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Original Article

Microwave-Assisted Synthesis of Anti-Microbial Chromones

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Abstract: Ten new chromone derivatives were synthesized from the original 2-4-6-trihydroxyacetophenone using microwave irradiation. The product's structures were confirmed by FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra data. The anti-microbial activities of the obtained compounds were tested by the disc diffusion method. The results showed that most chromones have significant biological activities against *Candida albicans*.

Keywords: 2-4-6-trihydroxyacetophenone, chromone, solvent-free, microwave-assisted synthesis.

1. Introduction

Chromones' biological and chemical properties have been extensively explored and largely reviewed for a long time. In the fact that the biological activities of molecules containing the chromone or benzopyranone ring on a large scale, they have been verified to be tyrosine and protein kinase inhibitors, together with anti-inflammatory, antiviral, antibacterial, anti-HIV, antioxidant, antihypertensive agents. The chromone derivatives are also active at benzodiazepine receptors [1-15]. Furthermore, they have been revealed to be anti-cancer agents [16-20]. Extracts from the plant Ammi visnaga seeds were used as a smooth muscle relaxant in the treatment of angina pectoris and asthma. Its active constituent, chromone has been used for centuries as a diuretic to relieve renal colic. Another active constituent, khellin, was used as a smooth muscle relaxant to treat angina pectoris and asthma in the 1950s [21]. Chromones have been synthesized by several methods, like Baker-Venkataraman rearrangement [22], Vilsmeier-Haack reaction, domino "Michael-retro-Michael-Aldol", domino addition of the nucleophile, ring opening, and ring closure reaction, and Knoevenagel condensation, *etc*. Moreover, the synthesis of organic compounds using microwave ovens is becoming an increasingly popular method that replaces the classical ones. This method proves to be a clean, cheap, and convenient method. It often affords higher yields in short reaction times and has been extended to almost all areas of chemistry. Numerous microwave-assisted organic reactions have been performed and reviewed in articles or books [23-38]. These reactions involved different ones, such as acylation and alkylation, aromatic nucleophilic substitution,

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condensation, cycloadditions, heterocyclization, rearrangements, the reaction of organometallic compounds, oxidation, and reduction [39-42]. This essay will examine the condensation reaction of some amines with 3-acetyl-5,7-dihydroxy-2-methyl-4H-chromen-4-one (2) under microwave irradiation. The original derivatives needed in the metabolites are 2-4-6-trihydroxyacetophenone, which was isolated from the Myrcia plants in the myrtaceae family. Furthermore, the synthesized chromones were screened for anti-microbial and antifungal activities [33].

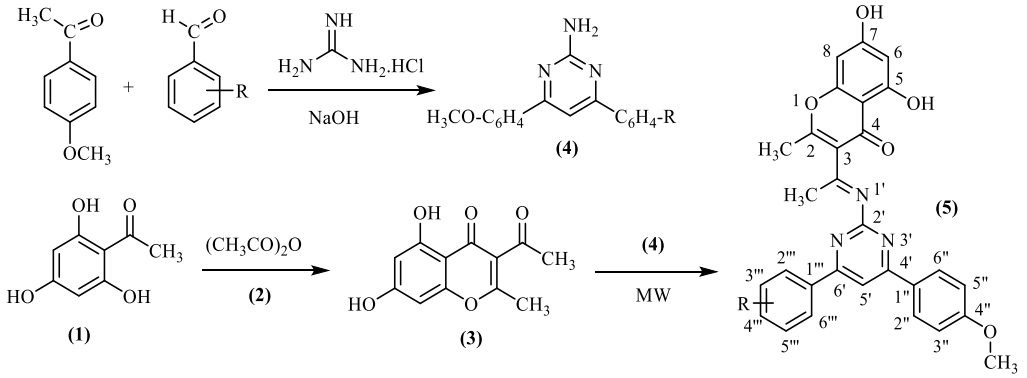
2. Materials and Methods

Synthesis chemicals including *p*-Methoxyacetophenone, Benzaldehyde, Guanidine hydrochloride, Sodium hydroxide, Ethanol, Toluene, and Acetic acid were purchased from Sigma-Aldrich (Missouri, USA) with ≥99% purity.

The test micro-organisms *E. coli, S. aureus, and C. albicans* were provided by the Center for Research and Applied Biology.

The melting point was measured using Thiele's apparatus in capillary and was uncorrected. The FTIR spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) by mixing with KBr and using the reflex-measure method. ^{1}H-NMR at 500 MHz ^{13}C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, Germany), using DMSO-*d6* as a solvent and TMS as an internal reference δ in ppm.

The biological activities of compounds **4a-j**, **5a-j** were tested by the agar plate diffusion method.



4a (R: H); 4b (R: *o*-Cl); 4c (R: *m*-Cl); 4d (R: *p*-Cl); 4e (R: *p*-Br); 4f (R: *p*-Me); 4g (R: *p*-iPr); 4h (R: *m*-OMe); 4i (R:*p*-OMe); 4j (R: *p*-NMe2)
5a (R: H); 5b (R: *o*-Cl); 5c (R: *m*-Cl); 5d (R: *p*-Cl); 5e (R: *p*-Br); 5f (R: *p*-Me); 5g (R: *p*-iPr); 5h (R: *m*-OMe); 5i (R:*p*-OMe); 5j (R: *p*-NMe2)

Figure 1. Synthesis of chromone derivatives.

2.1. General Procedure for Synthesis of Compounds (4a-j)

The mixture of the corresponding *p*-Methoxyacetophenone (0.02 mole) or substituted benzaldehyde (0.02 mole) and guanidine hydrochloride (0.015 mole) in the presence of sodium hydroxide (0.045 mole) was irradiated in the microwave oven (Figure 1). Power: 120 W; hold time: 3-5 min. After completion of the reaction, the mixture was treated with water (10 mL), and the precipitate was washed with water (50 mL), then with the mixture of ethanol and toluene (1:1 in volume) and dried to give the pure compounds **(4a-j)** [30-32].

2.2. General Procedure for Synthesis of Chromones (5a-j)

A mixture of 3-acetyl-5,7-dihydroxy-2-methyl-4H-chromen-4-one (**3**) (2.5 mmol) and

five drops of acetic acid, stirred for 30 minutes at 60-70 °C and then mixed carefully with amines (**4a-j**) were ground together in 5 mL-porcelain beaker. Then, the mixture was put into a household microwave oven (the power output was from 400 W to 640 W with a Sharp R229EK microwave oven). The adjustor of the microwave oven was set to the proper temperature (about 50 ^{o}C). The reactants were irradiated for 5-7 min. The mixture became dark-yellow pasty. The reaction was traced with thin-layer chromatography. The reaction mixture was cooled to room temperature, triturated with ethanol, filtered by suction, and recrystallized with ethanol: toluene (1:1 in volume) to afford ivory-white crystals, and dried to give pure chromones (**5a-f**) [33].

3. Results and Discussion

The derivatives of chromones could be synthesized by nucleophilic addition of corresponding amine compounds to 3-acetyl-5,7-dihydroxy-2-methyl-4*H*-chromen-4-one (**5a-j**). We performed this reaction using two microwave-assisted methods: refluxing in ethanol and executing under solvent-free conditions for several minutes. We have found that solvent-free conditions under microwave irradiation offer several advantages because solvents are often expensive, toxic, and difficult to remove in the case of aprotic dipolar solvents with a high boiling point. The synthetic processes can be represented in Figure 1.

The derivatives of 2-amino-4-(4′-methoxyphenyl)-6-arylpyrimidines (**4a-j**) were synthesized by the addition of guanidine hydrochloride to the corresponding substituted benzaldehyde and *p*-methoxyacetophenone, followed by the one-pot method (Figure 1). We performed this reaction using the microwave-assisted solvent-free method, for several minutes. Reaction yields were relatively high (55-70%). All these obtained compounds (**4a-j**) are soluble in common organic solvents (such as ethanol, toluene, benzene, DMF), and insoluble in water. In the ^{1}H-NMR spectra of 2-amino-4-(4′-methoxyphenyl)-6 arylpyrimidine derivatives (**4a-j**), there are resonance signals that are specified for protons in the amine group in the region of δ = 6.42-6.71 ppm. The aromatic proton signals showed clearly with three separated regions. One singlet signal around δ = 7.51-7.72 ppm could be assigned to proton H-5 in the pyrimidine ring. Protons in the methoxy group appeared at δ = 3.84 ppm. The signals in the most downfield region around δ = 7.50-8.20 ppm belong to the unsubstituted phenyl group. The IR spectra of compounds (**5a-j**) contained absorption at 1697-1765 cm^{-1} (C=O pyrone), 1523-1675 cm^{-1} (C = N), and 1023-1275 cm^{-1} (C-O-C, aryl ether). The ^{1}H-NMR spectra of compounds **5a-f** showed singlet signals at δ = 8.21-8.65 ppm (H-5′) and 16.3-16.5 ppm belonging to (5-OH) in the de-shielded region. Whereas, proton (7-OH) has its chemical shift at δ = 9.5-10.5 ppm. On the flip side, signals of aromatic protons appeared at δ = 7.44-7.96 ppm. On the contrary, the methyl signals at δ = 2.05-2.24 ppm. The ^{13}C-NMR spectra showed signals for the carbonyl group at δ = 175.0 ppm. In addition, there were resonance peaks in the shielded region at δ = 29.92-39.99 ppm that indicated the presence of methyl groups. By examining the biological activity of these derivatives, a varied range of inhibitory activity was noted for antibacterial effects against Gram-positive *S. aureus* and Gram-negative bacteria - *E. coli* and *Candida albicans* in the different concentrations. The efficiency antifungal activity was noticed, such as **5c, 5d, 5f** were the most active. However, the anti-microbial activity was less efficient. For instance, there was no noteworthy trend of observation for the **5a, 5i** compounds' activity against tested microbes, even in the highest tested concentration. The activity of the **5a** compound was also lower against all tested microbes except for antifungal activity. **5b - 5d** showed higher activity against *E.coli* than *S. aureus* when tested in two concentrations (Table 1).

Table 1. Response of various micro-organisms to substituted chromones

Entry	Diameter of zone inhibition (mm)					
	E.coli[a]		*S. aureus*[a]		*C. albicans*[a]	
	100 μg/ml	150 μg/ml	100 μg/ml	150 μg/ml	100 μg/ml	150 μg/ml
5a	(-)	(-)	(-)	(-)	26	29
5b	13	(19)	(-)	(9)	21	26
5c	(10)	(15)	(-)	(12)	28	31
5d	(15)	(18)	(-)	(-)	23	33
5e	(-)	(12)	25	28	25	31
5f	(9)	(17)	19	25	29	30
5g	(-)	(8)	23	29	25	29
5h	(9)	(-)	13	19	24	25
5i	(-)	9	(-)	(-)	23	27
5j	(-)	(-)	(-)	9	24	28
Ref	22[b]	30[b]	35[c]	41[c]	38[d]	45[d]

3.1. 2-Amino-4-Phenyl-6-(4″-Metoxyphenyl)-Pyrimidin (4a)

IR (KBr, cm^{-1}): νNH_2 = 3369; 3326 cm^{-1}, δNH_2= 1642 cm^{-1}, melting point: 151-152 ºC. Yield: 55%. Irradiation time 5 min. ^{1}H-NMR (DMSO-*d6*, δ, ppm): 6.6 (s, NH_2); 7.64 (s, H-5); 7.52-7.50 (m, H-2′); 8.02-8.18 (m, H-3′ & H-5′); 7.52-7.50 (m, H-4′ & H-6′); 7.06 (d, 2H, *J* = 9.0, H-2″ & H-6″); 8.19 (d, 2H, *J* = 8.3, H-3″ & H-5″); 3.84 (s, 4′-OCH_3).^{13}C-NMR (DMSO-*d6*, δ, ppm): 164.5 (C-2); 197.4 (C-4); 101.0 (C-5); 163 (C-6); 125.3 (C-1′); 125.5 (C-2′ & C-6′); 113.8 (C-3′ & C-5′); 161 (C-4′); 141.3 (C-1″); 123.4 (C-6″ & C-2″); 123.5 (C-3″ & C-5″); 127.5 (C-4″); 55.4 (OCH_3).

3.2. 2-Amino-4-(4′-Metoxyphenyl)-6-(2″-Clorophenyl)-Pyrimidin (4b)

IR (KBr, cm^{-1}): νNH_2 = 3326; 3194 cm^{-1}, δNH_2 = 1642 cm^{-1}, melting point: 161-162 ºC. Yield: 67%. Irradiation time 3 min. ^{1}H-NMR (DMSO-*d6*, δ, ppm): 6.3(s, NH_2); 7.82 (s, H-5); 7.78 (m, H-2′ & H-6′); 7.05(m, H-3′& H-5′); 7.52-7.50 (m, H-4′); 8.02-8.18 (m, H-5′); 7.75 (m, H-6″); 7.35-7.37 (m, H-4″ & H-5″); 7.7 (d; *J* = 8.9, H-3″); 3.81 (s; 4′-OCH_3). ^{13}C-NMR (DMSO-*d6*, δ, ppm): 163.5 (C-2); 187.5 (C-4); 101.0 (C-5); 162 (C-6); 128.1 (C-1′); 128.5 (C-2′ & C-6′); 114.5 (C-3′ & C-5′); 160 (C-4′); 139.3 (C-1″); 135.2 (C-2″); 135.5 (C-3″); 133.2 (C-4″); 133.8 (C-5″); 129.5 (C-6″); 55.8 (OCH_3).

3.3. 2-Amino-4-(4′-Metoxyphenyl)-6-(3″-Clorophenyl)-Pyrimidin (4c)

IR (KBr, cm^{-1}): νNH_2 = 3320; 3209 cm^{-1} δNH_2= 1621 cm^{-1}. Melting point: 130-131 ºC. Yield: 65%. Irradiation time 3 min. ^{1}H-NMR (DMSO-*d6*, δ, ppm): 6.71 (s, NH_2); 7.72 (s, H-5); 8.22 (d, 1H, *J* = 9.0 Hz, H-2′); 7.06 (d, 1H, *J* = 9.0 Hz, H-3′); 7.06; (d, 1H, *J* = 9.0 Hz, H-5′); 8.22; (d, *J* = 8.5, H-6′); 8.29-8.28 (m, H-2″); 7.57-7.54 (m, H-4″); 7.57-7.54 (m, H-5″); 8.20-8.18 (m, H-6″); 3.84 (s, 4′-OCH_3). ^{13}C-NMR (DMSO-*d6*, δ, ppm): 185.6 (C-4); 163.6 (C-2); 101.3 (C-5); 162.7 (C-6); 160.7 (C-4′); 114.8 (C-3′ & C-5′); 135.3 (C-1″); 130.5 (C-2″); 134.9 (C-3″); 127.5 (C-4″); 128.0 (C-5″); 125.0 (C-6″); 55.8 (OCH_3).

3.*4. 2-Amino-4-(4′-Metoxyphenyl)-6-(4″-Clorophenyl)-Pyrimidin (4d)*

IR (KBr, cm^{-1}): νNH_2 = 3329; 3208 cm^{-1}, δNH_2= 1645 cm^{-1}, melting point: 156-157 ºC. Yield: 78%. Irradiation time 3 min. ^{1}H-NMR

(DMSO-*d6*, *δ*, ppm): 6.75 (s, NH_2); 7.58 (s, H-5); 8.05 (d, 2H, *J* = 8.3, H-2′ & H-6′); 7.05 (d, 2H, *J* = 8.5, H-3′ & H-5′); 8.75 (d, *J* = 8.5, H-2″ & H-6″); 7.68 (d, 8.4, H-3″); 7.75 (d, 2H, *J* = 8.5, H-5″); 3.85 (s, 4′-OCH_3). ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 195.6 (C-4); 163.1 (C-2); 101.5 (C-5); 159.0 (C-6); 125.5 (C-1′); 126.5 (C-2′ & C-6′); 113.8 (C3′ & C-5′); 160.5 (C-4′); 138.3 (C-1″); 135,5 (C-2″); 133.5 (C-3″); 128.1 (C-4″); 133.4 (C-5″); 128.5 (C-6″); 55.8 (OCH_3).

3.5. 2-Amino-4-(4′-Metoxyphenyl)-6-(4″-Bromophenyl)-Pyrimidin (4e)

IR (KBr, cm^{-1}): νNH_2 = 3330; 3209 cm^{-1}, δNH_2 = 1642 cm^{-1}. Melting point: 170-171 ºC. Yield: 70%. Irradiation time 3 min. ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 6.69 (s, NH_2); 7.68 (s, H-5); 8.17 (d, 2H, *J* = 8.5, H-2′ & H-6′); 7.06 (d, 2H *J* =8.5, H-3′ & H-5′); 8.20 (d, 8.5, H-2″ & H-6″); 7.71 (d, 8.5, H-3″); 7.71 (d, 2H, *J* = 7.5, H-5″); 3.84 (s, 4′-OCH_3). ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 193.6 (C-4); 164.2 (C-2); 101.3 (C-5); 162.0 (C-6); 128.2 (C-1′); 128.5 (C-2′ & C-6′); 114.8 (C3′ & C-5′); 160.6 (C-4′); 134.3 (C-1″); 135,7 (C-2″); 132.7 (C-3″); 128.0 (C-4″); 132.3 (C-5″); 126.5 (C-6″); 55.8 (OCH_3).

3.6. 2-Amino-4-(4′-Metoxyphenyl)-6-(4″-Metylphenyl)-Pyrimidin (4f)

IR (KBr, cm^{-1}): νNH_2 = 3326; 3194 cm^{-1}, δNH_2= 1614 cm^{-1}, melting point: 125-126 ºC. Yield: 68%. Irradiation time 5 min. ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 6.6 (s, NH_2); 7.61 (s, H-5); 8,20 (d, 9,0, H2′ % H-6′); 7,06 (d, 8,5, H-3′ & H-5′); 8,10 (d, 2H, *J* = 8,5, H2″ & H-6″); 7,71 (d, 2H, *J* = 8,3, H-3″ & H-5″); 3.83 (s, 4′-OCH_3); 2.50(s, 4″-CH_3). ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 164.3 (C-2); 188.5 (C-4); 101.0 (C-5); 162.3 (C-6); 125.5 (C-1′); 125.5 (C-2′ & C-6′); 113.5 (C-3′ & C-5′); 160 (C-4′); 141.4 (C-1″); 122.4 (C-6″ & C-2″); 123.5 (C-3″ & C-5″); 127.3 (C-4″); 55.2 (OCH_3). 21.5 (4″-CH_3).

3.7. 2-Amino-4-(4′-Metoxyphenyl)-6-(4″-Isopropylphenyl)-Pyrimidin (4g)

IR (KBr, cm^{-1}): νNH_2 = 3380; 3309cm^{-1}, δNH_2 = 1639 cm^{-1}, melting point: 161-162 ºC. Yield: 80%. Irradiation time 3 min. ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 6.42 (s, NH_2); 7,51 (s, H-5); 8,17 (d, 2H, *J* = 9,0, H2′ & H6′); 7,05 (d, 2H, *J* = 9,0, H-3′ & H-5′); 8,08 (d; 2H, *J* = 8,5, H-2″ & H-6″); 6,79 (d, 2H, *J* = 7.0, H-3″ & H-5″); 3.83; 3,00(s, 4″- $N(CH_3)_2$); 3.85 (s, 4′-OCH_3).^{13}C-NMR (DMS O-*d6*, *δ*, ppm): 167.2 (C-2); 193.5 (C-4); 101.0 (C-5); 165 (C-6); 125.5 (C-1′); 125.1 (C-2′& C-6′); 114.5 (C-3′ & C-5′); 160 (C-4′); 140.3 (C-1″); 125.4 (C-6″ & C-2″); 123.2 (C-3″ & C-5″); 127.3 (C-4″); 55.4 (OCH_3). 41.3 ($2CH_3$).

3.8. 2-Amino-4-(4′-Metoxyphenyl)-6-(3″-Metoxyphenyl)-Pyrimidin (4h)

IR (KBr, cm^{-1}): νNH_2 = 3430;3190 cm^{-1}, δNH_2= 1642 cm^{-1}, melting point: 140-141 ºC. Yield: 67%. Irradiation time 3 min. ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 6.35 (s, NH_2); 7.85 (s, H-5); 7.85 (d, 2H, *J* = 7.8, H-2′ & H-6′); 7.12 (d, 2H, *J* = 7,26, H-3 & H-5′); 7.55 (m, H-6″); 7.20 (m, H-2″); 7.69 (m, H-5″); 7.02 (m, H-4″); 3.81 (s; OCH_3).^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 163.5 (C-2); 189.4 (C-4); 101.0 (C-5); 161 (C-6); 123.5 (C-1′); 125.1 (C-2′ & C-6′); 112.8 (C-3′ & C-5′); 160 (C-4′); 141.2 (C-1″); 125.4 (C-6″ & C-2″); 123.8 (C-3″ & C-5″); 127.2 (C-4″); 55.4 (OCH_3).

3.9. 2-Amino-4,6-bis(4′-Metoxyphenyl)-Pyrimidin (4i)

IR (KBr, cm^{-1}): νNH_2 = 3487; 3387 cm^{-1}, δNH_2= 1629 cm^{-1}, Melting point: 179-180 ºC. Yield: 55%. Irradiation time 5 min. ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 6.56 (s, NH_2); 7.59 (s, H-5); 8.19 (d, 8,5, H-2′ & H-6′); 7.05 (d, 8.5, H-3′ & H-5′); 8.19 (d, 8.5, H-2″ &H -6″); 7.05; d; 8.5, H-3″ & H-5″); 3.83 (s; 4′-OCH_3). ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 197.4 (C-2, C-4, & C-6); 127.5, 161.6 (C-4′ & C-4″); 143.3 (C-6′, C-6″); 101.0 (C-5); 113.8 (C-3′, C-5′ & C-3″, C-5″); 55.4 (OCH_3).

3.10. 2-Amino-4-(4′-Metoxyphenyl)-6-(4″-Dimetylaminophenyl)-Pyrimidin (4j)

IR (KBr, cm^{-1}): νNH_2 = 3482; 3297 cm^{-1}, δNH_2= 1621 cm^{-1}. Melting point: 175-176 ºC. Yield: 70%. Irradiation time 3 min. ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 6.42 (s, NH_2); 7.51 (s, H-5);

8.17 (d; 9.0, H-2′); 7.05 (d, 9.0, H-3′); 7.05 (d, 9.0, H-5′); 8.17; (d; 9.0, H-6′); 8.08 (d; 90, H-2″); 6.79 (d; 9.0, H-3″); 6.79; (d; 9.0, H-5″); 8.08 (d; 9.0, H-6″); 3.83 (s; 4′- OCH_3); 3.00; (s; 4″-$N(CH_3)_2$). ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 195.2 (C-4); 164.5 (C-2); 101.3 (C-5); 162.0 (C-6); 128.1 (C-1′); 127.5 (C-2′ & C-6′); 113.5 (C-3′& C-5); 161.3 (C-4′); 134 (C-1″); 111.5 (C-2″); 148.5 (C-3″); 114.1 (C-4″); 131.0 (C-5″); 117.5 (C-6″); 55.8 (OCH_3); 41,2 ($N(CH_3)_2$).

3.11. 5,7-dihydroxy-3-(1-((4-(4-methoxyphenyl)-6-phenylpyrimidin-2-yl)imino)ethyl)-2-methyl-4H-chromen-4-one (5a)

IR (KBr, cm^{-1}): 1750.15 (C = O), 1656.55 (C = N), 1575 (C = C), 1203 (C-O-C). ^{1}H-NMR (DMSO-*d6, δ*, ppm): 15.4 (s, 1H, 5-OH), 9.96 ppm (s, 1H, 7-OH); 8.08 (s. 1H, H-5′); 6.72 (s,1H, H-6); 6.89 (1H, H-8) 7.05 (m, 2H, H-3″, H5″); 7.85 (m, 2H, H-2″, H-6″); 7.90 (m, 2H, H-2‴& H-6‴); 7.56 (2H, H3‴ & H-5‴); 7.50 (1H, H-4‴); 2.05- 2.29 (6H, CH_3); 3.81 (3H, OCH_3) ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 177.5 (C=O); 175,4 (C=N), 169.5 (C-O); 165.5 (C-7); 164,5 (C-4′&C-6′); 165.5 (C-2′); 162.2 (C-2); 160.2 (C-8a); 102.9 (C-4a); 164.4 (C-6′ &C-4′); 160.5 (C-4″); 104.4 (C-5′); 128.5 (C-2″ & C-6″); 129.2 (C-3‴& C-5‴); 128.7 (C-4‴); 115.3 (C-3″ &C-5″); 18.5- 20.1(2C-CH_3); 55.8 (OCH_3).

3.12. 3-(1-((4-(2-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)imino)ethyl)-5,7-dihydroxy-2-methyl-4H-chromen-4-one (5b)

IR (KBr, cm^{-1}): 1765.16 (C = O), 1654.55 (C = N), 1573 (C = C), 1109 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.5 (s, 1H, 5-OH), 10.9 ppm (s, 1H, 7-OH); 8.02 (s, 1H, H-5′); 6.72 (s, 1H, H-6); 6.55 (1H, H-8); 7.39 (m, 2H, H-4″, H5″); 7.85 (m, 2H, H2″, H6″); 7.63 (d, J = 7.2, 1H, H-3‴); 7.10 (m, 2H, H-3″ & H-5″) 2.07- 2.29 (6H, CH_3); 3.80 (3H, OCH_3); ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 178.5 (C = O); 175,4 (C = N), 163.5 (C-O); 165.5 (C-7); 164.5 (C-4′&C-6′); 161.4 (C-2′); 162.3 (C-2); 162.2 (C-8a); 102.9 (C-4a); 128.5 (C-2‴& C-6‴); 160.4 (C-4″); 142.5 (C-1‴); 127.9 (C-2‴ & C-5‴); 135.5 (C-3‴); 128.8 (C-4‴) 20.1 (2C-CH_3); 55.8 (OCH_3).

3.13. (3-(1-((4-(3-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)imino)ethyl)-5,7-dihydroxy-2-methyl-4H-chromen-4-one (5c)

IR (KBr, cm^{-1}): 1754.12 (C = O), 1652.25 (C = N), 1563 (C = C), 1105 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.47 (s, 1H, 5-OH), 10.12 ppm (s, 1H, 7-OH); 8.55 (s, 1H, H-5′); 5.95(s, 1H, H-6); 6.07 (1H, H-8) 7.09 (m , 2H, H-3″& H-5″); 7.86 (m, 2H, H2″, H6″); 7.50 (m, 2H, H4‴& H5‴); 7.77 (d, *J* = 7.2 Hz, 1H, H6‴) 2.07- 2.29 (6H, CH_3); 3.83 (3H, OCH_3) ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 178.5 (C = O); 175,4 (C = N), 163.5 (C-O); 165.5 (C-7); 164,5 (C-4′&C-6′); 161.4 (C-2′); 162.3 (C-2); 162.2 (C-8a); 102.9 (C-4a); 128.5 (C-2‴ & C-6‴); 160.4 (C-4″); 142.5 (C-1‴); 127.9 (C-2‴ & C-5‴); 135.5 (C-3‴); 128.8 (C-4‴) 20.1 (2C-CH_3); 55.8 (OCH_3).

3.14. 3-(1-((4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)imino)ethyl)-5,7-dihydroxy-2-methyl-4H-chromen-4-one (5d)

IR (KBr, cm^{-1}): 1655.45 (C = O), 1651.28 (C = N), 1560 (C = C), 1209 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.49 (s, 1H, 5-OH), 11.2 ppm (s, 1H, 7-OH); 8.05 (s, 1H, H-5′); 6.75 (s, 1H, H-6); 7.89 (m, 2H, H-2‴ & H-6‴); 7.85 (m, 2H, H-2″ & H-6″); 7.65 (m, 2H, H-3‴& H-5‴); 7.04 (m, H-3″ & H-5″); 6.12 (s, 1H, H-8); 3.83 (3H, OCH_3 2.06 - 2.15 (6H, CH_3) ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 177.5 (C = O); 175,4 (C = N), 160.0 (C-O); 166.5 (C-7); 164,2 (C-4′&C-6′); 163.5 (C-2′); 162.3 (C-2); 162.2 (C-8a); 102.9 (C-4a); 134.5 (C-1‴); 128.9 (C-2‴& C-6‴); 160.4 (C-4″); 128.5 (C-3‴ & C-5‴); 134.4 (C-4‴); 129.0 (C-2″ & C-6″); 115.4 (C-3″ & C-5″); 160.1 (C-4‴); 20.1(2C-CH_3); 55.8 (OCH_3).

3.15. 3-(1-((4-(4-Bromophenyl)-6-(4-Methoxyphenyl) Pyrimidin-2-yl) Imino) Ethyl)-5,7-Dihydroxy-2-Methyl-4H-Chromen-4-one (5e)

IR (KBr, cm^{-1}): 1752.12 (C = O), 1659.20 (C = N), 1562 (C = C), 1107 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.47 (s, 1H, 5-OH),

10.9 ppm (s, 1H, 7-OH); 8.55 (s, 1H, H-5′); 5.95 (s, 1H, H-6); 7.79 (m, 2H, H-2‴ & H-6‴); 7.85 (m, 2H, H-2″ & H-6″); 7.55 (m, 2H, H-3‴& H-5‴); 7.09 (m, H-3″ & H-5″); 6.02 (s, 1H, H-8); 3.81 (3H, OCH_3 2.07- 2.35 (6H, CH_3) ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 177.9 (C = O); 178,4 (C = N), 162.5 (C-O); 165.5 (C-7); 164,5 (C-4′&C-6′); 163.5 (C-2′); 162.3 (C-2); 162.2 (C-8a); 102.9 (C-4a); 134.5 (C-1‴); 128.5 (C-2‴& C-6‴); 160.4 (C-4″); 118.5 (C-3‴ & C-5‴); 134.4 (C-4‴); 128.5 (C-2″ & C-6″); 114.5 (C-3″ & C-5″); 162.1 (C-4‴) 15.5; 20.1(2C-CH_3); 55.8 (OCH_3).

3.16. 5,7-Dihydroxy-3-(1-((4-(4-Methoxyphenyl)-6-(p-Tolyl)Pyrimidin-2-yl)Imino)ethyl)-2-Methyl-4H-Chromen-4-One (5f)

IR (KBr, cm^{-1}): 1752.12 (C = O), 1659.20 (C = N), 1562 (C = C), 1107 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.50 (s, 1H, 5-OH), 10.9 ppm (s, 1H, 7-OH); 8.55 (s, 1H, H-5′); 5.95 (s, 1H, H-6); 7.79 (m, 2H, H-2‴ & H-6‴); 7.85 (m, 2H, H-2″ & H-6″); 7.55 (m, 2H, H-3‴ & H-5‴); 7.09 (m, H-3″ & H-5″); 6.02 (s, 1H, H-8); 3.80 (3H, OCH_3 2.07- 2.35 (6H, CH_3) ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 177.4 (C = O); 175,4 (C = N), 160.2 (C-O); 166.5 (C-7); 163,5 (C-4′&C-6′); 160.5 (C-2′); 162.3 (C-2); 162.5 (C-8a); 102.9 (C-4a); 132.5 (C-1‴); 125.5 (C-2‴& C-6‴); 160.5 (C-4″); 125.3 (C-3‴ & C-5‴); 131.4 (C-4‴); 128.5 (C-2″ & C-6″); 114.5 (C-3″ & C-5″); 161.2 (C-4‴) 15.5; 22.3(6C-CH_3); 55.8 (OCH_3).

3.17. 5,7-Dihydroxy-3-(1-((4-(4-Isopropylphenyl)-6-(4-Methoxyphenyl) Pyrimidin-2-yl)Imino)ethyl)-2-Methyl-4H-Chromen-4-one (5g)

IR (KBr, cm^{-1}): 1763.15 (C = O), 1653.25 (C = N), 1552 (C = C), 1205 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.53 (s, 1H, 5-OH), 11.5 ppm (s, 1H, 7-OH); 8.58 (s, 1H, H-5′); 5.93 (s, 1H, H-6); 7.69 (m, 2H, H-2‴ & H-6‴); 7.85 (m, 2H, H-2″ & H-6″); 7.50 (m, 2H, H-3‴ & H-5‴); 7.08 (m, H-3″ & H-5″); 6.02 (s, 1H, H-8); 3.81 (3H, OCH_3 2.07- 2.25 (6H, CH_3); 1.25 (6H, ipr); 3.01 (1H- CH); ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 175.5 (C = O); 175,4 (C = N), 160.1 (C-O); 164.5 (C-7); 164,5 (C-4′&C-6′); 163.5 (C-2′); 162.2 (C-2); 160.5 (C-8a); 102.9 (C-4a); 133.5 (C-1‴); 125.5 (C-2‴& C-6‴); 160.6 (C-4″); 125.3 (C-3‴ & C-5‴); 131.4 (C-4‴); 128.5 (C-2″ & C-6″); 114.9 (C-3″ & C-5″); 145.2 (C-4″) 15.9; 25. (6C-CH_3); 25.5 (3C-ipr); 145.3 (1C-CH); 55.8 (OCH_3).

3.18. 5,7-Dihydroxy-3-(1-((4-(3-Methoxyphenyl)-6-(4-Methoxyphenyl) Pyrimidin-2-yl) Imino)ethyl)-2-Methyl-4H-Chromen-4-one (5h)

IR (KBr, cm^{-1}): 1675.09 (C = O), 1642.15 (C = N), 1533 (C = C), 1175 (C-O-C). ^{1}H-NMR (DMSO-*d6* , *δ*, ppm): 16.57 (s, 1H, 5-OH), 11.15 ppm (s, 1H, 7-OH); 8.59 (s, 1H, H-5′); 5.85(s,1H, H-6); 6.03 (1H, H-8) 7.09 (m, 2H, H-3″, H5″); 7.85 (m, 2H, H2″, H6″); 7.00 (m, 1H, H4‴); 7.56 (1 H, H5‴); 7.57 (d, *J* = 7.2 Hz, 1H, H6‴) 2.07- 2.29 (6H, CH_3); 3.81 (6H, OCH_3) ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 179.5 (C = O); 173,4 (C = N), 163.5 (C-O); 165.5 (C-7); 164,5 (C-4′&C-6′); 164.8 (C-2′); 163.3 (C-2); 161.5 (C-8a); 102.9 (C-4a); 161.5 (C-4″ & C-3‴); 139.5 (C-1‴); 132 (C-5‴); 129.3 (C-2″ & C-6″); 115.8 (C-3″ & C-5″); 115 (C-4‴); 115.5 (C- 6‴); 112.5 (C-2‴); 115.5-21.9 (6C-CH_3); 58.9 (6C-OCH_3).

3.19. 3-(1-((4,6-bis(4-Methoxyphenyl)Pyrimidin-2-yl)Imino)ethyl)-5,7-Dihydroxy-2-Methyl-4H-Chromen-4-one (5i)

IR (KBr, cm^{-1}): 1750.9 (C = O), 1659.25 (C = N), 1560 (C = C), 1207 (C-O-C). ^{1}H-NMR (DMSO-*d*, *δ*, ppm): 16.47 (s, 1H, 5-OH), 10.9 ppm (s, 1H, 7-OH); 8.58 (s, 1H, H-5′); 5.94 (s, 1H, H-6); 7.55 (m, 4H, H-2‴ & H-6‴; H-2″ & H-6″); 7.55 (m, 4H, H-3‴& H-5‴; H-3″ & H-5″); 6.02 (s, 1H, H-8); 3.81 (6H, OCH3); 2.07- 2.25 (6H, CH_3); ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 177.9 (C = O); 178,4 (C = N), 162.5 (C-O); 165.5 (C-7); 164,5 (C-4′&C-6′); 163.5 (C-2′); 162.3 (C-2); 162.2 (C-8a); 102.9 (C-4a); 129.5 (C-1″ & C-1‴); 128.5 (C-2‴& C-6‴; C-2″ & C-6″); 115.9 (C-3″ & C-5″; C-3‴ &C-5‴); 160.5 (C-4″ & C-4‴); 55.8 (OCH_3).

3.20. 3-(1-((4-(4-(Dimethylamino)Phenyl)-6-(4-Methoxyphenyl)Pyrimidin-2-yl)Imino)ethyl)-5,7-Dihydroxy-2-Methyl-4H-Chromen-4-one (5j)

IR (KBr, cm^{-1}): 1720.5 (C = O), 1654.55 (C = N), 1565 (C = C), 1157 (C-O-C). ^{1}H-NMR (DMSO-*d6*, *δ*, ppm): 16.47 (s, 1H, 5-OH), 10.9 ppm (s, 1H, 7-OH); 8.58 (s, 1H, H-5′); 5.94 (s, 1H , H-6); 8.59 (s, 1H, H5′); 7.95 (m, 2H, H- 2″ & H-4″); 7.73 (m, 2H, H-2‴ & H-4‴); 7.15 (m, 2H, H-3″ & H5″); 7.02 (m, 2H, H-3‴ & H-5‴); 6.05 (s, 1H, H-8); 2.05- 2.45 (6H; CH_3); ^{13}C-NMR (DMSO-*d6*, *δ*, ppm): 175.9 (C = O); 175,4 (C = N), 165.5 (C-O); 166.5 (C-7); 165,5 (C-4′&C-6′); 164.5 (C-2′); 162.2 (C-2); 160.2 (C-8a); 102.9 (C-4a); 161.2 (C-4″); 159.2 (C-4‴); 128.5 (C-2″ & C6″); 127.9 (C-2‴ & C-6‴); 115.5 (C-3″ & C-5″); 112.7 (C-3‴ & C-5‴); 45.5 (2C-NMe2); 14.9-20.5 (2C-CH_3); 88.9 (OCH_3).

4. Conclusion

To sum up, everything that has been stated so far, this review sheds light on an efficient and environmentally friendly procedure for the solvent-free synthesis of ten new chromone derivatives promoted by microwave irradiation by hetero-cyclization of the corresponding *p*-Methoxyacetophenone or substituted benzaldehyde and guanidine hydrochloride in the presence of sodium hydroxide. Our methodology allows for the preparation of a variety of chromones in pure form in only 3-5 min with good yields (70-85%).

The structures of these compounds were established based on the ^{1}H-NMR, and ^{13}C-NMR spectroscopy methods. The obtained results through the disk diffusion method showed promising activities against bacteria, fungi, namely, *E.coli*, *S. aureus*, and *C. albicans* in the studied concentration range.

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