Research article

Synthesis of new flavonoid derivatives based on 3-hydroxy-4′-dimethylamino flavone and study the activity of some of them as antifungal

Hadi Aqel Khdera [a],[*], Sawsan Youseff Saad [a], Aoula Moustapha [b], Farouk Kandil [c]

[a] Chemistry Department, Faculty of Sciences, Tishreen University, Lattakia, Syria
[b] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Baath University, Homs, Syria
[c] Chemistry Department, Faculty of Sciences, Damascus University, Damascus, Syria

ARTICLE INFO

ABSTRACT

Chalcone was prepared in a new route by reacting o-hydroxyacetophenone with 4-dimethylaminobenzaldehyde using piperidine as a catalyst. 3-Hydroxy-2-[4-(dimethylamino)phenyl] benzopyran-4-one were prepared by Algar-Flynn-Oyamada method by cyclization of chalcone using Hydrogen peroxide. A series of alkyl and ester derivatives of the flavonoid 3-hydroxy-2-[4-(dimethylamino)phenyl] benzopyran-4-one were prepared by reacting the above mentioned compound with different chemical reagents (Methyl iodide, Allyl bromide, Benzyl chloride, Bromoacetylcoumarin, Chloroacetamide, Chloroacetyl chloride, Phthalic anhydride, Maleic anhydride, Phthalimide, Cinnamoyl chloride) with potassium carbonate and acetone or DMF as a solvent. The physical and spectroscopic properties of the new compounds were studied by (FT-IR, ^{13}C-NMR and ^{1}H-NMR) spectral methods. The purity of the synthesized compounds were confirmed using TLC thin layer chromatography. The biological activity of some synthetic flavonoids (A_2, A_5, A_7, A_8, A_9, A_{12}) at two different concentrations (0.5 mg/ml, 0.25 mg/ml) were studied on three types of fungi: *Aspergillus flavus*, *Acremonium strictum*, *Penicillium expansum*. Some of this compounds showed high activity against the tested fungi.

1. Introduction

Flavonoids and their derivatives have gained the attention of biologists and chemists because they play a major role in nature. It has wide applications in the pharmaceutical field, as they are Antioxidants, Anticancers, Antidepressants, Antibacterials, Anti-inflammatory…etc [1, 2, 3, 4]. And in the field of the Food Industry (as coloring materials and sweeteners) [5]. In addition to being used in agriculture as insecticides [6]. It also gave a new insight into laboratory technology to explore the effectiveness of plant cell tissue implantation to produce chemical compounds similar to those of the mother plant [7]. Flavonoids are polyphenolic compounds with low molecular weight [8, 9], widely found in plants. It has biological activity [10] and play vital role in photosynthesis cells [11]. The structure of flavonoids consists of fifteen basic carbon atoms with a general formula $C_{15}H_{10}O_2$ (C_6–C_3–C_6). The basic nucleus of flavonoids is 2-phenyl benzo-γ-pyrone (2-phenyl chromone). Which consists of two Benzen rings (A and B), Figure 1 one of which is condensed with the Pyran ring (C) and the other is branched [11].

Flavonoids can be classified according to their sources [12]. Some of them are intermediates in the biosynthesis, such as: chalcones,

flavanone, flavanone-3-ol, flavan-3,4-diol. The end products of biosynthesis are anthocyanins, flavones and flavonols. There are two other classes of flavonoids related to the aromatic ring (B): isoflavones: in which the aromatic ring (B) is at position C_3, and neoflavonoids: in which the aromatic ring (B) is at position C_4. Flavonoids possess antibacterial, antifungal, antiviral, anti-allergic, anti-inflammatory and antioxidant activity [1, 2, 3, 4]. Studies have shown that the activity of flavonoids against microbes depends on its chemical composition, which is affected in particular by the number and position of different functional groups such as: hydroxy, methoxy, halogens, nitro, methyl, cyano-substituted groups in the two aromatic rings (A, B) [13, 14, 15, 16]. Studies have shown that the substitution pattern at site 3 of the C-ring has a regulatory role on biological activity and metab olism.

Researcher Jayashree and his colleagues [17] were able to synthesize a series of ester derivatives of flavonoids by reacting the esterification of the –OH enolic group at the C_3 position of the flavonoid 3-hydroxy-2-[4-(dimethylamino)phenyl] benzopyran-4-one with acid chlorides with pyridine as an intermediate.
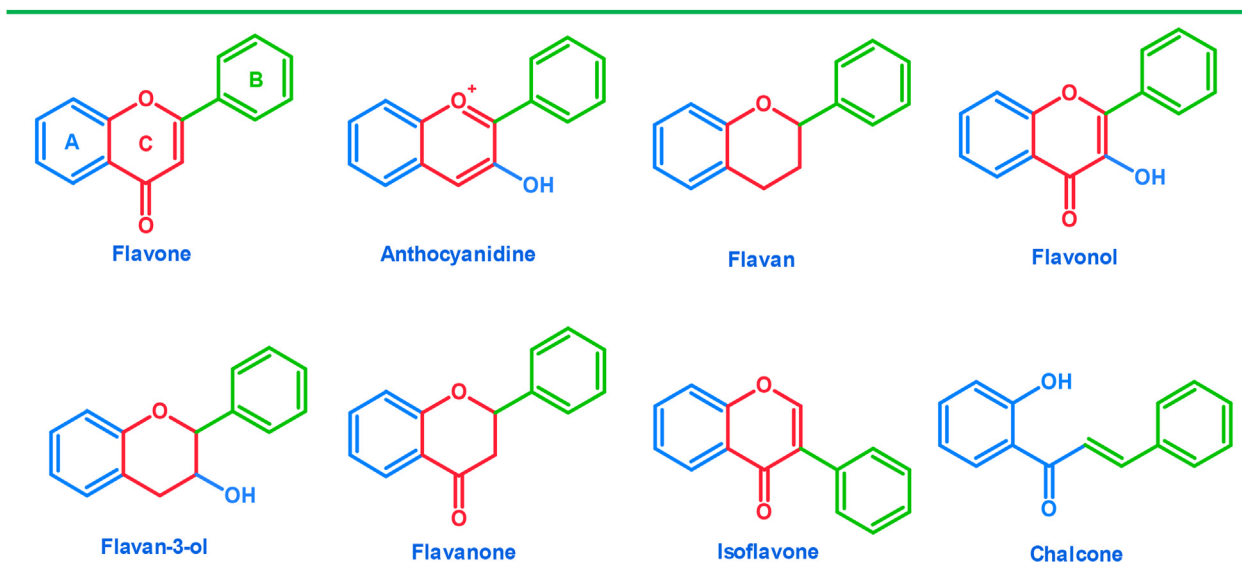

Figure 1. Basic structures of flavonoids subclasses.

American researchers at the University of California [18] were able to synthesize a series of 48 compounds from 3-O-alkyl quercetin derivatives through several stages in the laboratories of the Cancer Research Center.

In our research, we used the condensation method to prepare chalcone using an organic alkali (piperidine) as a catalyst through the reaction of o-hydroxyacetophenone and p-dimethylamino benzaldehyde. A series of alkyl and ester derivatives were prepared by reacting 3-hydroxyflavone with different alkyl halides (methyl iodide, allyl bromide, benzyl chloride, bromoacetylcoumarin, chloroacetamide) and carboxylic acid derivatives (phthalic anhydride, maleic anhydride, phthalimide, chloroacetyl chloride, cinnamoyl chloride).

2. Experimental

2.1. General information

All compounds were purified by recrystallization and chromatographically separated using Preparative-TLC. The course of the reactions were monitored by thin-layer chromatography (TLC) on aluminum plates coated with silica gel with a fluorescent indicator (DC-Fertigfolien ALU-GRAM Xtra SIL G/UV$_{254}$) and using a DESAGA-UVIS/254/366 nm UV lamp. Melting points were determined using the Stauart Electrothermeal Entineering LTD (measuring melting points up to 400 Č). Infrared spectra were recorded using Bruker FT-IR alpha T within a potassium bromide disc. ^{13}C-NMR and ^{1}H-NMR spectra were recorded via a 400 MHz Bruker-Avance Spectrometer using (DMSO-d$_6$) solvent with compound (TMS) as standard reference at the High Atomic Energy Authority – Damascus.

Chemical and Starting Materials: The solvents used were from different companies (Sigma Aldrich, Merck, Fluka, BDH) (absolute ethanol, dry acetone, N,N-dimethylformamide DMF, hexane, dry ether, ethyl acetate,...), the materials used are: o-Hydroxyacetophenone, 4-Dimethylaminobenz aldehyde, methyl iodide, benzyl chloride, allyl bromide, chloroacetyl chloride, chloroacetamide, thionyl chloride, phthalic anhydride, maleic anhydride, Hydrogen peroxide 35%, ethyl acetoacetate, Salicyl aldehyde, potassium hydroxide, potassium carbonate, concentrated hydrochloric acid from different companies (Merck, Fluka, BDH, Sigma Aldrich), Potato Dextrose Agar P.D.A (HIMEDIA).

2.2. Chemistry

New flavonoid derivatives were synthesized from o-hydroxyacetophenone and 4-dimethylamino benzaldehyde according to the following scheme.

2.2.1. Preparation of some primary organic materials used in the synthesis of flavonoid derivatives

2.2.1.1. Preparation of 3-acetyl coumarin [19]. 3-Acetylcoumarin was prepared according to the method used in reference [19]. Yield (95%). Melting point 120–122 Č.

2.2.1.2. Preparation of 3-(bromoacetyl) coumarin [19]. 3-Bromo-acetylcoumarin was prepared according to the method used in reference [19]. Yield (85%). Melting point 166–168 Č.

2.2.1.3. Preparation of cinnamoyl chloride [18]. 100 ml of (0.008 mol, 1.2 g) of cinnamic acid and 5–6 ml of thionyl chloride were added to a Erlenmeyer flask, stirred well at 50 Č for 2 h. After the reaction were completed, the thionyl chloride were evaporated using a rotary evaporator and a colorless oily liquid were obtained, which is cinnamoyl chloride.

2.2.1.4. Preparation of phthalimide [20]. Phthalimide was prepared according to the method used in reference [19]. Yield (R$_f$ = 0.25. Melting Point: 232–234 Č.

2.2.2. Synthesis of the flavonoid 2-[4-(dimethylamino) phenyl]-3-hydroxy-4H-1-benzopyran-4-one (A$_2$)

The flavonoid compound is synthesized from chalcone according to the following stages.

2.2.2.1. Synthesis of chalcone: (2E)-3-[4-(dimethylamino)phenyl]-1-(2-hydroxyphenyl) prop-2-en-1-one (A$_1$). This compound were previously prepared [21] using the aldol condensation method by condensa–tion of the compound o-hydroxyacetophenone with the compound 4-dimethylaminobenzaldehyde using NaOH as a catalyst and the yield were (94.2%). We used a new method to prepare this compound using an organic alkaloid (piperidine) according to the following [22]: (0.04 mol, 5.44 g) of o-hydroxyacetophenone and (0.04 mol, 5.96 g) of 4-Dimethylaminobenzaldehyde were added in 100 ml of absolute ethanol, 4–5 ml of piperidine were added to the previous solution. The mixture were refluxed for 5 h, the reaction monitored using TLC. After cooling the solution a precipitate were formed which were separated by filtration. 2 ml piperidine were added to the filtrate and refluxed for 4 h. The precipitate formed were filtered, washed with water and ethanol several times, and recrystallized with ethanol, resulting in a precipitate of Bright

pink colour. The purity of the prepared compound were confirmed by TLC technology using the mixture (ether:hexane 2:3).

2.2.2.2. A₁. (2E)-3-[4-(Dimethylamino)phenyl]-1-(2-hydroxyphenyl) prop-2-en-1-one.
Bright pink solid; Yield: 80.9%; mp 178–180 °C; R_f = 0.47 (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 3650 (OH), 2890 (C–H$_{aliphatic}$), 1596 (C=O pyrone), 1432–1485 (C=C), 1202 (C–O).

2.2.2.3. Synthesis of 2-[4-(dimethylamino) phenyl]-3-hydroxy-4H-1-benzopyran-4-one (A₂) [21].
This compound was previously prepared according to the method used in reference [21].

2.2.2.4. A₂. 2-[4-(Dimethylamino)phenyl]-3-hydroxy-4H-1-benzopyran-4-one.
Bright yellow solid; Yield: 82%; mp 190–191 °C; R_f = 0.36 (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 3295 (OH), 2910 (C–H$_{aliphatic}$), 1597 (C=O pyrone), 1482–1558 (C=C), 1152–1287 (C–O); ^{1}H-NMR (400 MHz, DMSO-d₆, δ ppm): 3.02 (s, 6H, 2 CH₃), 6.85–8.12 (m, 8H, aromatic ring), 9.19 (s, H, OH); ^{13}C-NMR (100 MHz, DMSO-d₆, δ ppm): 40.55 (2 CH₃), 111.71 (C$_{3',5'}$), 118.35 (C₈), 118.95 (C$_{1'}$), 121.86 (C$_{10}$), 123.70 (C₆), 125.08 (C₅), 129.39 (C$_{2',6'}$), 133.57 (C₇), 137.72 (C₃), 147.29 (C$_{4'}$), 151.51 (C₂), 154.72 (C₉), 172.43 (C=O pyron).

2.2.3. Synthesis of new alkyl derivatives of flavonoid (A₂)

2.2.3.1. Synthesis of the compound 2-[4-(dimethylamino)phenyl]-3-[(prop-2-en-1-yl)oxy]-4H-1-benzopyran-4-one (A₃) [23,24].
(0.00177 mol, 0.5 g) of the flavonoid compound (A₂) were dissolved in 50 ml of dry acetone, an excess amount of potassium carbonate K₂CO₃ were added, while stirring well for 5 min, (0.00177 mol, 0.22 g) of Allyl bromide dissolved in 10 ml acetone were added dropwise, the reaction mixture were stirred for 48 h at 50–60 °C. The mixture were poured into a beaker containing crushed ice and neuterlised with dilute hydrochloric acid, the formed precipitate were filtered, washed with water and then recrystallized with ethanol, resulting in a yellow precipitate. Its purity were confirmed by TLC using the mixture (ether:hexane 2:3).

2.2.3.2. A₃. 2-[4-(Dimethylamino)phenyl]-3-[(prop-2-en-1-yl)oxy]-4H-1-benzopyran-4-one.
Yellow solid; Yield: 78.9%; mp 76–78 °C; R_f = 0.33 (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 2820–2900 (C–H$_{aliphatic}$), 1722 (C=O pyrone), 1469–1594 (C=C), 1100–1288 (C–O); ^{1}H-NMR (400 MHz, DMSO-d₆, δ ppm): 3.02 (s, 6H, 2 CH₃), 4.58 (d, 2H, O–CH₂), 5.19–5.33 (dd, 2H, =CH₂), 5.97 (m, H, =CH), 6.83–8.03 (m, 8H, aromatic ring); ^{13}C-NMR (100 MHz, DMSO-d₆, δ ppm): 40.22 (CH₃, 2 CH₃), 72.46 (CH₂), 111.72 (C$_{3',5'}$), 117.18 (C₈), 118.34 (=CH₂), 118.59 (C$_{1'}$), 123.92 (C$_{10}$), 125.19 (C₆), 125.27 (C₅), 130.13 (C$_{2',6'}$) 133.98 (=CH), 134.54 (C₇),138.14 (C₃), 152.15 (C$_{4'}$), 154.92 (C₉), 156.53 (C₂), 173.69 (C=O pyrone).

2.2.3.3. Synthesis of 2-[4-(dimethylamino)phenyl]-3-methoxy-4H-1-benzo pyran-4-one (A₄) [23,24].
This compound were previously synthesized [17] via a methylation reaction of the flavonoid compound using dimethyl sulfate (CH₃)₂SO₄ using potassium carbonate as catalyst and the yield were (68%).

We used a new method to prepare this compound according to the following [24, 25]: (0.00177 mol, 0.5 g) of the flavonoid compound (A₂) were Dissolve in 50 ml of dry acetone, an excess of potassium carbonate K₂CO₃ were added and stirred well for 5 min, then (0.00177 mol, 0.25 g) of methyl iodide dissolved in 10 ml acetone were added dropwise and stirred well for 48 h at 50–60 °C. The reaction mixture were poured into a beaker containing crushed ice and neuterlised with dilute hydrochloric acid, the formed precipitate were filtered, washed with water and then recrystallized in absolute ethanol, resulting in a yellow precipitate. Its purity were confirmed by TLC using the mixture (ether:hexane 2:3). After comparing the new method (using methyl iodide) and the previously

used method (using dimethyl sulfate), the yield were higher according to the new method (82.8%).

2.2.3.4. A₄. 2-[4-(Dimethylamino)phenyl]-3-methoxy-4H-1-benzopyran-4-one.
Yellow solid; Yield: 82.8%; mp 123–125 °C; R_f = 0.22 (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 2900 (C–H$_{aliphatic}$), 1593 (C=O pyrone), 1467–1556 (C=C), 1127–1198 (C–O).

2.2.3.5. Synthesis of 2-({2-[4-(dimethylamino) phenyl]-4-oxo-4H-1-benzopyran-3-yl} oxy) acetamide (A₅) [23,24,25].
(0.00177 mol, 0.5 g) of the flavonoid compound (A₂) were dissolved in 50 ml of N, N-dimethylformamide DMF, excess of potassium carbonate K₂CO₃ were added with good stirring for 5 min, then (0.00177 mol, 0.17 g) of chloroacetamide dissolved in 10 ml DMF were added to it dropwise under good stirring for 48 h at 50–60 °C. The mixture were poured into a beaker containing crushed ice and neuterlised with dilute hydrochloric acid, the precipitate formed were filtered, washed with water and dried. The resulting flavonoid were separated by P-TLC using ethyl acetate mobile phase. A yellow precipitate is produced. Its purity were confirmed by TLC technology using the mixture (acetone:hexane 2:3).

2.2.3.6. A₅. 2-({2-[4-(Dimethylamino)phenyl]-4-oxo-4H-1-benzo pyran-3-yl} oxy) acetamide (A₅).
Yellow solid; Yield: 66.7%; mp 187–188 °C; R_f = 0.37 (acetone:hexane 2:3); IR (KBr, cm^{-1}) υ: 3417 (NH₂), 2922 (C–H$_{aliphatic}$), 1704 (C=O amide), 1616 (C=O pyrone), 1477–1548 (C=C), 1115–1290 (C–O); ^{1}H-NMR (400 MHz, DMSO-d₆, δ ppm): 3.02 (s, 6H, 2 CH₃), 4.74 (s, 2H, O–CH₂), 7.30 (s, 2H, NH₂), 6.80–8.04 (m, 8H, aromatic ring); ^{13}C-NMR (100 MHz, DMSO-d₆, δ ppm): 40.67 (CH₃, 2 CH₃), 68.51 (CH₂), 111.69 (C$_{3',5'}$), 117.24 (C₈), 118.93 (C$_{1'}$), 123.81 (C$_{10}$), 124.74 (C₆), 127.35 (C₅), 128.52 (C$_{2',6'}$), 134.25 (C₇), 137.79 (C₃), 151.89 (C$_{4'}$), 155.17 (C₉), 157.74 (C₂), 169.52 (C=O amide), 174.74 (C=O pyron).

2.2.3.7. Synthesis of 3-(benzyloxy)-2-[4-(dimethyl amino) phenyl]-4H-1-benzopyran-4-one (A₆) [23,24].
(0.00177 mol, 0.5 g) of the flavonoid compound (A₂) were dissolved in 50 ml of dry acetone, excess of K₂CO₃ potassium carbonate were added and sti–rred well for 5 min, then (0.00177 mol, 0.23 g) of benzyl chloride dissolved in 10 ml acetone added to it dropwise with good stirring for 48 h at 50–60 °C. The reaction mixture were poured into a beaker containing crushed ice and neuterlised with dilute hydrochloric acid. The flavonoid compound were extracted from the aqueous solution using n-hexane, the extraction process were repeated twice (2 × 40 ml) and the solvent were evaporated using a Rotary evaporator, the precipitate were washed with water and ethanol, resulting in a bright yellow precipitate. Its purity were confirmed by TLC technology using the mixture (ether:hexane 2:3).

2.2.3.8. A₆. 3-(Benzyloxy)-2-[4-(dimethylamino)phenyl]-4H-1-benzo pyran-4-one.
Yellow solid; Yield: 76.9%; mp 98–100 °C; R_f = 0.36 (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 2889 (C–H$_{aliphatic}$), 1597 (C=O pyrone), 1483–1560 (C=C), 1191–1281 (C–O); ^{1}H-NMR (400 MHz, DMSO-d₆, δ ppm): 3.02 (s, 6H, 2 CH₃), 5.05 (s, 2H, O–CH₂), 6.80–8.10 (m, 13H, aromatic ring), ^{13}C-NMR (100 MHz, DMSO-d₆, δ ppm): 40.66 (CH₃, 2 CH₃), 73.16 (CH₂), 111.73 (C$_{3',5'}$), 117.13 (C₈), 118.63 (C$_{1'}$), 124.01 (C$_{10}$), 125.31 (C₆), 128.47 (C$_{2'',4'',6''}$), 128.50 (C₅), 128.71 (C$_{2',6'}$), 130.18 (C$_{3'',5''}$), 134.04 (C₇), 137.46 (C$_{1''}$), 138.27 (C₃), 152.19 (C$_{4'}$), 154.96 (C₉), 156.74 (C₂), 173.74 (C=O pyron).

2.2.3.9. Synthesis of 3-({[2-(4-Dimethylaminophenyl)-4-oxo-4H-1-benzopyran-3-yl]oxy}acetyl)-2H-1-benz opyran-2-one (A₇) [23,24].
(0.00177 mol, 0.5 g) of the flavonoid compound (A₂) were dissolve in 20 ml of N, N-dimethylformamide DMF, an excess of potassium carbonate K₂CO₃ were added, with good stirring for 5 min, then (0.00177 mol, 0.47 g) of bromo-acetylcoumarin dissolved in 5 ml DMF were added dropwise with continuous stirring for 72 h at 100 °C. The mixture were poured into a

beaker containing crushed ice and neuterlised with dilute hydrochloric acid. The formed precipitate were filtered, washed with water and then recrystallized with absolute ethanol, resulting in a brown precipitate. Its purity were confirmed by TLC technology using the mixture (acetone:-hexane 2:3).

2.2.3.10. A_7- 3-({[2-(4-Dimethylaminophenyl)-4-oxo-4H-1-benzo pyran-3-yl] oxy} acetyl)-2H-1-benzopyran-2-one. Brown solid; Yield: 76%; mp 278–280 $\overset{\circ}{C}$; $R_f = 0.46$ (acetone:hexane 2:3); IR (KBr, cm^{-1}) υ: 2865–2956 (C–H$_{aliphatic}$), 1715 (C=O lactone), 1668 (C=O acetyl), 1606 (C=O pyrone), 1558 (C=C), 1115–1273 (C–O); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.02 (s, 6H, 2 CH$_3$), 5.49 (s, 2H, O–CH$_2$), 6.78–8.05 (m, 12H, aromatic ring), 8.56 (s, 1H, H$_{4''}$); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 40.48 (CH$_3$, 2 CH$_3$), 68.04 (CH$_2$), 111.82 (C$_{3',5'}$), 115.75 (C$_{8''}$), 116.25 (C$_8$), 118.35 (C$_{10''}$), 119.55 (C$_{1'}$), 122.51 (C$_{10}$), 123.21 (C$_6$), 125.30 (C$_5$), 125.34 (C$_{6''}$), 127.73 (C$_{2',6'}$), 127.87 (C$_{5''}$), 129.33 (C$_{7''}$), 130.70 (C$_{3''}$) 135.49 (C$_7$), 136.69 (C$_{4''}$), 136.96 (C$_3$), 150.71 (C$_{4'}$), 152.84 (C$_{9''}$), 155.87 (C$_9$), 159.33 (C$_2$), 160.09 (C=O lactone), 174.36 (C=O pyron), 192.87 (C=O ketone).

2.2.4. Synthesis of 3-chloro-2-[4-(dimethyl amino)phenyl]-4H-1-benzopyran-4-one (A_8) [17]

10 ml of thionyl chloride SOCl$_2$ were added to (0.00142 mol, 0.4 g) of flavonoid (A_2), and the mixture were heated at 50–60 $\overset{\circ}{C}$ for 4 h. The remaining thionyl chloride were evaporated, the precipitate were washed with water and ethanol, then recrystallized with absolute ethanol, resulting in a violet precipitate. Its purity were confirmed by TLC using the mixture (ether:hexane 2:3).

2.2.4.1. A_8. 3-Chloro-2-[4-(dimethylamino)phenyl]-4H-1-benzopyran-4-one. Dark purple solid; Yield: 94%; mp 156–158 $\overset{\circ}{C}$; $R_f = 0.15$ (ether:-hexane 2:3); IR (KBr, cm^{-1}) υ: 1700 (C=O pyrone), 1430–1558 (C=C), 1020.85 (C–O), 755 (C–Cl); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.01 (s, 6H, 2 CH$_3$), 6.84–8.13 (m, 8H, aromatic ring); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 40.62 (CH$_3$, 2CH$_3$), 111.29 (C$_{3',5'}$), 115.90 (C$_8$), 119.67 (C$_{1'}$), 124.04 (C$_{10}$), 123.33 (C$_6$), 125.92 (C$_5$), 127.59 (C$_{2',6'}$), 134.93 (C$_7$), 102.13 (C$_3$), 151.03 (C$_{4'}$), 155.72 (C$_9$), 167.90 (C$_2$), 178.14 (C=O pyron).

2.2.5. Synthesis of new ester derivatives of flavonoid (A_2)

2.2.5.1. Synthesis of 2-[4-(dimethylamino) phenyl]-4-oxo-4H-1-benzopyran-3-yl chloro acetate (A_9) [23,24]. (0.0035 mol, 1 g) of the flavonoid compound (A_2) were Dissolved in 50 ml of dry acetone, an excess of potassium carbonate were added and stirred well for 5 min, then (0.0035 mol, 0.4 g) of Chloroacetyl chloride dissolved in 10 mL of acetone were added to it dropwise with continuous stirring for 48 h at room temperature. The resulting mixture were poured into a beaker containing crushed ice, the formed precipitate were filtered and washed withwater and ethanol, then recrystallized with absolute ethanol, resulting in a yellow precipitate. Its purity were confirmed by TLC using the mixture (ether:hexane 2:3).

2.2.5.2. A_9. 2-[4-(Dimethylamino)phenyl]-4-oxo-4H-1-benzopyran-3-yl chloroacetate. Yellow solid; Yield: 75%; mp 155–157 $\overset{\circ}{C}$; $R_f = 0.29$ (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 2888 (C–H$_{aliphatic}$), 1778 (C=O ester), 1591 (C=O pyrone), 1478–1517 (C=C), 1118–1288 (C–O), 757 (C–Cl); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.02 (s, 6H, 2 CH$_3$), 4.27 (s, 2H, CH$_2$), 6.85–8.11 (m, 8H, aromatic ring); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 40.13 (CH$_3$, 2CH$_3$), 42.45 (CH$_2$), 112.04 (C$_{3',5'}$), 115.22 (C$_8$), 118.91 (C$_{1'}$), 121.84 (C$_{10}$), 123.12 (C$_6$), 125.43 (C$_5$), 129.42 (C$_{2',6'}$), 133.54 (C$_3$), 134.82 (C$_7$), 151.53 (C$_{4'}$), 152.71 (C$_2$), 155.27 (C$_9$), 165.64 (C=O ester), 170.47 (C=O pyon).

2.2.5.3. Synthesis of flavonoids derivatives (A_{10}–A_{13}) [23,24]. (0.001066 mol, 0.3 g) of the flavonoid compound (A_2) were dissolve in 20 ml of

DMF, an excess of potassium carbonate were added to it and stirred well for 5 min, then (Maleic anhydride or phthalic anhydride or phthalimide or cinnamoyl chloride (0.001066 mol) dissolved in 5 ml of DMF were added to it drop by drop and stirred under reflux for 24 h. The mixture were poured into a beaker containing crushed ice and the medium were neuterlised with diluted hydrochloric acid. The flavonoids were extracted from the aqueous phase using dichloromethane (3 × 30 ml). The organic extracts were collected, dried using anhydrous magnesium sulfate and the solvent were evaporated. The precipitate were recrystallized with absolute ethanol, resulting in a yellow precipitate. Its purity were confirmed by TLC using the mixture (ether:hexane 2:3).

2.2.5.4. A_{10}. (2E)-4-({2-[4-(Dimethylamino)phenyl]-4-oxo-4H-1-benzo-pyran-3-yl}oxy)-4-oxobut-2-enoic acid. Dark yellow solid; Yield: 87.5%; mp 129–131 $\overset{\circ}{C}$; $R_f = 0.18$ (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 3415 (OH), 2869–2907 (C–H$_{aliphatic}$), 1723 (C=O ester), 1682 (C=O acid), 1605 (C=O pyrone), 1484–1553 (C=C), 1173–1276 (C–O); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.02 (s, 6H, 2 CH$_3$), 6.47 (d, H$_β$, CH), 6.65(d, H$_α$, CH), 6.81–8.04 (m, 8H, aromatic ring), 13.14 (s, H, COOH); ^{13}C-NMR.

(100 MHz, DMSO-d$_6$, δ ppm): 40.46 (CH$_3$, 2 CH$_3$), 111.72 (C$_{3',5'}$), 116.70 (C$_8$), 119.39 (C$_{1'}$), 121.76 (C$_{10}$), 123.42 (C$_6$), 125.60 (C$_5$), 128.22 (C$_{2',6'}$), 133.28 (C$_3$), 133.96 (CH), 134.01 (CH), 134.17 (C$_7$), 147.36 (C$_{4'}$), 153.64 (C$_2$), 154.62 (C$_9$), 157.13 (C=O ester), 167.10 (C=O acid), 174.49 (C=O pyron).

2.2.5.5. A_{11}. 2-[({2-[4-(Dimethylamino)phenyl]-4-oxo-4H-1-benzopyran-3-yl}oxy) carbonyl]benzoic acid. Yellow solid; Yield: 77%; mp 146–148 $\overset{\circ}{C}$; $R_f = 0.21$ (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 3415 (OH), 2910 (C–H$_{aliphatic}$), 1724 (C=O ester), 1684 (C=O acid), 1606 (C=O pyrone), 1435–1536 (C=C), 1135–1232 (C–O); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.02 (s, 6H, 2 CH$_3$), 6.81–8.27 (m, 12H, aromatic ring), 13.11 (s, H, COOH); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 40.53 (CH$_3$, 2 CH$_3$), 111.68 (C$_{3',5'}$), 116.80 (C$_8$), 119.41 (C$_{1'}$), 121.88 (C$_{10}$), 123.45 (C$_6$), 125.29 (C$_{3''}$), 125.66 (C$_5$), 128.22 (C$_{2',6'}$), 128.49 (C$_{6''}$), 132.77 (C$_{1'',2''}$), 133.31 (C$_3$), 133.97 (C$_{4'',5''}$), 134.08 (C$_7$), 147.34 (C$_{4'}$), 153.63 (C$_2$), 153.48 (C=O ester), 154.68 (C$_9$), 168.18 (C=O acid), 174.37 (C=O pyron).

2.2.5.6. A_{12}. 2-[4-(Dimethylamino)phenyl]-4-oxo-4H-1-benzopyran-3-yl 2-carbamoyl benzoate. Yellow solid; Yield: 78%; mp 138–140 $\overset{\circ}{C}$; $R_f = 0.24$ (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 3474 (NH$_2$), 2856 (C–H$_{aliphatic}$), 1723 (C=O ester), 1684 (C=O amid), 1605 (C=O pyrone), 1435–1535 (C=C), 1134–1276 (C–O); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.02 (s, 6H, 2 CH$_3$), 6.82–8.19 (m, 12H, aromatic ring), 7.91 (s, 2H, NH$_2$); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 40.44 (CH$_3$, 2 CH$_3$), 111.71 (C$_{3',5'}$), 116.72 (C$_8$), 119.40 (C$_{1'}$), 121.87 (C$_{10}$), 123.44 (C$_6$), 124.08 (C$_{6''}$), 125.59 (C$_5$), 128.21 (C$_{2',6'}$), 128.30 (C$_{3''}$), 130.16 (C$_{2''}$), 131.61 (C$_{1''}$), 132.45 (C$_{4''}$), 133.28 (C$_3$), 134.11 (C$_{5''}$), 134.12 (C$_7$), 147.38 (C$_{4'}$), 153.65 (C$_2$), 154.67 (C$_9$), 153.51 (C=O ester), 165.78 (C=O amid), 174.46 (C=O pyron).

2.2.5.7. A_{13}. 2-[4-(Dimethylamino)phenyl-4-oxo-4H-1-benzopyran-3-yl (2E)-3-phenylprop-2-enoate. Yellow solid; Yield: 83.7%; mp 131–133 $\overset{\circ}{C}$; $R_f = 0.26$ (ether:hexane 2:3); IR (KBr, cm^{-1}) υ: 2983–3026 (C–H$_{aliphatic}$), 1723 (C=O ester), 1606 (C=O pyrone), 1448–1535 (C=C), 1158–1281 (C–O); ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.02 (s, 6H, 2 CH$_3$), 6.44 (d, H, H$_α$), 7.63 (d, H, H$_β$), 6.81–8.05 (m, 13H, aromatic ring); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 40.45 (CH$_3$, 2 CH$_3$), 111.72 (C$_{3',5'}$), 115.31 (C$_α$), 116.73 (C$_8$), 119.39 (C$_{1'}$), 121.76 (C$_{10}$), 123.41 (C$_6$), 125.58 (C$_5$), 127.79 (C$_{4''}$), 128.13 (C$_{2'',6''}$), 128.21 (C$_{2',6'}$), 128.77 (C$_{3'',5''}$), 133.30 (C$_3$), 134.21. (C$_7$), 134.90 (C$_{1''}$), 147.35 (C$_{4'}$), 147.83 (C$_β$), 153.66 (C$_2$), 154.62 (C$_9$), 157.20 (C=O ester), 174.54 (C=O pyron).

2.3. Study of antifungal activity [26]

The anti-fungal activity of Six flavonoids were studied by Petri dish method against three types of fungi: *Aspergillus flavus, Acremonium*
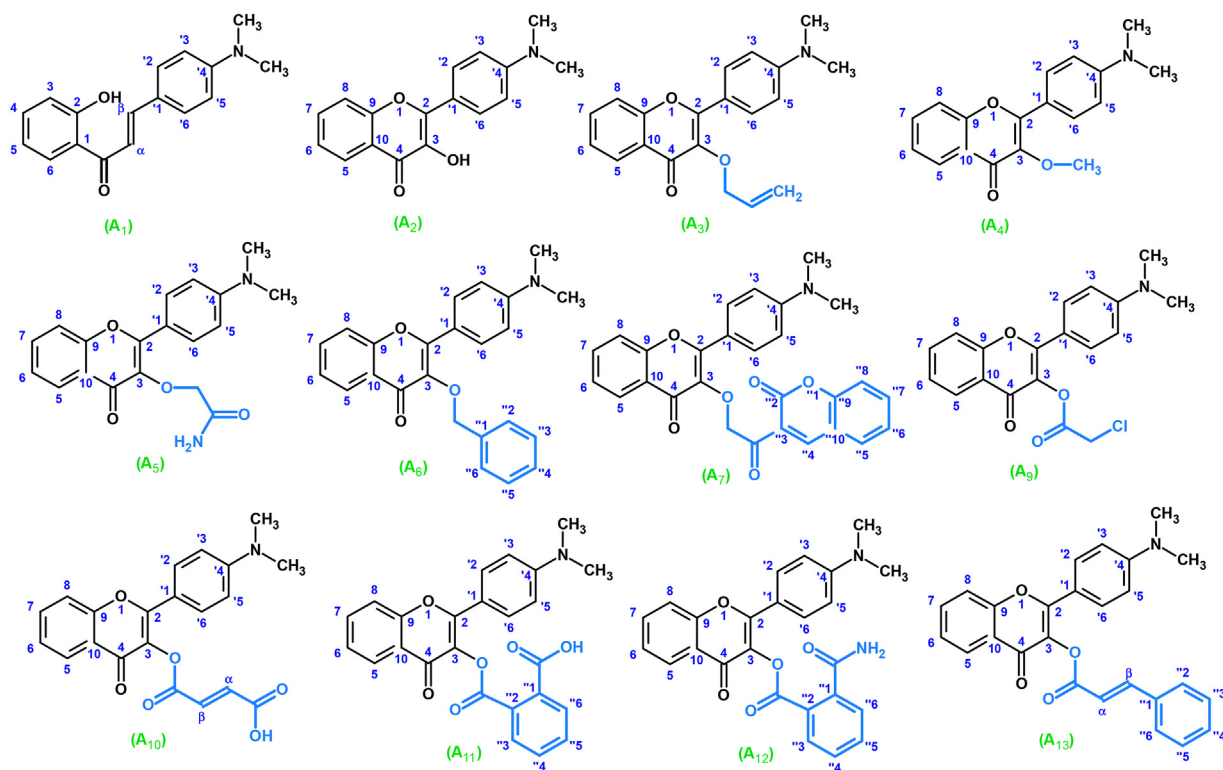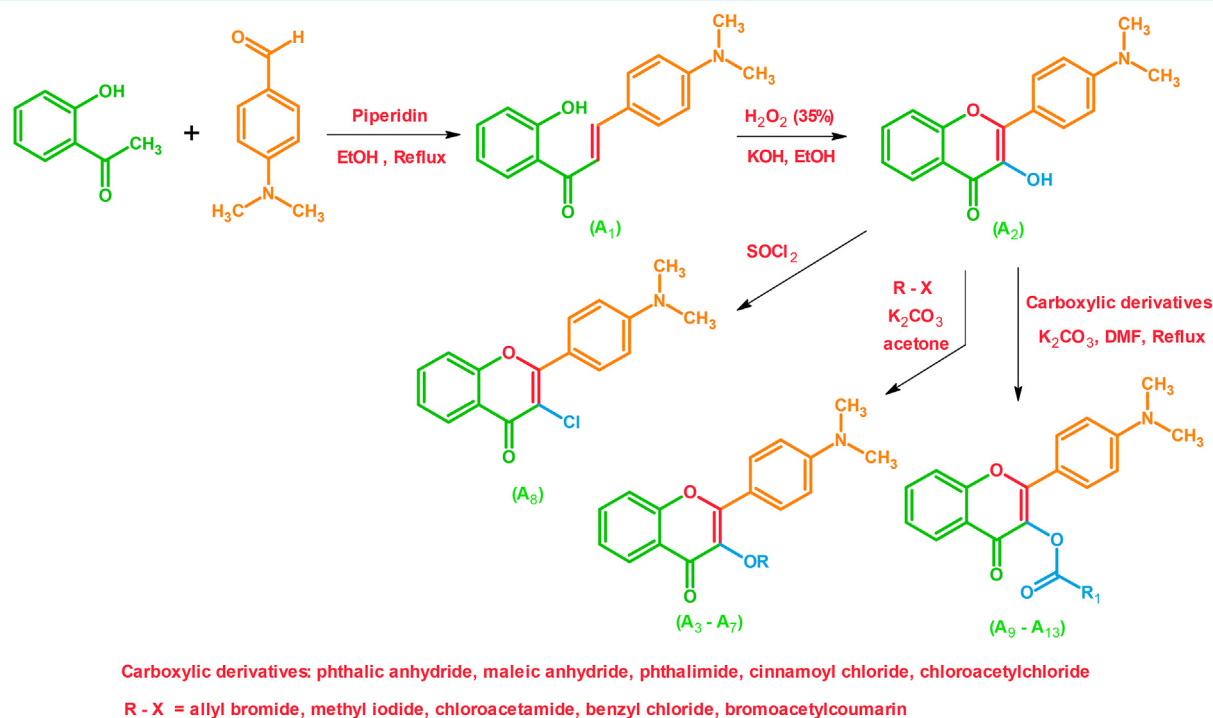
Figure 2. Reaction scheme for the synthesis of alkyl and ester derivatives of flavonoids and their chemical structures.

strictum, and *Penicillium expansum* This is according to Suarez-Jimenez et al. [26]. With some modifications to suit the research, in the Microbiology Laboratory under the supervision of Prof. Dr. Maysa Yazigi – Botany Department – Faculty of Science – Tishreen University. Different amounts of the compounds were dissolved in DMSO dimethyl sulfoxide before mixing with the agar nutrient medium (100 ml in P.D.A) whose temperature were 45 °C to obtain the two concentrations (0.5 mg/ml,

0.25 mg/ml). The medium were poured into Petri dishes with a diameter of 9 cm and left to cool and solidify. A 5 mm disc were placed from the tips of the active fungi colony at the age of 7 days, each fungus separately, and placed on both ends of the Petri dish and at the two concentrations studied. The dishes were incubated at 25 ± 1 °C for 7 days, and control dishes were prepared in each experiment by culturing the mushrooms on P.D. A medium free of the chemical compound. Four replicates were

Table 1. Shows the physical properties of the new flavonoids.

Compound	Yield %	Molecular formula	Color	m.w (g/mol)	m.p °C	R_f
A_1	80.9	$C_{17}H_{17}O_2N$	Bright pink	267.3	178–180	0.47[a]
A_2	82	$C_{17}H_{15}O_3N$	Bright yellow	281.3	190–191	0.36[a]
A_3	78.9	$C_{20}H_{19}O_3N$	Yellow	321.3	76–78	0.33[a]
A_4	82.8	$C_{18}H_{17}O_3N$	Yellow	295.3	123–125	0.22[a]
A_5	66.7	$C_{19}H_{18}O_4N_2$	Yellow	339.3	187–188	0.37[b]
A_6	76.9	$C_{24}H_{21}O_3N$	Yellow	371.3	98–100	0.36[a]
A_7	76	$C_{28}H_{21}O_6N$	Brown	467.3	278–280	0.46[b]
A_8	94	$C_{17}H_{14}O_2NCl$	Dark purple	299.75	156–158	0.15[a]
A_9	75	$C_{19}H_{16}O_4NCl$	Yellow	357.78	155–157	0.19[a]
A_{10}	87.5	$C_{21}H_{17}O_6N$	Dark Yellow	379.36	129–131	0.18[a]
A_{11}	77	$C_{25}H_{19}O_6N$	Yellow	429.42	146–148	0.21[a]
A_{12}	78	$C_{25}H_{20}O_5N_2$	Yellow	428.43	138–140	0.24[a]
A_{13}	83.7	$C_{26}H_{21}O_4N$	Yellow	411.44	131–133	0.26[a]

[a] Ether:hexane 2:3.
[b] Acetone: hexane 2:3.

performed for each compound and each concentration separately and for the control dishes as well, after which the average diameters of colony growth were calculated and then the percentage of inhibition were calculated from the following relationship:

$$Inhibition\% = (dc - dt) / dc \times 100$$

where dc: is the average diameter of the control colonies, dt: is the average diameter of the treated colonies.

3. Results and discussion

3.1. Chemistry

In this research, the chalcone compound A_1 was synthesized via new synthesise route with a high yield (80.9%). The cyclooxidation process were performed on A_1 and we obtained the flavonoid compound A_2 with a yield of 82%. By different reactions on compound A_2, we obtained ten new flavonoid derivatives with different functional groups and yields ranging between (66.7–94%). The alkylation, esterification and chlorination reactions were carried out on the –OH enolic group, of which synthesis reactions were very few.

The colors of the resulting derivatives ranged between yellow and brown and their melting points varied between (76–78 °C) for flavonoid A_3 and (278–280 °C) for A_7 flavonoids. The low melting point of compound A_3 is due to the presence of an unsaturated carbon chain that lowers its melting points. While compound A_7 is characterized by a large molecular weight and the presence of ketone groups and a lactone ring. As for the two compounds A_{10} and A_{13}, they are close in chemical structure and contain an unsaturated esteric group, their melting points are close. Compounds A_{11} and A_{12} are similar in chemical structure and melting points, where the melting point of compound A_{11}, which has a carboxylic group, is slightly higher than the melting point of compound A_{12}, which has an amide group. The lower melting points of the flavonoid derivatives (A_3–A_6, A_8–A_{13}) compared to compound A_2 is due to the presence of alkyl groups and ester groups, while the basic compound A_2 contains an –OH enolic group that increases its melting point.

The chlorination reaction using Thionyl chloride gave a high yield of 94%. It is generally known that the reaction of the alcoholic group with Thionyl chloride is very fast and takes place in a short time. Compound A_2 was successfully reacted with bromoacetyl coumarin, despite the presence of a steric obstruction, as it took a long time to finish the

Table 2. Percentage inhibition of fungal strains (*Acremonium strictum, Aspergillus flavus, Penicillium expansum*) in the presence of different concentrations of synthetic flavonoids (A_2, A_5, A_7, A_8, A_9. A_{12}).

Fungi Compound	*Acremonium strictum*		*Aspergillus flavus*		*Penicillium expansum*	
	250 ppm (0.25 mg/ml)	500 ppm (0.5 mg/ml)	250 ppm (0.25 mg/ml)	500 ppm (0.5 mg/ml)	250 ppm (0.25 mg/ml)	500 ppm (0.5 mg/ml)
A_2	81.33	100	41.02	65.64	60.87	100
A_5	70	100	6.41	46.15	42.15	100
A_7	52.22	53	17.94	17.94	22.74	50.98
A_8	46.66	58.88	4.1	37.17	48.23	91.37
A_9	76.88	100	15.38	60.51	19.60	58.03
A_{12}	73.33	100	17.94	38.46	26.66	71.76

reaction, and the yield was 76%. Figure 2 shows a general scheme for the synthesis of A_3–A_{13} flavonoid derivatives. Table 1 includes the physical properties (melting point, sample color, yield, Molecular formula, molecular weight, R_f) of the new flavonoids (see Figure 2).

Infrared spectroscopy of the synthesized alkyl derivatives (A_3, A_4, A_5, A_6) revealed the disappearance of the absorption band characteristic of the (–OH) group of the basic flavonoid compound and the appearance of new bands belonging to the methylene (–CH_2) group, the (C=C) ethylene group and the (-NH_2) amide which confirms the chemical structure of the prepared compounds. Spectroscopic analysis also revealed new absorption bands for compound (A_7) belonging to the (C=O) and (C=C) ethylene groups in the lactone ring. Spectroscopic analysis of compound (A_8) showed the disappearance of the absorption band characteristic of (–OH) and the appearance of a new absorption band belonging to the group (C–Cl). The spectroscopic analysis of the compounds (A_9, A_{10}, A_{11}, A_{12}, A_{13}) showed the disappearance of the absorption band belonging to the (–OH) group and the emergence of.

new absorption bands belonging to the esteric, amide and acidic (C=O) groups, which confirms the chemical structure of the new compounds, in addition to several other bands in the fields of Different spectra are shared by all spectra to some extent.

The spectroscopic analysis by (^{1}H-NMR) spectroscopy showed multiple chemical shifts of different protons for all the prepared compounds, the most characteristic of which are the chemical shifts of the protons of the (–CH_2) group and (–NH_2) group in the amide group, as well as the chemical shifts of the allyl group protons, the benzyl group protons and the protons of the group (C=C) ethylene, which confirms the chemical structure of the prepared flavonoids. As for the (^{13}C-NMR) spectra of the prepared compounds, they showed multiple peaks, the most distinct of which are those belonging to the carbon of the methylene group and C=C group in the unsaturated alpha-beta ester groups, and the allyl group carbons, as well as the carbon of the carbonyl group in both the amide group, the ester group and the lactone ring. In addition to other peaks Common to all prepared compounds.

3.1.1. Antifungal activity

The antifungal activity were tested on six flavonoids (A_2, A_5, A_7, A_8, A_9, A_{12}) against three strains of fungi: *Acremonium strictum*, *Aspergillus flavus*, and *Penicillium expansum*. The results shown in Table 2 showed that the compounds (A_2, A_5, A_9, A_{12}) had a high degree of inhibition for *Acremonium strictum*, where the percentage of inhibition was 100% at 500 ppm. And the least inhibited were (A_7, A_8), where the percentage of inhibiting them was (53%, 58.88%), respectively. While the effectiveness of compound A_2 was higher at the concentration of 250 ppm, where the percentage of inhibition was 81.33%, and the lowest was the effectiveness of compound A8, where the percentage of inhibition was 46.66%.

The two compounds (A_2, A_5) showed a higher activity on the fungus *Penicillium expansum* at the concentration of 500 ppm, where the percentage of its inhibition was 100%, while the least effective was the
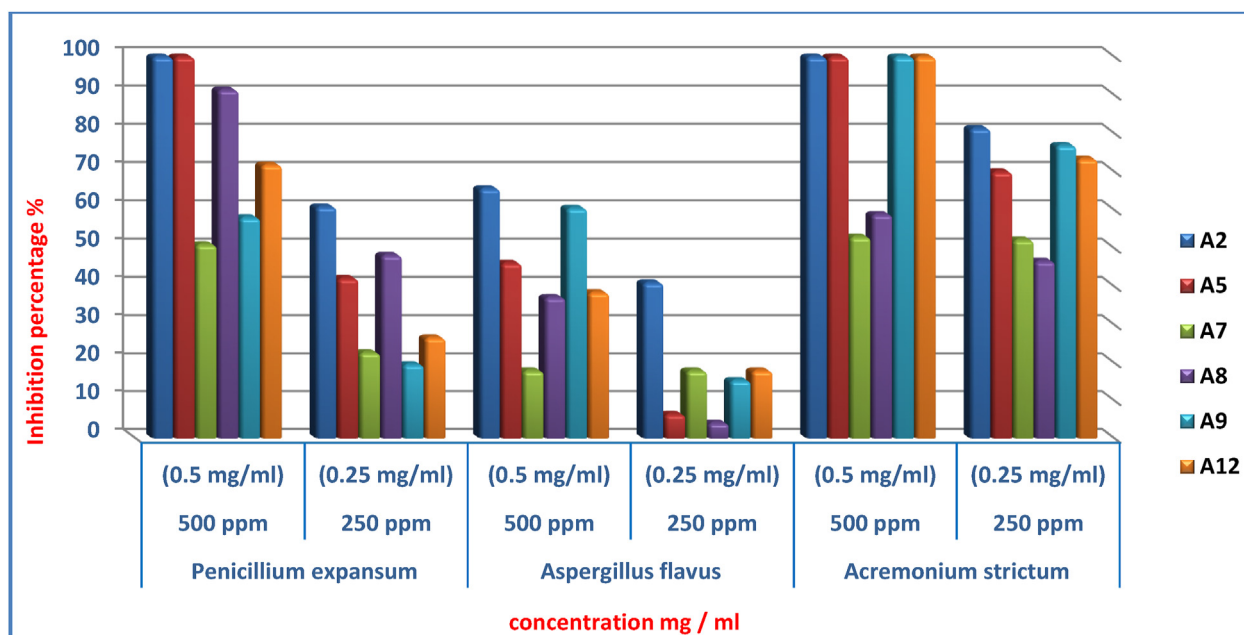
Figure 3. Results of the biological activity of flavonoids (A_2, A_5, A_7, A_8, A_9. A_{12}) against fungal strains (*Acremonium strictum, Aspergillus flavus, Penicillium expansum*).

compound A_7, where the percentage of inhibition was 50.98%. As for the concentration of 250 ppm, the effectiveness of compound A_2 was the highest, reaching 60.87%, while the lowest was the effectiveness of compound A_9, where the percentage of inhibition was 19.60%.

All studied compounds showed medium activity on *Aspergillus flavus*, and the most inhibiting compound A_2 at a concentration of 500 ppm reached 65.64%, while the least effective of compound A8 at a concentration of 250 ppm was 4.1%. The high activity of the compounds (A_2, A_5, A_{12}) is due to the presence of functional groups (–OH, O=C–NH$_2$ aliphatic and aromatic), as it was found that the compound containing the aliphatic amide group was more effective on *Penicillium expansum* than the compound containing the aromatic amide group. Figure 3 shows the results of biological activity of flavonoids (A_2, A_5, A_7, A_8, A_9, A_{12}) against fungal strains (*Acremonium strictum, Aspergillus flavus, Penicillium expansum)*.

4. Conclusions

Ten new flavonoid derivatives were synthesized in an easy way and with high yield (66.7–94%), including four alkyl derivatives, five ester derivatives and a new chlorine derivative. All reactions were carried out on the –OH enolic group at the C_3 position of the Pyran ring. The course of the reactions was monitored by TLC thin layer chromatography. All compounds were purified by recrystallization and chromatographically separated using Preparative-TLC. The new compounds showed good thermal stability up to 280 C̊. The structure of the prepared compounds was confirmed by spectroscopic methods (FT-IR, ^{13}C-NMR, ^{1}H-NMR). The synthetic compounds showed moderate to good antifungal efficacy. Studying the structural relationship with biological activity on a wide range of fungi and comparing it with very important standard drugs that need follow-up later. The study is important for the synthesis of new flavonoid derivatives and their proposal as a broad-spectrum antifungal agent in the field of medical and pharmaceutical sciences.

Declarations

Author contribution statement

Hadi Aqel Khdera: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Sawsan Saad, Farouk Kandil: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Aoula Moustapha: Analyzed and interpreted the data.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e12062.

References

[1] H. Cheong, S.Y. Ryu, M.H. Oak, S.H. Cheon, G.S. Yoo, Studies of structure activity relationship of flavonoids for the anti-allergic actions, Arch Pharm. Res. 21 (1998) 478–480.

[2] V. García-Mediavilla, I. Crespo, P.S. Collado, A. Esteller, S. Sánchez-Campos, The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells, Eur. J. Pharmacol. 557 (2007) 221–229.

[3] T.P. Cushnie, A.J. Lamb, Antimicrobial activity of flavonoids, Int. J. Antimicrob. Agents 26 (2005) 343–356.

[4] A.B. Hendrich, Flavonoid-membrane interactions: possible consequences for biological effects of some polyphenolic compounds 1, Acta Pharmacol. Sin. 27 (2006) 27–40.

[5] N. Srivastava, R. Bezwada, Flavonoids: the Health Boosters. White Paper, Indofine Chemical Company, Hillsborough, NJ, 2015.

[6] M. Wink, Phytochemical diversity of secondary metabolites, in: Encyclopedia of Plant and Crop Science, 2004, pp. 915–919.

[7] S. Anand, Various approaches for secondary metabolite production through plant tissue culture, Pharmacia 1 (2010) 1–7.

[8] S.P. Fernandez, C. Wereowski, L.M. Loscalzo, R.E. Granger, G.A.R. Johnston, A.C. Paladini, M. Marder, Central nervous system depressant action of flavonoid glycosides, Eur. J. Pharmacol. 539 (3) (2006) 168–176.

[9] K.E. Heim, A.R. Tagliaferro, D.J. Bobliya, Flavonoids antioxidants: Chemistry, metabolism and structure-activity relationships, J. Nutr. Biochem. 13 (10) (2002) 572–584.

[10] P.C.H. Hollman, M.B. Katan, Dietary flavonoids: intake, health effects and bioavailability, Food Chem. Toxicol. 37 (1999) 937–942.

[11] T.P.T. Cushnie, A.J. Lamb, Antimicrobial activity of flavonoids, Int. J. Antimicrob. Agents 26 (5) (2005) 343–356.

[12] S.D. Sarker, L. Nahar, Chemistry for Pharmacy Students: General, Organic and Natural Product Chemistry, John Wiley & Sons, England, 2007.

[13] J.S. Choi, H.Y. Chung, S.S. Kang, M.J. Jung, J.W. Kim, et al., The structure–activity relationship of flavonoids as scavengers of peroxynitrite, Ptr 16 (2002) 232–235.

[14] P. Cos, L. Ying, M. Calomme, J.P. Hu, K. Cimanga, et al., Structure-activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers, J. Nat. Prod. 61 (1998) 71–76.

[15] J.G. Yang, B.G. Liu, G.Z. Liang, Z.X. Ning, Structure-activity relationship of flavonoids active against lard oil oxidation based on quantum chemical analysis, Molecules 14 (2009) 46–52.

[16] O. Farkas, J. Jakus, K. Héberger, Quantitative structure–antioxidant activity relationships of flavonoid compounds, Molecules 9 (2004) 1079–1088.

[17] b. Jayashree, N.F. anjum, Y. nayak, V. kumar, Synthesis of substituted 3-hydroxy flavones for antioxidant and antimicrobial activity, Pharmacology 3 (2008) 586–595.

[18] P. Rajaram, Z. Jiang, G. Chen, A. Rivera, A. Phasakda, Q. Zhang, S.l. Zheng, G. Wang, Q.H. Chen, Nitrogen-containing derivatives of O-tetramethylquercetin: synthesis and biological profiles in prostate cancer cell models, Bioorg. Chem. (2019). S0045-2068(18).30979-9.

[19] F. Sonmeza, B.Z. Kurtb, I. Gazioglu, Design, synthesis and docking study of novel coumarin ligands as potential selective acetylcholinesterase inhibitors, J. Enzym. Inhib. Med. Chem. 32 (1) (2017) 285–297.

[20] Vogel' S Textbook of Practical Organic Chemistry by Brian S. Furniss, Antony J. Hannaford, Peter W. G. Smith & Austin R. Tatchell; fifth ed.; page: 1065-1066.

[21] v. c. patil, Synthesis and in vitro antiplaque activity of chalcone, flavonol and flavanol derivatives, ijpsr 3 (12) (2012) 5006–5014.

[22] P. Venkatesan, S. Sumathi, Piperidine mediated synthesis of N-heterocyclic chalcones and their antibacterial activity, J. Heterocycl. Chem. 47 (2010) 81.

[23] R. Liu, H. Zhang, M. Yuan, Synthesis and biological evaluation of apigenin derivatives as antibacterial and antiproliferative agents, Molecules 18 (2013) 11496–11511.

[24] J. Kozłowska, B. Potaniec, B.Z. arowska, M. Anioł, Synthesis and biological activity of novel O-alkyl derivatives of naringenin and their oximes, Molecules 22 (1485) (2017) 1–14.

[25] X. Han, Y.L. Yu, D. Ma, Z.Y. Zhang, X.H. Liu, Synthesis, telomerase inhibitory and anticancer activity of new 2-phenyl-4Hchromone derivatives containing 1,3,4-oxadiazole moiety, J. Enzym. Inhib. Med. Chem. 36 (1) (2021) 345–361.

[26] G. Suárez-Jiménez, M. Cortez-Rocha, C. Rosas-Burgos, A. Burgos-Hernández, M. Plascencia-Jatomea, F. Cinco-Moroyoqui, Antifungal activity of plant methanolic extracts against Fusarium verticillioides (Sacc.) nirenb. And Fumonisin B1 production 25, 2007, pp. p134–142. Número 2.