

## Microwave assisted synthesis of 2'- / 3'-azaflavones/azaflavonones and their N-alkyl derivatives

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**Abstract:** 2'-Azaflavone (**6**) and 3'-azaflavone (**7**); were synthesized by a simple environmentally friendly microwave-assisted one-pot method for the cyclization of 2'-hydroxy  $\beta$ '-2-azachalcon- $\beta$ -ol (**1**), 2'-hydroxy (*E*)-2-azachalcone (**2**), 2'-hydroxy (*E*)-3-azachalcone (**3**) under solventless conditions using K-10 clay. In addition to these synthesis, 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**) were synthesized using silica-supported sodium hydrogen sulphate then the treatment with base, respectively. Additionally, for antimicrobial activities N-alkyl substituted 3'-azaflavonium and 2'-azaflavonium bromides (**10-12**) were prepared from compounds **3**, **4** - **5** and **8** - **9**.

**Keywords:** Azaflavone; azaflavonone; microwave; azachalcone. © 2016 ACG Publications. All rights reserved.

### 1. Introduction

The development of chemistry has been intensely associated with the discovery of new reagents and new styles of introducing energy into chemical reactions. Although the ability of microwaves (MW) to heat water and other polar materials has been known for half a century or more, it was not until 1986 that two groups of researchers separately declared the application of MW heating to organic synthesis.<sup>1</sup>

Microwave-assisted one-pot method for the cyclization of chalcones and azachalcones reactions the formation of flavones and flavonones generally not predict priorly. However, many trials have been done during the formation of flavones and flavonones reactions and the reaction conditions changing for preferred product. This study was designed to contribute the cyclization reactions and already provide the insight flavones and flavonone formation.

Flavonoids are natural polyphenol compounds of plant beginning and extensively distributed in the plant kingdom and display different pharmacological activities.<sup>2,3</sup> The usual method to synthesize the flavones for the cyclization of 2'-hydroxychalcones involve extended time and the use of corrosive reagents and strong alkalis in not good yields.<sup>4,5</sup> Azaflavones and azaflavonones are homolog of flavones with an annular nitrogen atom in the phenyl ring and have been synthesized with an oxidative ring closure of substituted 2'-hydroxy-2/3/ or 4-azachalcones with selenium dioxide in

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low yield.<sup>6-9</sup> There have been a variety of methods to synthesis the flavones or azaflavonones by a solid state by dehydrative cyclization of *o*-hydroxy or *o*-amino compounds in clay using microwaves or using the catalyst NaHSO<sub>4</sub>-SiO<sub>2</sub> by reflux methods<sup>10-13</sup>

In this study, we detailed an efficient and simple method for the synthesis of a hydroxyl azaflavone for the chemical and biological interest, through the cyclization of the corresponding 2'-hydroxy (*E*)-2-azachalcone and 2'-hydroxy (*E*)-3-azachalcone using K-10 clay under solventless conditions by using microwave. In addition, these azaflavonones synthesis, 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**) were synthesized microwave-assisted one-pot method for the cyclization of 2-(pyridin-2-yl methinol)-2'-hydroxy-2''-azachalcone (**4**) and 2-(pyridin-3-yl methinol)-2'-hydroxy-3''-azachalcone (**5**) under solventless conditions using silica-supported sodium hydrogen sulphate then the treatment with base, respectively. The catalyst NaHSO<sub>4</sub>-SiO<sub>2</sub> can be easily prepared, removed from the reaction mixture, and work under heterogeneous conditions (Figure 1). In our continuous interest of antimicrobial agents, a series of N-alkyl substituted azaflavonium bromide were synthesized.

The present work deals with the synthesis, spectral characterization and results of biological activity assays of 2'-hydroxy β'-2-azachalcon-β-ol (**1**), 2'-hydroxy (*E*)-2-azachalcone (**2**), 2'-hydroxy (*E*)-3-azachalcone (**3**), 2-(pyridin-2-yl methinol)-2'-hydroxy-2''-azachalcone (**4**), 2-(pyridin-3-yl methinol)-2'-hydroxy-3''-azachalcone (**5**), 2'-azaflavone (**6**), 3'-azaflavone (**7**), 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**), N-decyl-(2*E*)-1-(2-hydroxyphenyl)-3-pyridin-3-ylprop-2-en-1-one bromide (**10**), N-decyl-3-(pyridin-2-yl methyl)-2'-azaflavonium bromide (**11**) and N,N'-Didecyl-3-(pyridin-3-yl methyl)-3'-azaflavonium dibromide(**12**).

## 2. Experimental

NMR spectra were proofed on a Varian Mercury NMR at 200 MHz in CDCl<sub>3</sub>. NMR data assignment was based on <sup>1</sup>H, <sup>13</sup>C, APT, <sup>1</sup>H-<sup>1</sup>H COSY, and ACD NMR program. The mass spectral analyses were carried out on a Micromass Quattro LC-MS/MS spectrophotometer. The elemental analyses were achieved on a Costech ECS 4010 instrument. Infrared spectra were obtained with a Perkin-Elmer 1600 FT-IR (4000-400 cm<sup>-1</sup>) spectrometer. Melting points were determined by using a Thermo-var apparatus fitted with a microscope and are uncorrected. UV-vis spectral analyses were carried out on a Unicam UV2-100 at 25 °C. The reactions are carried out in DBK manual microwave instrument (750W). Thin-layer chromatography (TLC) was carried out on Merck precoated 60 Kieselgel F<sub>254</sub> analytical aluminum acidic or basic plates.

*Materials and methods.* *o*-Hydroxy acetophenone and 2/3-pyridinecarbaldehyde were purchased from Aldrich/Fluka and used without further purification. The solvents (chloroform, n-hexane, ethanol, methanol, acetonitrile, ethyl acetate, and diethyl ether) used were either of analytical grade or bulk solvents distilled before use.

### 2.1 General procedure for synthesis of compounds (1-5):

The compounds 1-5 were prepared according to the literature<sup>12-13, 14-15</sup> (compound **1**; 47% yield, R<sub>f</sub>= 0.47, ethyl acetate, compound **4**; 82% yield, R<sub>f</sub>= 0.41, ethyl acetate and compound **5**; 62% yield, R<sub>f</sub>= 0.32, ethyl acetate).

#### 2'-Hydroxy β'-2-azachalcon-β-ol (**1**):

Yellowish oils; UV λ<sup>CHCl<sub>3</sub></sup><sub>max</sub> nm: 320(ε, 2880), 254 (ε, 9222). FT-IR (KBr): 3465, 3051, 2846, 1606, 1463, 1363, 1304. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, ppm): 3.14, (dd, J=12.4 Hz, J=7.4 Hz, 1H, H-2), 5.61 (dd, J= 10.8, 5.4, 1H, H-3), 7.08 (d, J=8.4 Hz, 1H, H-3'), 7.51(td, J= 7.4 Hz, 2.0 Hz, 1H, H-4'), 7.05 (t, J= 7.0 Hz, 1H, H-5'), 7.93 (dd, J= 9.4 Hz, J= 1.8 Hz, 1H, H-6'), 8.62 (dd, J= 5.6 Hz, J= 1.2 Hz, 1H, H-3''), 7.28 (t, J= 4.4 Hz, 1H, H-4''), 7.78 (td, J= 7.4 Hz, J= 1.6Hz, 1H, H-5''), 7.61 (d, J= 8.0Hz, 1H, H-6''), 12.71(bs, 1H, -OH), 3.01 (s, 1H, -CH<sub>2</sub>OH). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, ppm): 205.45 C=O, 42.57

$C_2(C_\alpha)$ , 79.55  $C_3(C_\beta)$ , 120.96  $C_{1'}$ , 160.77  $C_2$ , 117.91  $C_3$ , 135.99  $C_4$ , 120.78  $C_5$ , 126.83  $C_6$ , 157.36  $C_{1''}$  ( $C_1$ ), 149.20  $C_{3''}$  ( $C_3$ ), 123.24  $C_{4''}$  ( $C_4$ ), 136.95  $C_{5''}$  ( $C_5$ ), 121.55  $C_{6''}$  ( $C_6$ ); positive LC-MS/MS: 245(62)  $[M+2]^+$ , 244(48),  $[M+1]^+$ , 243(61)  $[M]^+$ , 105(100)  $[M-138]^+$ ; Anal. calc. for (Molecular formula): C 69.12, H 5.39, N 5.76; found: C 69.12, H 5.39, N 5.74.

*2-(Pyridin-2-yl methinol)-2'-hydroxy-2''-azachalcone (4)*:

Orange amorphous solid; Mp: 114-116°C, UV  $\lambda^{CHCl_3}_{max}$  nm: 366 ( $\epsilon$ , 1693), 312 ( $\epsilon$ , 9146), 240 ( $\epsilon$ , 9562). FT-IR (KBr): 3586, 3046, 2930, 1640, 1484, 1434, 1386, 1208, 1179.  $^1H$ -NMR (200 MHz,  $CDCl_3$ , ppm): 8.06 (s, 1H, H-3), 7.01 (dd,  $J=10.2$  Hz,  $J=2.0$  Hz, 1H, H-3'), 7.22 (m, 1H, H-4'), 7.12 (m, 1H, H-5'), 7.97 (dd,  $J=10.2$  Hz,  $J=2.2$  Hz, 1H, H-6'), 8.47 (dd,  $J=5.8$  Hz,  $J=2.0$  Hz, 1H, H-3''), 7.35 (d,  $J=5.8$  Hz, 1H, H-4''), 7.72 (m, 1H, H-5''), 7.40 (d,  $J=5.8$  Hz, 1H, H-6''), 7.88 (s, 1H, CHOH), 8.60 (dd,  $J=5.8$  Hz,  $J=2.0$  Hz, 1H, H-3'''), 7.59 (d,  $J=5.8$  Hz, 1H, H-4'''), 7.72 (m, 1H, H-5'''), 7.52 (d,  $J=5.8$  Hz, 1H, H-6'''), 9.12 (s, 1H, -OH).  $^{13}C$ -NMR (50 MHz,  $CDCl_3$ , ppm): 182.71 C=O, 136.55  $C_2(C_\alpha)$ , 135.44  $C_3(C_\beta)$ , 122.50  $C_{1'}$ , 159.61  $C_2$ , 121.40  $C_3$ , 135.02  $C_4$ , 122.06  $C_5$ , 118.36  $C_6$ , 151.71  $C_{1''}$  ( $C_1$ ), 149.33  $C_{3''}$  ( $C_3$ ), 128.05  $C_{4''}$  ( $C_4$ ), 135.94  $C_{5''}$  ( $C_5$ ), 123.40  $C_{6''}$  ( $C_6$ ), 77.48 (CH-OH), 158.23  $C_{1''}$  ( $C_1$ ), 149.64  $C_{3''}$  ( $C_3$ ), 127.49  $C_{4''}$  ( $C_4$ ), 136.44  $C_{5''}$  ( $C_5$ ), 122.87  $C_{6''}$  ( $C_6$ ); positive LC-MS/MS: 334(100)  $[M+2]^+$ , 333(12),  $[M+1]^+$ , 332(10)  $[M]^+$ , 331(50)  $[M-1]^+$ ; Anal. calc. for (Molecular formula): C 72.28, H 4.85, N 8.43; found: C 72.27, H 4.85, N 8.43.

*2-(Pyridin-3-yl methinol)-2'-hydroxy-3''-azachalcone (5)*:

Orange oils; UV  $\lambda^{CHCl_3}_{max}$  nm: 350 ( $\epsilon$ , 3506), 294 ( $\epsilon$ , 13934). FT-IR (KBr): 3343, 3035, 2947, 1674, 1473, 1462, 1311, 709.  $^1H$ -NMR (200 MHz,  $CDCl_3$ , ppm): 7.82 (s, 1H, H-3), 6.69 (d,  $J=8.0$  Hz, 1H, H-3'), 7.13 (td,  $J=8.0$  Hz,  $J=1.6$  Hz, 1H, H-4'), 6.66 (m, 1H, H-5'), 7.64 (dd,  $J=9.8$  Hz,  $J=2.0$  Hz, 1H, H-6'), 8.28 (d,  $J=2.0$  Hz, 1H, H-2''), 8.22 (dd,  $J=6.2$  Hz,  $J=1.6$  Hz, 1H, H-4''), 6.94 (t,  $J=4.2$  Hz, 1H, H-5''), 6.42 (s, 1H, -CHOH), 8.50 (d,  $J=2.4$  Hz, 1H, H-2'''), 8.31 (dd,  $J=8.0$  Hz,  $J=1.6$  Hz, 1H, H-4'''), 6.99 (t,  $J=7.2$  Hz, 1H, H-5'''), 7.30 (d,  $J=8.0$  Hz, 1H, H-6'''), 12.31 (s, 1H, -OH).  $^{13}C$ -NMR (50 MHz,  $CDCl_3$ , ppm): 180.81 C=O, 129.20  $C_2(C_\alpha)$ , 134.75  $C_3(C_\beta)$ , 121.31  $C_{1'}$ , 157.89  $C_2$ , 118.28  $C_3$ , 135.71  $C_4$ , 122.00  $C_5$ , 136.30  $C_6$ , 132.60  $C_{1''}$  ( $C_1$ ), 149.59  $C_{2''}$  ( $C_2$ ), 150.04  $C_{4''}$  ( $C_4$ ), 123.35  $C_{5''}$  ( $C_5$ ), 127.28  $C_{6''}$  ( $C_6$ ), 75.61 (CH-OH), 133.01  $C_{1''}$  ( $C_1$ ), 148.39  $C_{2''}$  ( $C_2$ ), 149.82  $C_{4''}$  ( $C_4$ ), 123.39  $C_{5''}$  ( $C_5$ ), 136.26  $C_{6''}$  ( $C_6$ ); positive LC-MS/MS: 334(7)  $[M+2]^+$ , 333(5),  $[M+1]^+$ , 332(100)  $[M]^+$ , 195(61)  $[M-137]^+$ ; Anal. calc. for (Molecular formula): C 72.28, H 4.85, N 8.43; found: C 72.27, H 4.83, N 8.42.

*2.2 General procedure for synthesis of compounds (6-9)*:

2'-Hydroxy  $\beta$ -hydroxyl dihydro-2-azachalcone (**1**), 2'-hydroxy-2-azachalcone (**2**), and 2'-hydroxy-3-azachalcone (**3**) (0.02 mol each) was dissolved in chloroform and was uniformly adsorbed on the surface of K-10 clay3 (1 g) in a Pyrex round-bottomed flask. The solvent was evaporated under vacuum, and then the adsorbed material was transferred to a Teflon bath (2 cm diameter, 10 mL) and inserted in a larger silica (neutral alumina) Teflon bath (5 cm diameter, 30 mL) inside a microwave oven. The mixture was irradiated for 3 min in a microwave oven at 700 W. The reaction mass was dissolved in methanol and filtered off. The extracts were evaporated to leave crude mixtures, which were then purified by column chromatography over silica (n-hexane (30 ml), n-hexane-ethyl acetate (3:1, (50 ml)), ethyl acetate (120ml)) and the desired products were obtained from fr. 5-8 and 5-11 (**6,7**) in high yield (78% and 83%), respectively. (TLC (ethyl acetate)):  $R_f$  0.55 and 0.57, respectively.

2-(Methinol-4-pyridinyl)-2'-hydroxy-2-azachalcone (**4**) and 2-(methinol-4-pyridinyl)-2'-hydroxy-3-azachalcone (**5**) (0.02 mol each) was dissolved in chloroform and were uniformly adsorbed on the surface of  $NaHSO_4-SiO_2$  catalyst [5] (1 g) in a pyrex round bottomed flask, separately. The solvent was evaporated under vacuum, and then the adsorbed material was transferred to a Teflon bath (2 cm diameter, 10 ml) and inserted in a bigger silica (Kieselgel 60  $HF_{254}$ ) teflon bath (5 cm diameter, 30 ml) inside the microwave oven. The mixture was irradiated for 2 minutes in microwave oven at 700

W. The reaction mass was dissolved in methanol and made basic solution with 2M NaOH, then the solvent was evaporated under vacuum. The products were eluted with chloroform and the chloroform extracts were evaporated to leave crude mixtures which were purified by column chromatography over alumina (ethyl acetate-methanol 3:1, 3:2, or 2:4) to afford the pure corresponding products (**8**, **9**) in high yields (99%, and 73% yield,  $R_f = 0.57$ , and  $0.58$ , ethyl acetate-methanol, 3:0.5), respectively.

*2'-Azaflavonone (2-pyridin-2-yl-2,3-dihydro-4H-chromen-4-one) (6):*

Light orange amorphous solid, Mp: 37-40°C, UV  $\lambda_{\text{max}}^{\text{CHCl}_3}$  nm: 326 ( $\epsilon$ , 2380). FT-IR (KBr): 3060, 2923, 1691, 1577, 1463, 1436, 1304, 1116, 763.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 5.58 (dd,  $J = 10.8$  Hz,  $J = 4.2$  Hz, 1H, H-2), 3.14 (dd,  $J = 11.2$  Hz,  $J = 3.2$  Hz, 1H, H-3), 7.67 (d,  $J = 7.8$  Hz, 1H, H-5), 7.23 (m, 1H, H-6), 7.32 (m, 1H, H-7), 7.22 (d,  $J = 7.8$  Hz, 1H, H-8), 8.62 (d,  $J = 4.6$  Hz, 1H, H-3'), 7.27 (m, 1H, H-4'), 7.71 (m, 1H, H-5'), 7.59 (d,  $J = 4.6$  Hz, 1H, H-6').  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , ppm): 79.80  $\text{C}_2$ , 42.73  $\text{C}_3$ , 191.68  $\text{C}_4$ , 127.07  $\text{C}_5$ , 121.75  $\text{C}_6$ , 136.15  $\text{C}_7$ , 118.09  $\text{C}_8$ , 161.00  $\text{C}_9$ , 121.23  $\text{C}_{10}$ , 157.65  $\text{C}_{1'}$ , 149.42  $\text{C}_{3'}$ , 123.40  $\text{C}_{4'}$ , 137.11  $\text{C}_{5'}$ , 120.95  $\text{C}_{6'}$ ; positive LC-MS/MS: 226(63),  $[\text{M}+1]^+$ , 225(36)  $[\text{M}]^+$ , 185(100)  $[\text{M}-40]^+$ ; Anal. calc. for (Molecular formula): C 74.65, H 4.92, N 6.22; found: C 74.64, H 4.93, N 6.23.

*3'-Azaflavonone (2-pyridin-3-yl-2,3-dihydro-4H-chromen-4-on) (7):*

Brownish oils; UV  $\lambda_{\text{max}}^{\text{CHCl}_3}$  nm: 322 ( $\epsilon$ , 2438), 256 ( $\epsilon$ , 8044), 236 ( $\epsilon$ , 7930). FT-IR (KBr): 3036, 2924, 1691, 1577, 1472, 1463, 1304, 1222, 765.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 5.56 (dd,  $J = 15.8$  Hz,  $J = 3.2$  Hz, 1H, H-2), 2.96 (m, 1H, H-3), 7.96 (d,  $J = 7.8$  Hz, 1H, H-5), 7.07 (m, 1H, H-6), 7.56 (m, 1H, H-7), 7.11 (d,  $J = 7.8$  Hz, 1H, H-8), 8.76 (s, 1H, H-2'), 8.67 (d,  $J = 4.8$  Hz, 1H, H-4'), 7.41 (dd,  $J = 12.8$  Hz,  $J = 5$  Hz, 1H, H-5'), 7.87 (d,  $J = 6.4$  Hz, 1H, H-6').  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , ppm): 77.27  $\text{C}_2$ , 44.25  $\text{C}_3$ , 191.02  $\text{C}_4$ , 127.05  $\text{C}_5$ , 121.93  $\text{C}_6$ , 136.34  $\text{C}_7$ , 118.00  $\text{C}_8$ , 161.07  $\text{C}_9$ , 120.76  $\text{C}_{10}$ , 134.25  $\text{C}_{1'}$ , 147.79  $\text{C}_{2'}$ , 150.07  $\text{C}_{4'}$ , 123.61  $\text{C}_{5'}$ , 133.66  $\text{C}_{6'}$ ; positive LC-MS/MS: 264(7),  $[\text{M}+\text{K}]^+$ , 227(15),  $[\text{M}+2]^+$ , 226(59),  $[\text{M}+1]^+$ , 224(36)  $[\text{M}-1]^+$ , 106(100)  $[\text{M}-120]^+$ ; Anal. calc. for (Molecular formula): C 74.65, H 4.92, N 6.22; found: C 74.66, H 4.92, N 6.23.

*3-(Pyridin-2-yl methyl)-2'-azaflavone (8):*

Brownish amorphous solid; Mp: 132-134°C, UV  $\lambda_{\text{max}}^{\text{CHCl}_3}$  nm: 332 ( $\epsilon$ , 9849), 258 ( $\epsilon$ , 34208). FT-IR (KBr): 3060, 2924, 1634, 1563, 1468, 1432, 1133, 759.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 8.18 (dd,  $J = 8.4$  Hz,  $J = 1.6$  Hz, 1H, H-5), 7.34 (td,  $J = 7.4$  Hz,  $J = 1.6$  Hz, 1H, H-6), 7.77 (td,  $J = 8.2$  Hz,  $J = 2.4$  Hz, 1H, H-7), 7.45 (dd,  $J = 8.4$  Hz,  $J = 0.6$  Hz, 1H, H-8), 8.40 (dt,  $J = 6.6$  Hz,  $J = 0.6$  Hz, 1H, H-3'), 6.99 (t,  $J = 12.4$  Hz, 1H, H-4'), 7.48 (td,  $J = 7.4$  Hz,  $J = 1.8$  Hz, 1H, H-5'), 7.99 (d,  $J = 7.6$  Hz, 1H, H-6'), 4.36 (s, 2H,  $\text{CH}_2$ ), 8.65 (dt,  $J = 6.4$  Hz,  $J = 0.6$  Hz, 1H, H-3''), 7.25 (t,  $J = 7.8$  Hz, 1H, H-4''), 7.62 (td,  $J = 8.4$  Hz,  $J = 1.4$  Hz, 1H, H-5''), 7.33 (d,  $J = 8.4$  Hz, 1H, H-6'').  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , ppm): 151.50  $\text{C}_2$ , 122.49  $\text{C}_3$ , 178.38  $\text{C}_4$ , 124.80  $\text{C}_5$ , 124.50  $\text{C}_6$ , 133.56  $\text{C}_7$ , 117.92  $\text{C}_8$ , 155.87  $\text{C}_9$ , 122.49  $\text{C}_{10}$ , 159.81  $\text{C}_{1'}$ , 148.80  $\text{C}_{3'}$ , 125.79  $\text{C}_{4'}$ , 135.97  $\text{C}_{5'}$ , 120.76  $\text{C}_{6'}$ , 159.81  $\text{C}_{1''}$ , 149.32  $\text{C}_{3''}$ , 122.77  $\text{C}_{4''}$ , 136.52  $\text{C}_{5''}$ , 124.32  $\text{C}_{6''}$ , 33.37 ( $\text{CH}_2$ ); positive LC-MS/MS: 337(100),  $[\text{M}+\text{Na}]^+$ , 315(8)  $[\text{M}+1]^+$ , 229(15)  $[\text{M}-85]^+$ ; Anal. calc. for (Molecular formula): C 76.42, H 4.49, N 8.91; found: C 76.41, H 4.49, N 8.92.

*3-(Pyridin-3-yl methyl)-3'-azaflavone (9):*

Brownish amorphous solid; Mp: 91-93°C, FT-IR (KBr): 3038, 2924, 1637, 1574, 1465, 1421, 1383, 1222, 1025, 761. UV  $\lambda_{\text{max}}^{\text{CHCl}_3}$  nm: 306 ( $\epsilon$ , 6719), 244 ( $\epsilon$ , 14805).  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 7.86 (d,  $J = 8.0$  Hz, 1H, H-5), 7.46 (m, 1H, H-6), 7.73 (t,  $J = 7.0$  Hz, 1H, H-7), 7.50 (d,  $J = 7.8$  Hz, 1H, H-8), 8.85 (s, 1H, H-2'), 8.78 (d,  $J = 4.8$  Hz, 1H, H-4'), 7.17 (dd,  $J = 12.6$  Hz,  $J = 4.6$  Hz, 1H, H-5'), 8.25 (d,  $J = 7.8$  Hz, 1H, H-6'), 3.97 (s, 2H,  $\text{CH}_2$ ), 8.32 (s, 1H, H-2''), 8.41 (d,  $J = 4.4$  Hz, 1H, H-4''), 7.43 (m, 1H, H-5''), 7.48 (d,  $J = 4.6$  Hz, 1H, H-6'').  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , ppm): 177.59  $\text{C}_2$ , 120.62  $\text{C}_3$ ,

177.59 C<sub>4</sub>, 123.37 C<sub>5</sub>, 125.97 C<sub>6</sub>, 135.68 C<sub>7</sub>, 117.90 C<sub>8</sub>, 160.14 C<sub>9</sub>, 122.67 C<sub>10</sub>, 128.95 C<sub>1'</sub>, 147.51 C<sub>2</sub>, 151.42 C<sub>4'</sub>, 125.38 C<sub>5'</sub>, 134.04 C<sub>6'</sub>, 135.01 C<sub>1''</sub>, 149.00 C<sub>2''</sub>, 149.16 C<sub>4''</sub>, 123.37 C<sub>5''</sub>, 135.86 C<sub>6''</sub>, 28.46 (CH<sub>2</sub>); positive LC-MS/MS: 316(26), [M+2]<sup>+</sup>, 315(100) [M+1]<sup>+</sup>, 297(7) [M-17]<sup>+</sup>; Anal. calc. for (Molecular formula): C 76.42, H 4.49, N 8.91; found: C 76.42, H 4.46, N 8.92.

### 2.3 General procedure for synthesis of compounds (10-12):

3'-Azaflavonone (**7**), 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**) (0.02 mol) with 1-bromodecane (0.05 mol) in acetonitrile (30 ml) was refluxed separately for 12-24 h. On completion of the reaction, followed by TLC examination, the acetonitrile was removed using a rotary evaporator and the residue was purified by column chromatography (column, length 30 cm, diameter 2 cm) on silica gel (25 g, Merck, 230-400 mesh). The column was eluted successively with the following solvent and solvent mixture: ethyl acetate (30 ml), ethyl acetate-methanol (3:1, 20 ml and 3:2, 20 ml) and methanol (30 ml) then methanol-water (5:1, 30 ml). Fractions (15-20 ml each) were collected and monitored by analytical TLC. The desired products **10-12** were obtained from fractions 4,5-6-12, 8-16, (76, 81, and 81% yield, R<sub>f</sub> = 0.38, ethyl acetate-methanol, 4:1; 0.53 and 0.59, ethyl acetate-methanol, 4:1, basic alumina TLC), respectively.

2-(methinol-4-pyridinyl)-2'-hydroxy-2-azachalcone (**4**) and 2-(methinol-4-pyridinyl)-2'-hydroxy-3-azachalcone (**5**) (0.02 mol) with 1-bromodecane (0.05 mol) in acetonitrile (30 ml) was refluxed separately for 12-24 h. On completion of the reaction, followed by TLC examination, the acetonitrile was removed using a rotary evaporator and the residue was purified by column chromatography (column, length 30 cm, diameter 2 cm) on silica gel (25 g, Merck, 230-400 mesh). The column was eluted successively with the following solvent and solvent mixture: ethyl acetate (30 ml), ethyl acetate-methanol (3:1, 20 ml and 3:2, 20 ml) and methanol (30 ml) then methanol-water (5:1, 30 ml). Fractions (15-20 ml each) were collected and monitored by analytical TLC. The desired products **11-12** were obtained from fractions 10-12, 11-16, (76, and 72% yield, R<sub>f</sub> = 0.53 and 0.59, ethyl acetate-methanol, 4:1, basic alumina TLC), respectively.

### *N*,-decyl-(2*E*)-1-(2-hydroxyphenyl)-3-pyridin-3-ylprop-2-en-1-one bromide (**10**):

Brownish amorphous solid; Mp: 93-96°C, UV λ<sup>CHCl<sub>3</sub></sup><sub>max</sub> nm: 372 (ε, 2397), 290 (ε, 11167). FT-IR (KBr): 3384, 3048, 2925, 1648, 1590, 1464, 1373, 1312, 1158, 759. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, ppm): 7.73 (d, J = 14.4 Hz, 1H, H-2), 8.68 (d, J = 14.4 Hz, 1H, H-3), 6.91 (d, J = 8.0 Hz, 1H, H-3'), 7.44 (t, J = 7.4 Hz, 1H, H-4'), 6.89 (t, J = 7.4 Hz, 1H, H-5'), 8.70 (d, J = 8.0 Hz, 1H, H-6'), 10.60 (s, 1H, H-2''), 9.14 (d, J = 5.4 Hz, 1H, H-4''), 8.05 (t, J = 7.8 Hz, 1H, H-5''), 8.71 (d, J = 5.4 Hz, 1H, H-6''), 5.31 (t, J = 7.2 Hz, 2H, H-1'''), 2.037 (bs, 2H, H-2'''), 1.29, 1.18 (bs, 14H, H-3'''-9'''), 0.83 (t, J = 7.0 Hz, 3H, H-10'''), 12.37 (s, 1H, -OH). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, ppm): 192.57 C<sub>1</sub>, 129.10 C<sub>2</sub>, 137.47 C<sub>3</sub>, 119.36 C<sub>1'</sub>, 163.38 C<sub>2'</sub>, 117.86 C<sub>3'</sub>, 137.11 C<sub>4'</sub>, 119.66 C<sub>5'</sub>, 135.16 C<sub>6'</sub>, 135.61 C<sub>1''</sub>, 143.73 C<sub>2''</sub>, 144.31 C<sub>4''</sub>, 131.97 C<sub>5''</sub>, 131.81 C<sub>6''</sub>, 61.90 C<sub>1'''</sub>, 26.00 C<sub>2'''</sub>, 32.03; 31.69; 29.28; 29.26; 29.12; 28.99; 22.52 C<sub>3'''-9'''</sub>, 14.00 C<sub>10'''</sub>; positive LC-MS/MS: 448(12) [M+H(<sup>81</sup>Br)]<sup>+</sup>, 447(31) [M(<sup>81</sup>Br)]<sup>+</sup>, 446(28) [M+H(<sup>79</sup>Br)]<sup>+</sup>, 445(12) [M(<sup>79</sup>Br)]<sup>+</sup>, 444(48) [M-H(<sup>79</sup>Br)]<sup>+</sup>, 367(25) [M-<sup>79</sup>Br/<sup>81</sup>Br+H]<sup>+</sup>, 366(95) [M-<sup>79</sup>Br/<sup>81</sup>Br]<sup>+</sup>, 226(100) [M-220]. Anal. calc. for (Molecular formula): C 64.57, H 7.22, N 3.14; found: C 64.57, H 7.24, N 3.13.

### *N*,-decyl-3-(pyridin-2-yl methyl)-2'-azaflavonium bromide (**11**):

Brownish amorphous solid; Mp: 100-102°C, UV λ<sup>CHCl<sub>3</sub></sup><sub>max</sub> nm: FT-IR (KBr): 3057, 2924, 1714, 1633, 1574, 1514, 1469, 1386, 1301, 1167, 950, 761. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, ppm): 8.25 (d, J = 7.8 Hz, 1H, H-5), 7.88 (m, 1H, H-6), 8.13 (t, J = 7.8, 1H, H-7), 7.88 (t, J = 8.8 Hz, 1H, H-8), 10.00 (d, J = 4.6 Hz, 1H, H-3'), 7.58 (m, 1H, H-4'), 7.98 (m, 1H, H-5'), 8.22 (d, J = 4.6 Hz, 1H, H-6'), 4.85 (s, 2H, CH<sub>2</sub>), 8.71 (d, J = 4.6 Hz, 1H, H-3''), 7.50 (m, 1H, H-4''), 7.95 (m, 1H, H-5''), 7.56 (d, J = 4.6 Hz, 1H, H-6''), 5.19 (t, J = 7.7 Hz, 2H, H-1'''), 2.17, 1.57, 1.24 (bs, 16H, H-2'''-9'''), 0.86 (t, J = 3.8 Hz, 3H, H-10'''). <sup>13</sup>C-NMR

(50 MHz, CDCl<sub>3</sub>, ppm): 155.35 C<sub>2</sub>, 122.31 C<sub>3</sub>, 178.96 C<sub>4</sub>, 126.21 C<sub>5</sub>, 126.13 C<sub>6</sub>, 137.73 C<sub>7</sub>, 116.33 C<sub>8</sub>, 156.83 C<sub>9</sub>, 145.91 C<sub>10</sub>, 145.91 C<sub>11</sub>, 149.83 C<sub>3'</sub>, 126.96 C<sub>4'</sub>, 144.06 C<sub>5'</sub>, 118.24 C<sub>6'</sub>, 58.43 (CH<sub>2</sub>), 150.18 C<sub>1''</sub>, 147.45 C<sub>3''</sub>, 125.82 C<sub>4''</sub>, 135.04 C<sub>5''</sub>, 125.80 C<sub>6''</sub>, 31.83 C<sub>1'''</sub>, 30.72; 29.46; 29.40; 29.25; 28.87; 26.42; 22.65; C<sub>2'''-9'''</sub>, 14.10 C<sub>10'''</sub>; positive LC-MS/MS: 537(41) [M+H(<sup>81</sup>Br)]<sup>+</sup>, 536(28) [M(<sup>81</sup>Br)]<sup>+</sup>, 535(28) [M+H(<sup>79</sup>Br)]<sup>+</sup>, 534(41) [M(<sup>79</sup>Br)]<sup>+</sup>, 533(25) [M-H(<sup>79</sup>Br)]<sup>+</sup>, 456(58) [M-<sup>79</sup>Br/<sup>81</sup>Br+H]<sup>+</sup>, 455(100) [M-<sup>79</sup>Br/<sup>81</sup>Br]<sup>+</sup>, 315(25) [M-220]. Anal. calc. for (Molecular formula): C 67.29, H 6.59, N 5.23; found: C 67.29, H 6.59, N 5.21.

*N,N'*-Didecyl-3-(pyridin-3-yl methyl)-3'-azaflavonium dibromide (**12**):

Brownish amorphous solid; Mp: 48-50°C, UV λ<sup>CHCl<sub>3</sub></sup><sub>max</sub> nm: 394 (ε, 6819), 318 (ε, 17433), 300 (ε, 17864), 286 (ε, 19610). FT-IR (KBr): 3060, 2924, 1736, 1622, 1463, 1378, 1312, 1167, 1108, 877, 758. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, ppm): 8.39 (d, J= 8.0 Hz, 1H, H-5), 7.45 (t, J= 9.8 Hz, 1H, H-6), 7.75 (t, J= 10.2 Hz, 1H, H-7), 7.68 (d, J= 7.2 Hz, 1H, H-8), 9.12 (s, 1H, H-2'), 8.75 (d, J= 6.0 Hz, 1H, H-4'), 7.95 (t, J= 8.4 Hz, 1H, H-5'), 7.66 (d, J= 7.2 Hz, 1H, H-6'), 2.18 (s, 2H, CH<sub>2</sub>), 8.79 (s, 1H, H-2''), 8.69 (d, J= 6.2 Hz, 1H, H-4''), 7.38 (m, 1H, H-5''), 7.33 (d, J= 8.2 Hz, 1H, H-6''), 4.96 (t, J= 6.8 Hz, 2H, H-1'''), 4.27 (t, J= 7.2 Hz, 2H, H-1'''), 2.02, 1.69, 1.24 (m, 32H, H-2'''-9''', H-2''''-9''''), 0.86 (t, J= 4.4Hz, 6H, H-10''', 10'''). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, ppm): 148.1 C<sub>2</sub>, 117.8 C<sub>3</sub>, 176.0 C<sub>4</sub>, 126.4 C<sub>5</sub>, 123.9 C<sub>6</sub>, 128.5 C<sub>7</sub>, 114.4 C<sub>8</sub>, 155.3 C<sub>9</sub>, 124.3 C<sub>10</sub>, 113.1 C<sub>11</sub>, 133.0 C<sub>2'</sub>, 144.0 C<sub>4'</sub>, 123.3 C<sub>5'</sub>, 126.8 C<sub>6'</sub>, 58.42 (CH<sub>2</sub>), 137.9 C<sub>1''</sub>, 133.0 C<sub>2''</sub>, 143.2 C<sub>4''</sub>, 123.3 C<sub>5''</sub>, 128.5 C<sub>6''</sub>, 62.4 C<sub>1'''</sub>, 59.2 C<sub>1'''</sub>, 31.9; 31.8; 31.4; 29.5; 29.2; 26.4; 26.2; 22.7 C<sub>2'''-9'''</sub>-C<sub>2'''-9'''</sub>, 14.2 C<sub>10'''</sub>, <sub>10'''</sub>; positive LC-MS/MS: 757(24) [M+H(<sup>81</sup>Br)]<sup>+</sup>, 756(22) [M(<sup>81</sup>Br)]<sup>+</sup>, 755(21) [M+H(<sup>79</sup>Br)]<sup>+</sup>, 754(20) [M(<sup>79</sup>Br)]<sup>+</sup>, 595(100) [M-<sup>79</sup>Br/<sup>81</sup>Br+H]<sup>+</sup>, 594 (26) [M-<sup>79</sup>Br/<sup>81</sup>Br]<sup>+</sup>, 315(25) [M-220]. Anal. calc. for (Molecular formula): C 63.49, H 7.46, N 3.70; found: C 63.50, H 7.46, N 3.72.

### 3. Results and Discussion

In this work, 2'-hydroxy (*E*)-2-azachalcone (**2**) and 2'-hydroxy (*E*)-3-azachalcone (**3**) have been prepared with the Claisen-Schmidt condensation of a suitable 2-hydroxyacetophenone with 2-pyridinecarbaldehyde and 3-pyridinecarbaldehyde with three equivalents of aqueous NaOH solution and yields the trans-isomer of the corresponding α, β-unsaturated ketones (**2**) according to the route indicated in Figure 1.<sup>12-13,14-15</sup> Traditionally, base-catalyzed condensation of acetophenone with aromatic aldehydes yields the α, β-unsaturated compounds. The rapid elimination of water from the initially formed ketol generates a fully conjugated product. But, we encountered an unanticipated effect on the reaction involving 3-pyridinecarboxaldehyde and 2-pyridinecarboxaldehyde with 2-hydroxyacetophenone. Treatment of one equivalent of 2-hydroxyacetophenone and three equivalents of 2/3-pyridinecarboxaldehyde with three equivalent aqueous NaOH solution result in formation of a first precipitate (**2-3**), then solution left over night and gave a second precipitate (**4-5**) in good yield, 82%, 62%, respectively. These experimental results showed that, after the first addition of 2/3-pyridinecarboxaldehyde to 2-hydroxyacetophenone gave initial ketol (**2-3**). Before the dehydration of initial product, addition of the second equivalent of 2/3-pyridinecarboxaldehyde gave -(Pyridin-2-yl methinol)-2'-hydroxy-2''-azachalcone (**4**) and 2-(Pyridin-3-yl methinol)-2'-hydroxy-3''-azachalcone (**5**). The recommended mechanism for the formation of compounds **1-5** is outlined in Figure 1. When we do the same reaction with four equivalent aqueous Na<sub>2</sub>CO<sub>3</sub>, it gives exclusively 2'-hydroxy β'-2-azachalcone-β-ol (**1**) in 47% yield.

2'-Hydroxy-2-azachalcone, 2'-hydroxy-3-azachalcone and its derivatives are valuable intermediate for the construction of azaflavones and azaflavonones.<sup>7,9</sup> Hence, firstly we attempted to synthesize 3'-azaflavone and 2'-azaflavone using K-10 clay under solvent-free conditions for the cyclization of 2'-hydroxy-2-azachalcone and 2'-hydroxy-3-azachalcone by using microwaves, which furnished the 2'-azaflavone (**6**) 78% and 3'-azaflavone (**7**) in 83% yield, respectively (Figure 1).

Substituted 2-(pyridin-2-yl methinol)-2'-hydroxy-2''-azachalcone (**4**), 2-(pyridin-3-yl methinol)-2'-hydroxy-3''-azachalcone (**5**) were also subjected to different condition (Figure 1). Unlike the first experimental condition, we attempted to synthesize by using NaHSO<sub>4</sub> on silica gel under solvent free conditions for the cyclization of compound **4** and **5** by using microwave, then treatment with base, which furnished the 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**) were obtained in 99% and 73% yield, respectively.

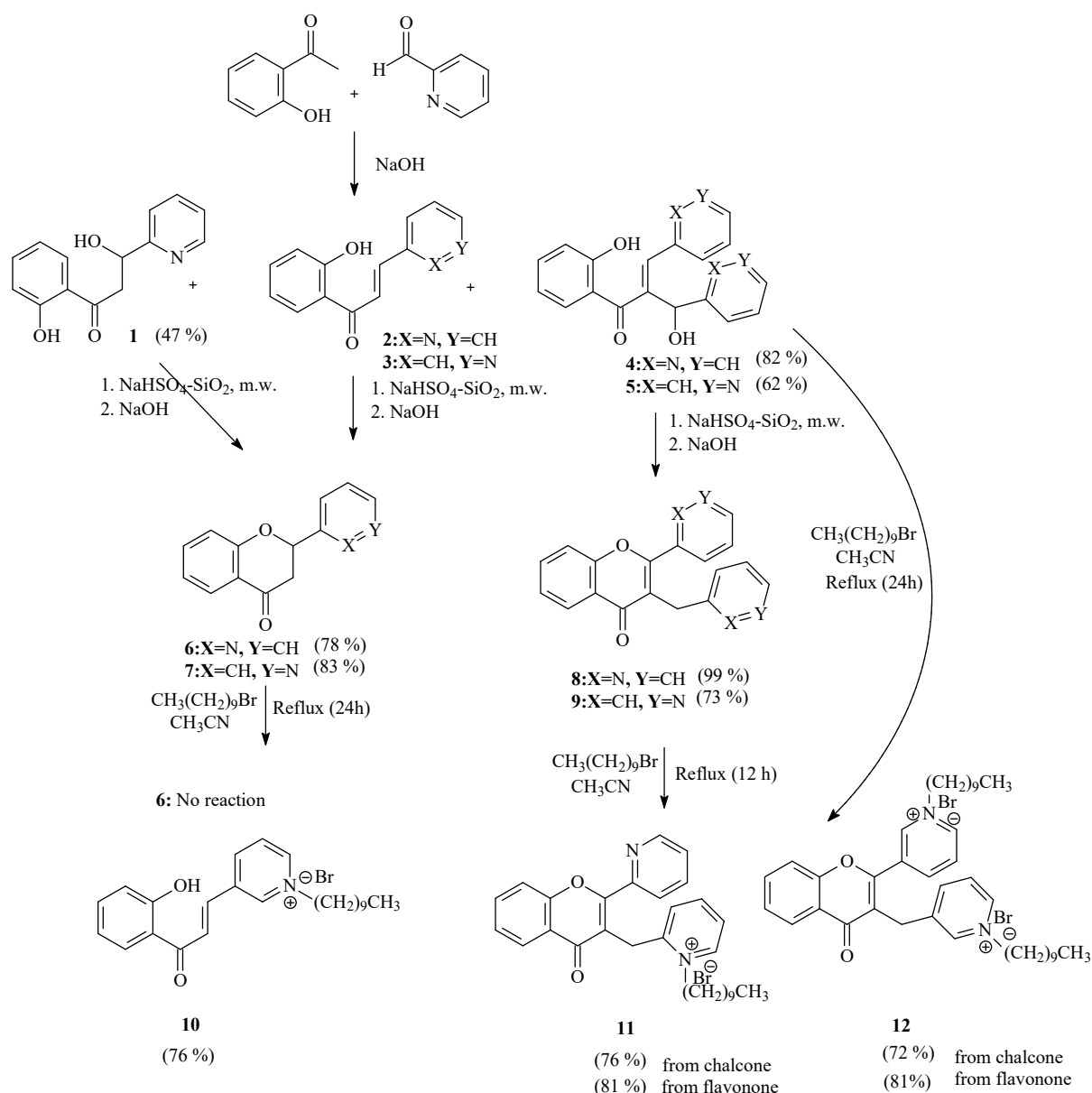
It is interesting that, compound **6** and **7** were synthesized by a simple environmentally friendly microwave-assisted one-pot method for the cyclization of compound **1-3** under solventless conditions using K-10 clay. On the contrary these, first methods when compound **8** and **9** were synthesized microwave-assisted one-pot method for the cyclization of compound **4** and **5** under solventless conditions using silica-supported sodium hydrogen sulphate then the treatment with base, respectively. Flavone and flavonone compounds synthesis were achieved same reaction condition via different microwave power in this study. It appears to have a different perspective to the literature on this aspect.

N-Alkyl derivatives of (*E*)-4-azachalcones attract widespread interest because many of them have exhibited a wide variety of biological activities<sup>12-13, 14-19</sup>. Due to this, *N*-alkyl derivatives of 2'-azaflavonones and 3'-azaflavonones (**9-12**) were synthesized. Literature data revealed that the length of the *N*-alkyl chain influences the antimicrobial activity<sup>12-13, 17-18</sup>. The highest activity relates to the presence of ten carbon atoms in the bromoalkyl chain of the aza-compounds. Thus, *n*-decyl bromide was chosen for the *N*-alkylation of compounds **3**, **4-5**, and **8-9**. Three new bromides of *N*-alkyl substituted derivatives of 2'-3'-azaflavonones and azachalconone (**10-12**) were synthesized by the reaction of compounds **3**, **4-5**, and **8-9** with 1-bromodecane in boiling acetonitrile. Finally, we synthesized *N*-alkyl derivatives (**10-12**) two different pathway (Figure 1). Alkylation of compound **4** and **5** the same product obtained for these reactions approximately the same product yield. Biological activities of synthesized compounds were found to be contrary to the expectations too low.

All the new compounds (**1, 4-12**) were characterized based on spectral data studies (<sup>1</sup>H, <sup>13</sup>C, APT, <sup>1</sup>H-<sup>1</sup>H COSY NMR, FT-IR, UV, Elemental analysis, and LC-MS/MS), whose results agreed with the proposed structure.

In conclusion, the present microwave-assisted one-pot procedure gives an efficient and rapid synthesis of 2'/3'-azaflavonone (**6-7**) and 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**).

The azaflavones are similar to flavones-type natural compounds. Because of the biological activities of flavones and its derivatives<sup>13,15</sup>, 2'/3'-azaflavonone (**6-7**) and 3-(pyridin-2-yl methyl)-2'-azaflavone (**8**) and 3-(pyridin-3-yl methyl)-3'-azaflavone (**9**) and their *N*-alkyl derivatives (**10-12**) were synthesized. It is interesting to alkylation reaction products of compounds **4, 5** and compounds **8, 9**. The same product obtained for these reactions approximately the same product yield. This study results have been a significant contribution from this aspect for flavon-flavonon type microwave syntheses.



**Figure 1.** Synthetic pathway for compounds **1-12**

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