F + Na]<sup>+</sup> (m/z): 340.0992; Calcd.: 340.1008.

*Methyl 2-amino-4-(2,5-dimethoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4d)* M.p.: 222–223 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.90–2.03 (m, 3H, CH<sub>3</sub>), 2.29–2.33 (m, 2H, CH<sub>2</sub>), 2.51–2.56 (m, 2H, CH<sub>2</sub>), 3.58 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 4.76 (s, 1H, CH), 6.17 (s, 2H, NH<sub>2</sub>), 6.64–6.67 (m, 1H, ArH), 6.72 (s, 1H, ArH), 6.90 (d, *J*=3.08 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 20.36, 26.97, 31.44, 36.90, 50.78, 55.67, 56.59, 79.03, 111.99, 112.74, 116.05, 117.44, 122.63, 134.12, 149.73, 152.57, 153.14, 158.87, 163.48, 169.80, 196.56; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=6.17 (s, 2H, NH<sub>2</sub>); FT-IR: 3391, 3270, 2952, 2839, 1727, 1685, 1590, 1428; HRMS of [C<sub>19</sub>H<sub>21</sub>NO<sub>6</sub> + Na]<sup>+</sup> (m/z): 382.1266; Calcd.: 382.1267.

*Methyl 2-amino-4-(2-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4e)* M.p.: 231–232 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.86–1.89 (m, 1H, CH<sub>2</sub>), 1.97–2.04 (m, 1H, CH<sub>2</sub>), 2.20–2.25 (m, 1H, CH<sub>2</sub>), 2.30–2.33 (m, 1H, CH<sub>2</sub>), 2.66 (t, *J*=6.08 Hz, 2H, CH<sub>2</sub>), 3.51 (s, 3H, OCH<sub>3</sub>), 4.89 (s, 1H, CH), 7.06 (t, *J*=7.88 Hz, 1H, ArH), 7.21 (d, *J*=7.8 Hz, 1H, ArH), 7.29 (t, *J*=6.64 Hz, 1H, ArH), 7.47 (d, *J*=6.8 Hz, 1H, ArH), 7.68 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 19.81, 26.37, 30.65, 33.99, 36.39, 50.19, 76.74, 115.65, 123.18, 130.01, 132.47, 144.95, 153.41, 158.99, 163.94, 168.44, 195.65; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=7.68 (s, 2H, NH<sub>2</sub>); FT-IR: 3409, 3292, 2949, 1724, 1689, 1645, 1514; HRMS of [C<sub>17</sub>H<sub>16</sub>BrNO<sub>4</sub> + Na]<sup>+</sup> (m/z): 400.0157; Calcd.: 400.0160.

*Methyl 2-amino-4-(3-(trifluoromethyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4f)* M.p.: 214–216 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.94–2.08 (m, 2H, CH<sub>2</sub>), 2.30–2.32 (m, 2H, CH<sub>2</sub>), 2.57–2.62 (m, 2H, CH<sub>2</sub>), 3.56 (s, 3H, OCH<sub>3</sub>), 5.32 (s, 1H, CH), 6.21 (s, 2H, NH<sub>2</sub>), 7.22 (t, *J*=7.56 Hz, 2H, ArH), 7.38 (t, *J*=7.4 Hz, 1H, ArH), 7.51 (d, *J*=7.92 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 20.19, 27.00, 36.82, 50.70, 53.70, 80.66, 117.82, 126.30, 126.93, 126.97, 129.94, 130.62, 131.15, 144.70, 158.15, 162.90, 169.47, 196.26; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=6.21 (s, 2H, NH<sub>2</sub>); <sup>19</sup>F NMR (376.58 MHz, DMSO): –53.68; FT-IR: 3500,

3415, 3308, 2948, 1689, 1650, 1526, 1307; HRMS of [C<sub>18</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>4</sub> + Na]<sup>+</sup> (m/z): 390.0928; Calcd.: 390.0929.

*Methyl 2-amino-4-(2-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4g)* mp 235–237 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.76–1.95 (m, 2H, CH<sub>2</sub>), 2.14–2.25 (m, 2H, CH<sub>2</sub>), 2.55–2.59 (m, 2H, CH<sub>2</sub>), 3.45 (s, 3H, OCH<sub>3</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 4.60 (s, 1H, CH), 6.76–6.80 (m, 1H, ArH), 6.85 (t, *J*=7.44 Hz, 1H, ArH), 7.05–7.07 (m, 1H, ArH), 7.12 (t, *J*=5.76 Hz, 1H, ArH), 7.46 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 20.49, 26.85, 31.40, 36.91, 39.99, 50.72, 56.09, 76.63, 112.38, 115.28, 120.11, 127.59, 131.50, 133.55, 158.21, 160.12, 164.63, 169.13, 196.32; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=7.46 (s, 2H, NH<sub>2</sub>); FT-IR: 3389, 3251, 3192, 2946, 1683, 1637, 1529, 1460; HRMS of [C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub> + H]<sup>+</sup> (m/z): 330.0929; Calcd.: 330.0937.

*Methyl 2-amino-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4h)* M.p.: 218–220 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.80–1.86 (m, 1H, CH<sub>2</sub>), 1.92–1.98 (m, 1H, CH<sub>2</sub>), 2.13–2.20 (m, 1H, CH<sub>2</sub>), 2.25–2.30 (m, 1H, CH<sub>2</sub>), 2.61 (t, *J*=5.88 Hz, 2H, CH<sub>2</sub>), 3.38 (s, 3H, OCH<sub>3</sub>), 5.32 (s, 1H, CH), 7.29–7.34 (m, 2H, ArH), 7.53–7.57 (m, 1H, ArH), 7.71 (s, 2H, NH<sub>2</sub>), 7.73 (d, *J*=6.92 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 19.73, 26.41, 28.57, 36.29, 50.41, 76.37, 115.40, 123.81, 126.97, 130.23, 132.80, 140.65, 148.74, 159.16, 164.48, 168.13, 195.80; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=7.71 (s, 2H, NH<sub>2</sub>); FT-IR: 3518, 3401, 3292, 2947, 1688, 1649, 1519, 1351; HRMS of [C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub> + Na]<sup>+</sup> (m/z): 367.0908; Calcd.: 367.0906.

*Methyl 2-amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4i)* M.p.: 210–213 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.87–1.95 (m, 2H, CH<sub>2</sub>), 2.23–2.26 (m, 2H, CH<sub>2</sub>), 2.46–2.51 (m, 2H, CH<sub>2</sub>), 3.49 (s, 3H, OCH<sub>3</sub>), 4.94 (s, 1H, CH), 6.13 (s, 2H, NH<sub>2</sub>), 6.97 (t, *J*=7.72 Hz, 1H, ArH), 7.06 (t, *J*=7.36 Hz, 1H, ArH), 7.16 (d, *J*=6.56 Hz, 1H, ArH), 7.21 (d, *J*=7.68 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 20.24, 26.97, 32.99, 36.87, 50.78, 79.19, 116.17, 126.20, 127.34, 129.84, 132.11, 133.67, 142.01, 158.36, 163.45, 169.52, 196.39; <sup>15</sup>N NMR (40.55 MHz, DMSO-*d*<sub>6</sub>) δ=6.13 (s, 2H, NH<sub>2</sub>); FT-IR: 3453, 3392, 2954, 1721, 1687, 1603, 1492; HRMS of [C<sub>17</sub>H<sub>16</sub>ClNO<sub>4</sub> + Na]<sup>+</sup> (m/z): 356.1169; Calcd.: 356.1168.

*Methyl 2-amino-4-(2-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4j)* M.p.: 217–219 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ=1.96–2.05 (m, 2H, CH<sub>2</sub>), 2.31–2.35 (m, 2H, CH<sub>2</sub>), 2.56–2.60 (m, 2H, CH<sub>2</sub>), 3.60 (s, 3H, OCH<sub>3</sub>), 4.84 (s, 1H, CH), 6.21 (s, 2H, NH<sub>2</sub>), 6.88–6.93 (m, 1H, ArH), 7.01 (t, *J*=6.28 Hz, 1H, ArH), 7.08–7.11 (m, 1H, ArH), 7.29–7.33 (m, 1H, ArH); <sup>13</sup>C

NMR (100 MHz, DMSO- $d_6$ ): 20.28, 26.91, 29.77, 30.93, 36.80, 50.88, 53.54, 78.91, 115.30, 123.40, 123.43, 124.94, 124.98, 127.76, 129.11, 131.40, 131.45, 135.29, 135.39, 146.53, 146.61, 158.55, 160.03, 162.50, 163.63, 169.47, 196.45;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.21 (s, 2H,  $\text{NH}_2$ );  $^{19}\text{F}$  NMR (376.58 MHz, DMSO): -53.51; FT-IR: 3420, 3309, 2949, 1691, 1648, 1520, 1487; HRMS of  $[\text{C}_{17}\text{H}_{16}\text{FNO}_4 + \text{Na}]^+$  (m/z): 340.0956; Calcd.: 340.0961.

*Methyl 2-amino-4-(pyridine-3-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4k)* M.p.: 222–223 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.81–1.86 (m, 1H,  $\text{CH}_2$ ), 1.93–1.97 (m, 1H,  $\text{CH}_2$ ), 2.23–2.31 (m, 2H,  $\text{CH}_2$ ), 2.60–2.64 (m, 2H,  $\text{CH}_2$ ), 3.50 (s, 3H,  $\text{OCH}_3$ ), 4.52 (s, 1H, CH), 7.21–7.25 (m, 1H, ArH), 7.46–7.49 (m, 1H, ArH) 7.08–7.11 (m, 1H, ArH), 7.62 (s, 2H,  $\text{NH}_2$ ), 8.28 (d,  $J$  = 4.72 Hz, 1H, ArH), 8.38 (d,  $J$  = 1.96 Hz, 1H, ArH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 19.79, 26.26, 31.18, 36.16, 50.54, 76.62, 115.71, 123.28, 134.83, 141.71, 146.97, 149.06, 159.20, 164.53, 167.99, 196.04;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 7.62 (s, 2H,  $\text{NH}_2$ ); FT-IR: 3372, 2996, 1671, 1530, 1362, 1293; HRMS of  $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4 + \text{Na}]^+$  (m/z): 323.1009; Calcd.: 323.1008.

## Results and discussion

### Reaction optimization

Based on preliminary studies, 2-methoxy benzaldehyde (1 mmol), methyl cyanoacetate (1.1 mmol) and 1,3-cyclohexadione (1 mmol) were identified as ideal for the multicomponent reaction. The effect of solvent on the reaction were assessed under MWI and conventional heating conditions. The results using different non-polar, aprotic and protic solvents under conventional heating and MWI conditions are summarised in Table 1. No reaction occurred in absence of solvent, under conventional,

MWI, RT or reflux conditions. Non-polar solvents like *n*-hexane and toluene failed to produce any product, even after long reaction time at RT (Table 1, entries 3 and 4). However, the presence of polar aprotic solvents, DMF, THF and acetonitrile revealed a trace of anticipated product (Table 1, entries 5–7), under both conventional and MWI conditions. With polar protic solvents, MeOH, EtOH and water offered, good to excellent yields with both conventional heating and MWI, but MWI proved better in terms of yield and reaction times (Table 1, entries 8–10). The reason for the low yield, when using conventional heating could also be likely due to the steric demand for 2-substituted aromatics.

The polar protic solvents, when microwave irradiated generate more dipole moments and their dipole moments effectively align with the external electric field. Based on the impressive yields and short reaction times, the MWI procedure with environmentally benign water proved to be ideal. Hence, MWI with water was used for the further studies.

Under the optimized reaction conditions, the MWI approach was applied for preparation of series of benzopyran derivatives, employing different aromatic aldehydes and methyl cyanoacetate and 1,3-cyclohexadione. Table 2 summarizes the results. All the aldehydes reacted smoothly to afford the desired target molecules without any side products. The electronic nature of substituents on the aromatic aldehyde ring did not show any effect on the yield or reaction rate. Both electron withdrawing and donating substituents on the aldehyde ring gave the excellent yield for the respective product.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{15}\text{N}$  NMR,  $^{19}\text{F}$  NMR, HRMS and IR spectral data were used to evaluate the structures of all the newly synthesised molecules (4a–k). Spectra of all the compounds are incorporated in Additional file 1. The HMBC

**Table 1** Yields of benzopyran (4a) under diverse conventional heating and MWI conditions

Entry	Solvent	Condition	Conventional		MWI	
			Time (h)	Yield <sup>a</sup> (%)	Time (h)	Yield <sup>a</sup> (%)
1	–	R.T	12.0	–	6.0	–
2	–	Heat	10.0	–	6.0	–
3	<i>n</i> -Hexane	R.T	10.0	–	4.0	–
4	Toluene	R.T	10.0	–	4.0	–
5	THF	R.T	5.0	5	2.5	13
6	$\text{CH}_3\text{CN}$	R.T	5.5	6	3.0	10
7	DMF	R.T	6.0	9	2.5	15
8	MeOH	R.T	3.5	67	2.5	71
9	EtOH	R.T	2.5	71	0.5	84
10	$\text{H}_2\text{O}$	R.T	3.0	79	0.20	98

All products were characterized by  $^1\text{H}$ NMR,  $^{13}\text{C}$  NMR,  $^{15}\text{N}$  NMR and HR-MS spectral data

<sup>a</sup> Isolated yields; –: no reaction

**Table 2** Preparation of tetrahydrobenzo[b]pyran derivatives in water as solvent using MWI

Entry	R	Product	Yield (%)
1a	4-OMe	<b>4a</b>	96
1b	3-OMe	<b>4b</b>	92
1c	4-F	<b>4c</b>	94
1d	2,5-(OMe) <sub>2</sub>	<b>4d</b>	90
1e	2-Br	<b>4e</b>	93
1f	2-CF <sub>3</sub>	<b>4f</b>	89
1g	2-OMe	<b>4g</b>	98
1h	2-NO <sub>2</sub>	<b>4h</b>	94
1i	2-Cl	<b>4i</b>	89
1j	2-F	<b>4j</b>	92
1k	3-Pyridinyl	<b>4k</b>	95

New compounds/no literature for bps available

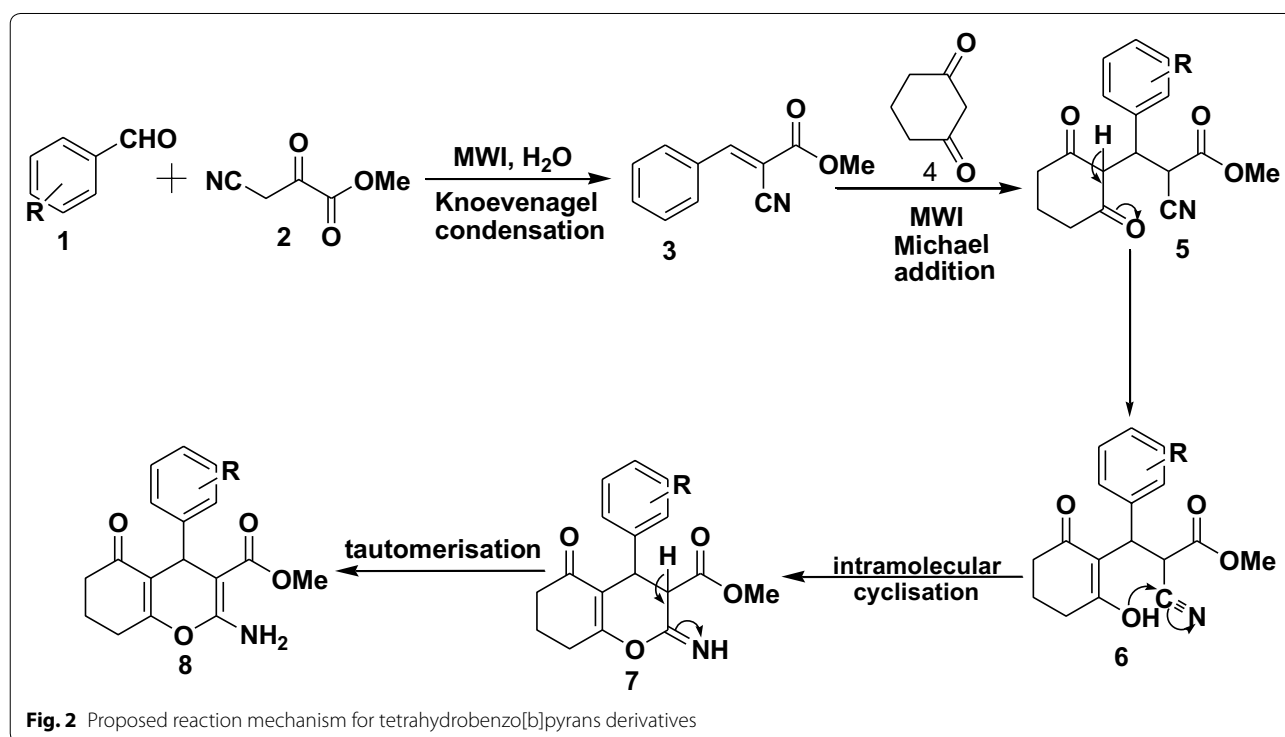
interactions of trial reaction **4g** are shown in Additional file 1: Figure S1. In the <sup>1</sup>H NMR spectra, the individual singlets peaks at  $\delta=3.45$ , 3.70, 4.60 and 7.46 indicate the presence of  $-\text{OCH}_3$ ,  $-\text{CH}$  and  $-\text{NH}_2$  protons. The selected HMBC interactions of **4g** are definite proof for the product formation. The  $-\text{CH}$  proton in the benzo pyran ring was assigned to the peak at  $\delta=4.60$  and it further interacts with carbon atoms (C-3, C-9, C-1a, C-2a, C-10, C-2, C-11, C-5) at  $\delta=76.63$ , 115.28, 133.55, 158.21, 160.12, 164.63, 169.13 and 196 ppm respectively. The

singlet at  $\delta=7.46$  was identified to the  $-\text{NH}_2$  proton in the benzo pyran ring (Additional file 1: Figure S2).

Although, no reaction intermediates could be identified, based on the reaction products and the literature reports, the probable mechanism for the synthesis of benzopyran derivatives under MWI is described (Fig. 2). Initially, an aromatic aldehyde (**1**) react with methyl cyanoacetate (**2**) via Knoevenagel condensation to afford an intermediate, cyanophenylacrylate (**3**) [45, 46]. The intermediate reacts with the active methylene moiety in (**4**) via Michael addition, through the electrophilic C=C bond to afford transient intermediate (**5**) [47]. Finally, the intermediate (**6**) undergoes intramolecular cyclisation followed by tautomerisation, to afford its respective benzopyran derivative.

### Conclusion

The MWI facilitated three-component synthesis of eleven novel tetrahydrobenzo[b]pyrans through one-pot reaction with water as solvent proved an expedient technique. It is applicable for the archive preparation of benzopyran systems in excellent yields, with no need for catalysts or organic solvents. This method offers extensive applications in the field of diversity-oriented synthesis, drug discovery, combinatorial chemistry and scaled-up preparations.



## Supplementary information

**Supplementary information** accompanies this paper at <https://doi.org/10.1186/s13065-019-0651-2>.

**Additional file 1.** Additional instrumental details, spectral data and details of product yields. **Figure S1:** Selected HMBC interactions of –CH & a (1–6) protons of **4g**. **Figure S2:**  $^1\text{H}$  and  $^{13}\text{C}$  chemical shift of compound **4g**. **Table S1:** Effect of various conditions for the synthesis of benzopyrans in presence of several catalysts.

### Abbreviations

$^1\text{H}$  NMR: proton nuclear magnetic resonance;  $^{13}\text{C}$  NMR: carbon-13 nuclear magnetic resonance;  $^{15}\text{N}$  NMR: nitrogen-15 nuclear magnetic resonance;  $^{19}\text{F}$  NMR: fluorine-19 nuclear magnetic resonance; C–C: carbon–carbon bond; C–O: carbon–oxygen bond; CH<sub>3</sub>CN: acetonitrile; Ca(OTf)<sub>2</sub>·Bu<sub>4</sub>NPF<sub>6</sub>: calciumtriflate and tetra-butyl hexafluoroammoniumphosphate; DMF: *N,N*-dimethylmethanamide; DMSO-*d*<sub>6</sub>: deuterated dimethyl sulfoxide; EtOH: ethanol; FT-IR: Fourier transform infrared spectroscopy; MeOH: methanol; MWI: microwave irradiation; MCR: multi component reaction; THF: tetrahydrofuran.

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### Declaration

All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria and This article is original, has not already been published in a journal, and is not currently under consideration by another journal. Authors agree to the terms of the BioMed Central Copyright and License Agreement.

### Authors' contributions

MK conducted most of the experimental work as part of his BSc. Honours research project. SM and SNM are postdoctoral fellows, who facilitated the research and in interpretation of the spectral data to assign the structures to the synthesised molecules. SJ is Senior Professor of Chemistry and supervisor of the project. All authors read and approved the final manuscript.

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Authors further declare that no funding was received for these studies.

### Availability of data and materials

A Additional file is provided incorporating the additional data. S1—All instruments' details, S2—Spectral information of the all synthesized compounds plus the 2D NMR data for **4g** compound, UV–Visible spectrum of benzopyran and details of product yields in Additional file 1: Table S1.

### Competing interests

The authors declare that they have no competing interests.

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