Microwave-Assisted Synthesis of Novel 2H-Chromene Derivatives Bearing Phenylthiazolidinones and Their Biological Activity Assessment

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Abstract: 6-Hydroxy-2-oxo-2H-chromene-4-carbaldehyde (2), 6-chloro-2-oxo-2H-chromene-4-carbaldehyde (3) and 6-hydrazinyl-4-methyl-2H-chromen-2-one (5) were prepared as single-pharmacophore motif key intermediates. Compounds 2, 3 and 5 were incorporated in a series of multicomponent reactions (MCRs), under microwave assistance as well as conventional chemical synthesis processes, to afford a series of three and/or four-pharmacophoric-motif conjugates 8a,b, 11, 13, 16, 17, 19 and 20 in good yields. The newly synthesized compounds were characterized by IR, NMR, $^{13}$C-NMR, MS and elemental analyses. Finally the synthesized compounds have been screened for their biological activity whereupon they exhibited remarkable antimicrobial activity on different classes of bacteria and the fungus.

Keywords: multicomponent reactions (MCRs); green synthesis; microwave irradiation; 2-H-chromene; thiazolidenone; biological activity
1. Introduction

Green chemistry is a new and rapidly emerging field of chemistry. Its growing importance is in utilization of the maximum possible resources in such a way that, there is negligible or minimum production of chemical waste. It is one of the best alternatives for traditional chemical synthesis processes. By applying the green synthesis method, we can not only avoid the use of hazardous, toxic solvents, but also the formation of by-products is avoided. Thus, they are perfectly amenable to automation for combinatorial synthesis [1]. In 1986, Gedye and Giguere reported for the first time that organic reactions could be conducted very rapidly under microwave irradiation.

Coumarins are a group of compounds that play important roles as food constituents, antioxidants, stabilizers and immunomodulatory substances, as fluorescent markers for use in analyses, in stains, and in clinical use for their [2,3] diuretic [4], anti-coagulant, anti-cancer [2], anti-HIV [5], antitumor [6], anti-inflammatory [7], anti-Alzheimer’s [8], anti-leukemic [9,10], antibacterial [11], anti-malarial activities [12], emetic [13], and anti-anaphylactic activities [14]. Moreover, they can also be employed as cosmetics and pigments [13] and utilized as potential biodegradable agrochemicals [15]. Some of these compounds have been already prepared in the presence of piperidine [16], diammonium hydrogen phosphate (DAHP), S-proline [17], K2CO3 under microwave irradiation [18], H6P2W18O62·18H2O [19], MgO [20] and tetrabutylammonium bromide (TBAB) [21]. Each method has its own advantages and disadvantages.

Finally, as third motif in this preface, 4-thiazolidinones are among the most common and important groups among the small ring heterocyclic compounds. There are many references reported in the literature highlighting their chemistry and uses. 4-Thiazolidinones exhibit various biological activities such as analgesic, antibacterial, antifungal, anti-oxidant, anti-inflammatory, anticonvulsant, anticancer, anti-HIV, anti-tubercular and anthelmintic properties [22–26].

In connection with our previous work [27–31] on the synthesis of heterocyclic compounds, in the present study we describe the preparation of some new phenylthiazolidinone derivatives and heterocyclic bases from 6-hydroxy-4-methyl-2H-chromen-2-one.

2. Results and Discussion

Chemistry

The synthetic strategies adopted for the synthesis of the intermediate and target compounds are depicted in Schemes 1–8. A one-pot, microwave assisted reaction condition was applied as well as conventional synthesis, by using 6-hydroxy-4-methyl-2H-chromen-2-one (1) in DMF containing 3–4 drops of glacial AcOH and selenium dioxide to give compound (2) (Scheme 1, Table 1). The latter compound was easily chlorinated via treatment with phosphoryl chloride in anhydrous EtOH yielding 6-chloro-2-oxo-2H-chromene-4-carbaldehyde (3) (Scheme 1, Table 1). The hydroxyl group in compound 1 was easily transformed into a chlorine to afford the 6-chlorocoumarin derivative 4, which, in turn was reacted with hydrazine hydrate in anhydrous EtOH to give 6-hydrazinyl-4-methyl-2H-chromen-2-one (5) (Scheme 1, Table 1). The IR spectrum of 2 showed the presence of absorption bands at 1695, 1710 and 3431 cm⁻¹ due to (2 C=Oastr) and (O—Hastr) functions respectively. Its 1H-NMR spectrum showed three singlet signals corresponding to the coumarin-C3, formyl and hydroxyl protons at δ 6.70,
10.45 and 12.01 ppm, respectively, and aromatic protons in the 7.70–7.98 ppm region, while the $^{13}$C-NMR spectrum of 2 showed the following signals: 91.1 (coumarin-C3), 119.8, 125.7, 126.6, 128.8, 133.7 and 150.1 (Ph), 162.4 (C=O), 192.5 (CHO). The mass spectrum of 2 displayed an intense ion peak at $m/z$ 190 (M$^+$, 51%) corresponding to C$_{10}$H$_6$O$_4$. The structure of 3 was established on the basis of its elemental analyses and spectral data, as well as its independent synthesis via oxidation reaction of chlorocoumarin derivative 4 with selenium dioxide which afforded a product identical in all aspects (mp and IR spectra) with that obtained previously from the reaction of 2 with phosphoryl chloride. The IR spectra of compounds 3 and 4 do not show any absorption bands corresponding to O–H groups while they show absorption bands at 1695–1710 cm$^{-1}$ due to C=O$_{ar}$ functions. The mass spectrum of 4 showed a molecular ion peak at $m/z$ 194 corresponding to its molecular formula (C$_{10}$H$_7$ClO$_2$). The mass spectrum of 5 showed a molecular ion peak at $m/z$ 190, corresponding to a molecular formula C$_{10}$H$_{10}$N$_2$O$_2$. Its $^1$H-NMR spectrum displayed new signals representing a hydrazide structure that appeared at 4.28 (–NH$\equiv$NH$_2$) and 9.21 (–NH$\equiv$NH$_2$) ppm (exchangeable with D$_2$O) integrating for two protons and one proton, respectively.

Scheme 1. Synthesis of 2H-chromen-2-one derivatives 2–5.

Method A: Microwave-assisted synthesis: AcOH, DMF as a solvent, 120 °C, 8–10 min; Method B: Conventional synthesis: AcOH, DMF as a solvent, reflux 4–7 h; Method C: Conventional synthesis: Anhydrous EtOH as a solvent, stirring at r.t. for 1 h, then refluxes for 2 h at 60 °C.

Spiro compounds represent an important class of naturally occurring molecules characterized by highly pronounced biological properties [32]. In this context, we explored the synthetic versatility of 6-hydroxy-4-methyl-2H-chromen-2-one (1) for the synthesis of spiro compounds containing the coumarin moiety. Thus, a one-pot, three-component, microwave assisted reaction condition was applied, as well as conventional synthesis, using cyclohexanone (or cyclopentanone), malononitrile (1:1 molar ratio) and 3–4 drops of glacial AcOH with DMF as a solvent and compound 1, to give the pyrano[2,3-$f$]chromene derivatives 8a,b, as indicated by elemental analysis and spectral data (Scheme 2, Table 1). Formation of the spiro compounds 8a,b was proceeded according to the proposed mechanistic pathway (Chart 1).
Table 1. Physical data of the synthesized compounds 2–16.

| Compounds | Mol. Formula | Mol. Wt. | Microwave | Conventional | Yield (%) | Melting Point (°C) |
|-----------|--------------|----------|-----------|--------------|-----------|-------------------|
|           |              |          | (min)     | (h)          | Microwave | Conventional      |
| 2         | C₁₀H₆O₄      | 190.15   | 8         | 5            | 97        | 85               | 217–219           |
| 3         | C₁₀H₇ClO₃    | 208.60   | -         | 1            | 96        | 75               | 145–147           |
| 4         | C₁₀H₇ClO₂    | 194.61   | -         | 1            | -         | 80               | 236–238           |
| 5         | C₁₀H₈N₂O₂    | 190.20   | 9         | 4            | 97        | 85               | 126–128           |
| 8a        | C₁₀H₈N₂O₃    | 308.12   | 9         | 4            | 98        | 78               | 167–169           |
| 8b        | C₁₀H₈N₂O₃    | 322.36   | 10        | 5            | 95        | 82               | 151–153           |
| 11        | C₁₀H₁₃N₂O₃S₂ | 427.45   | 9         | 7            | 96        | 89               | 251–253           |
| 13        | C₁₀H₁₆N₂O₅S | 352.41   | 8         | 4            | 98        | 80               | 278–280           |
| 16        | C₁₀H₁₂N₂O₅S₂ | 452.46   | 10        | 5            | 97        | 70               | 211–213           |
| 17        | C₁₀H₁₃N₂O₅S | 377.42   | 8         | 6            | 96        | 80               | 182–184           |
| 19        | C₁₂H₁₉N₅O₃S | 573.67   | 10        | 6            | 96        | 73               | 198–200           |
| 20        | C₁₂H₂₂N₄O₃S | 498.62   | 10        | 7            | 95        | 85               | 217–219           |

Scheme 2. Synthesis of spiro[cycloalkane-1,1'-pyrano[3,2-f]chromene]-2'-carbonitriles 8a,b.

Method A: Microwave-assisted synthesis: AcOH, DMF as a solvent, 120 °C, 8–10 min.

Method B: Conventional synthesis: AcOH, DMF as a solvent, reflux 4–6 h.

Chart 1. Mechanistic pathway of 3'-amino-10'-methyl-8'-oxo-8'H-spiro-[cyclohexane-1,1'-pyrano-[3,2-f]chromene]-2'-carbonitrile 8b.
The IR spectrum of product 8b, as an example, revealed absorption bands at 1695, 2217 and 3361 cm\(^{-1}\) characteristic for C=O, C≡N and NH\(_2\) groups, respectively. Its \(^1\)H-NMR spectrum showed multiplet signals for protons of the methylene groups centered around \(\delta\) 1.00–1.70 ppm in addition to the presence of two singlet signals, one at 2.43 ppm attributable to methyl protons and the other at 6.82 ppm, exchangeable with D\(_2\)O, attributed to the NH\(_2\) protons. The mass spectrum of compound 8b revealed a molecular ion peak at \(m/z\) 322 (M\(^+\), 57%), and a base peak was observed in the spectrum at \(m/z\) 176 (100%), which is compatible with its molecular formula C\(_{10}\)H\(_{18}\)N\(_2\)O\(_3\).

4-Formylcoumarin 2 reacted with 5-amino-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (9) and thioglycolic acid according to Method A and Method B, to give 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11) (Scheme 3, Table 1). Its IR spectrum displayed absorption bands at 1681–1708, 3156 and 3480 cm\(^{-1}\) due to three carbonyls, imino and hydroxyl groups, respectively. The mass spectrum of the product revealed a molecular ion peak at \(m/z\) 427 corresponding to its molecular formula C\(_{10}\)H\(_{13}\)N\(_2\)O\(_3\). Its \(^1\)H-NMR spectrum shows five singlet signals at \(\delta\) 2.43, 3.97, 6.46, 6.51, 6.61, 12.21 and 12.50 ppm due to the methyl, thiazolidinone-H5, thiophene-H5, coumarin-H3, thiazolidinone-H2, NH and OH groups, respectively, and multiplet signals in the \(\delta\) 7.03–7.51 ppm region due to the aromatic protons.

**Scheme 3.** Synthesis of 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11).

Similarly, 3-((4-methyl-2-oxo-2H-chromen-6-yl)amino)-2-phenylthiazolidin-4-one (13) was synthesized via reaction of 6-hydrazinyl-4-methyl-2H-chromen-2-one (5) with benzaldehyde (12) and thioglycolic acid (10) under the previous conditions (Scheme 4, Table 1). In the corresponding IR spectrum an absorption band due to the (C=O\(_{ar}\)) of the thiazolidinone was observed at 1708 cm\(^{-1}\), and another (N-H\(_{ar}\)) band was found at 3280 cm\(^{-1}\). The \(^1\)H-NMR spectrum of 13 showed singlet signals of the cyclized thiazolidinone at 3.95 and 5.91 ppm corresponding to -CH2- in the ring and the NH proton, respectively. In its \(^{13}\)C-NMR spectrum the up field resonances of the carbonyl carbon were observed at 170.4 beside that of the other coumarin carbonyl at 160.1 ppm.

The reaction of thiazolidinones 11 or 13 with dimethylformamide-dimethylacetal (DMF-DMA) (14) and hydroxylamine (15) as potential precursors for thiazolo[5,4-d]isoxazoles was also investigated. Thus, a one-pot, microwave assisted as well as conventional synthesis, by using 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11) or 3-(4-methyl-2-oxo-2H-chromen-6-ylamino)-2-phenylthiazolidin-4-one (13) with dimethylformamide-dimethylacetal (14) and hydroxylamine (15) in DMF as a solvent containing 3–4 drops of glacial AcOH yielded 5-(5-(6-hydroxy-2-oxo-2H-chromen-4-yl)thiazolo[5,4-d]isoxazol-6(5H)-yl)-2-methyl-
thieno[3,4-\textit{d}]pyrimidin-4(3\textit{H})-one (16) or 4-methyl-6-(5-phenylthiazolo[5,4-\textit{d}]isoxazol-6-ylamino)-2\textit{H}-chromen-2-one (17), respectively (Schemes 5 and 6, Table 1).

**Scheme 4.** Synthesis of 3-(4-methyl-2-oxo-2\textit{H}-chromen-6-ylamino)-2-phenylthiazolidin-4-one (13).

Method \textbf{A}: Microwave-assisted synthesis: Glacial AcOH, DMF as a solvent, 120 °C, 8–10 min.  
Method \textbf{B}: Conventional synthesis: Glacial AcOH, DMF as a solvent, reflux 4–7 h.

**Scheme 5.** Synthesis of thiazolo[5,4-\textit{d}]isoxazole derivative 16.

**Scheme 6.** Synthesis of 4-methyl-6(5-phenylthiazolo[5,4-\textit{d}]isoxazol-6-ylamino)-4\textit{a},8\textit{a}-dihydro-2\textit{H}-chromen-2-one (17).

The IR spectrum of 16 showed absorption bands at 3453, 3263, 1696 and 1681 cm\textsuperscript{-1} corresponding to O-H\textit{ar}, N-H\textit{ar} and two C=O\textit{ar} functions, respectively. Its $^1$H-NMR spectrum showed two sharp singlet signals at $\delta$ 4.95 and 8.14 and two broad singlet signals at 10.56 and 12.52 characteristic of thiazole-H2, isoxazole-H3, NH and OH protons, respectively, besides a multiplet in the $\delta$ 7.28–7.80 ppm region distinctive for aromatic protons. Its mass spectrum showed a molecular ion peak at $m/z$ 452, corresponding to its molecular formula (C\textsubscript{20}H\textsubscript{17}N\textsubscript{2}O\textsubscript{3}S\textsubscript{2}).

Moreover, the reactivity of the 4-thiazolidinone derivatives 11 and 13 a key intermediates for the synthesis of fused thiazolo[4,5-\textit{d}]pyrimidine derivatives has been investigated. Thus, a one-pot three-component condensation reaction of 5-(2-((6-hydroxy-2-oxo-2\textit{H}-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-\textit{d}]pyrimidin-4(3\textit{H})-one (11) or 3-(4-methyl-2-oxo-2\textit{H}-chromen-6-ylamino)-
3-phenylisothiazolidin-4-one (13) with benzaldehyde (12) and thiourea (18) proceeded smoothly in DMF containing 3-4 drops of glacial AcOH acid via microwave assisted as well as conventional synthesis to give 5-(2-((6-hydroxy-2-oxo-2H-chromen-4-yl)-7-phenyl-5-thioxo-5,6,7,7a-tetrahydrothiazolo[4,5-d]pyrimidin-3(2H)-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (19) or 6-(2,7-diphenyl-5-thioxo-5,6,7a-tetrahydrothiazolo[4,5-d]pyrimidin-3(2H)-ylamino)-4-methyl-4a,8a-dihydro-2H-chromen-2-one (20), respectively, (Schemes 7 and 8, Table 1).

**Scheme 7.** Synthesis of 7-phenyl-5-thiazo[4,5-d]pyrimidine derivative 9.

![](image1)

**Scheme 8.** Synthesis of 2,7-diphenyl-5-thioothiazolo[4,5-d]pyrimidine derivative 20.

![](image2)

Method A: Microwave-assisted synthesis: AcOH, DMF as a solvent, 120 °C, 8–10 min.
Method B: Conventional synthesis: AcOH, DMF as a solvent, reflux 4–7 h.

In the IR spectrum of the latter product absorption bands were observed at 1378, 1684 and 3250–3486 cm\(^\text{-1}\) corresponding to (C=S\(_\text{str}\)), (C=O\(_\text{str}\)) and (N-H\(_\text{str}\)) vibrations, respectively. The \(^1\)H-NMR spectrum of 19 indicated the presence of five singlet signals at \(\delta\) 2.41, 6.46, 6.51, 6.71, 12.20 and 12.52 ppm due the methyl, thiophene-H5, coumarin-H3, thiazole-H2, -NHCO- and OH groups, respectively, and two doublets centered around 3.41 and 4.21 ppm attributed to the –NH-C=S of the pyrimidine ring and pyrimidine-H6 respectively, and multiplet signals at 7.03–7.51 ppm due to aromatic protons. Its mass spectrum showed a molecular ion peak at \(m/z\) 573, corresponding to a molecular formula C\(_{27}\)H\(_{19}\)N\(_4\)O\(_4\)S\(_3\). The mass spectrum of 20 showed a molecular ion peak at \(m/z\) 498, corresponding to a molecular formula C\(_{27}\)H\(_{22}\)N\(_4\)O\(_3\)S\(_2\).

3. Experimental

3.1. General Information

6-Hydroxy-4-methyl-2H-chromen-2-one, dimethyformamide dimethylacetal (DMF-DMA), phosphoryl chloride, cyclohexanone, cyclopentanone, benzaldehyde, thioglycolic acid, glacial AcOH, thiourea and \(N,N\)-dimethylformamide (DMF) were purchased from Sigma Aldrich (Seelze, Germany).
Reaction progress was monitored by TLC on silica gel precoated F254 Merck plates (Merck, Dublin, Ireland). Developed plates were examined with ultraviolet lamps (254 nm). All melting points were determined on a Gallenkamp Electrothermal melting point apparatus and are uncorrected, IR spectra were recorded as potassium bromide pellets using a FTIR Vector 22 spectrophotometer (Bruker, Manasquan, NJ, USA). 1H-NMR and 13C-NMR spectra were recorded in DMSO-d6 solvent, respectively, on a WP spectrometer (300 MHz for 1H-NMR and 75 MHz for 13C-NMR) (Bruker, Marietta, GA, USA), and the chemical shifts are reported in δ units downfield from TMS used as an internal standard. Mass spectra were recorded on a MS-5988 spectrometer at 70 e.v. (Hewlett Packard, Palo Alto, CA, USA). Elemental analysis was carried out at the Microanalytical Center of Cairo University, Egypt.

3.2. Synthesis

3.2.1. General Procedure for Microwave-Assisted Synthesis of 6-Hydroxy-2-oxo-2H-chromene-4-carbaldehyde (2), Method A

An equimolar amount of 6-hydroxy-2-oxo-2H-chromene-4-carbaldehyde (1) (1 mmol) and selenium dioxide (1 mmol) was added in DMF (volume) along with 2-3 drops of glacial AcOH. This mixture was placed in a 100 mL round bottom flask and subjected to MW irradiation (800 W), at 120 °C temperature for 6 min. The completion of the reaction progress was monitored by using TLC (5% ethyl acetate-n-hexane). The product obtained was poured into crushed ice, filtered and washed with petroleum ether and ethyl acetate (1:4, 3 × 10 mL). The combined solvent extracts were concentrated in vacuo. The product was finally recrystallized from EtOH to afford product 2 in 97% yield.

3.2.2. General Procedure for Conventional Synthesis of 6-Hydroxy-2-oxo-2H-chromene-4-carbaldehyde (2), Method B

6-Hydroxy-2-oxo-2H-chromene-4-carbaldehyde (1, 1 mmol) was dissolved in boiling DMF containing 2-3 drops of glacial AcOH, and to this boiling solution was added portionwise, with stirring, powdered selenium dioxide (1 mmol). After complete addition, boiling and stirring were continued for 3 h. The completion of the reaction progress was monitored by using TLC (5% ethyl acetate-n-hexane). The product obtained was poured into crushed ice, filtered and washed with petroleum ether and ethyl acetate (1:4) (3 × 10 mL). The combined solvent extracts were concentrated in vacuo. The product was recrystallized from EtOH to obtain pure product 2 as a yellow solid, in 85% yield; mp 217–219 °C; IR (cm⁻¹): 1695, 1710 (2C=Oω), 3431 (O-Hω); 1H-NMR: 6.70 (s, 1H, coumarin-H3, 7.70–7.98 (m, 3H, Ar-H), 10.45 (s, 1H, CHO) and 12.01 (s, 1H, OH). 13C-NMR: 91.1 (coumarin-C3), 119.8, 125.7, 126.6, 128.8, 133.7 and 150.1 (benzene), 162.4 (C=O) and 192.5 (CHO). MS (m/z%) = 190 ([M]+, 51%). Anal. Calcd. for C10H6O4 (190.15): C, 63.16; H, 3.18; N 33.66%. Found: C, 63.01; H, 3.10; N, 33.46%.
3.2.3. Synthesis of 6-Chloro-2-oxo-2H-chromene-4-carbaldehyde (3)

Microwave-Assisted Synthesis, Method A

Compound 3 was prepared according to the general procedure 3.2.1 (Method A) described for compound 2 via the reaction of an equimolar amount of 6-chloro-4-methyl-2H-chromen-2-one (4, 1 mmol) and selenium dioxide (1 mmol) to obtain pure product 3 in 96% yield.

Conventional Synthesis, Method B

Prepared according to the general procedure 3.2.2 (Method B) described for compound 2 via the reaction of an equimolar amount of 6-chloro-4-methyl-2H-chromen-2-one (4, 1 mmol) and selenium dioxide (1 mmol) to obtain pure product 3 in 75% yield.

Conventional Synthesis, Method C

To a stirred mixture of 6-hydroxy-2-oxo-2H-chromene-4-carbaldehyde (2, 1.90 g, 1 mmol) and anhydrous EtOH (30 mL) was added dropwise POCl₃ (5 mL) at 5–10 °C. The reaction mixture was then stirred for an additional 1 h at room temperature and then heated for 2 h at 60 °C. After the reaction was completed, the mixture was poured onto crushed ice (200 g) under vigorous stirring. The mixture was kept overnight at 0 °C; resulted solid was collected by filtration and washed successively with water and then was air-dried to provide 3, and finally recrystallized from EtOH, as an orange solid, in 60% yield; mp 145–147 °C; IR (cm⁻¹): 1695–1710 (2C=O str); ¹H-NMR: 6.70 (s, 1H, coumarin-H3, 7.70–7.98 (m, 3H, Ar-H) and 10.35 (s, 1H, CHO). ¹³C-NMR: 91.1 (coumarin-C3), 119.8, 125.7, 126.6, 128.8, 133.7 and 150.1 (benzene), 162.4 (C=O) and 189.5 (CHO). MS (m/z %) = 208 (M⁺, 71%). Anal. Calcd for C₁₀H₅ClO₃ (208.60): C, 57.58; H, 2.42; Cl, 17.00; O, 23.01%. Found: C, 56.48; H, 2.22; Cl, 16.89; O, 22.81%.

3.2.4. Synthesis of 6-Chloro-4-methyl-2H-chromen-2-one (4), Method C

This compound was prepared according to the general procedure 3.2.2.3 (Method C) described for compound 3 via the reaction of hydroxylcoumarin (1, 1 mmol) with POCl₃ (5 mL) to afford 4 as a yellow solid which recrystallized from a mixture of EtOH/ DMF (3:1) as yellow crystals; in 80% yield; mp 236–238 °C; IR (cm⁻¹): 1695-1710 (2 C=O str); ¹H-NMR: 2.48 (s, 3H, CH₃), 6.63 (s, 1H, coumarin-H3, 7.02–7.53 (m, 3H, Ar-H). ¹³C-NMR: 18.9 (Me), 115.6 (coumarin-C3), 119.8, 125.7, 126.6, 128.8, 133.7 and 150.1 (benzene), 161.4 (C=O). MS (m/z %) = 194 (M⁺, 45%). Anal. Calcd for C₁₀H₇ClO₂ (194. 61): C, 61.72; H, 3.63; Cl, 18.22; O, 16.44%. Found: C, 61.67; H, 3.45; Cl, 18.13; O, 16.24%.

3.2.5. Synthesis of 6-Hydrazinyl-4-methyl-2H-chromen-2-one (5)

Microwave-Assisted Synthesis, Method A

Prepared according to the general procedure 3.2.1 (Method A) described for compound 2 via the reaction of an equimolar amount of 6-chloro-4-methyl-2H-chromen-2-one (4, 1 mmol) and hydrazine hydrate (1 mmol) to obtain pure product 5 in 97% yield.
Conventional Synthesis of 6-Hydrazinyl-4-methyl-2H-chromen-2-one (5), Method B

A mixture of chlorocoumarin 2 (1.90 g, 1 mmol) and hydrazine hydrate (0.5 mL, 1 mmol) in EtOH (30 mL) containing triethylamine (0.1 mL) was refluxed at 80 °C for 4 h, the reaction mixture was concentrated under reduced pressure and the residue washed with acidified cold water and then triturated with MeOH. The pale yellow product was filtered, washed well with MeOH, in 85% yield; mp 126–128 °C.

IR: 1695 (C=O), 3212–3243 (NH str and NH2 str). H-NMR (DMSO-d6): 1.32 (s, 3H, CH3), 4.28 (br., s, 2H, NH2, D2O-exchangeable), 7.21–7.65 (m, 3H, Ar-H), 9.21 (br., s, 1H, NH, D2O-exchangeable); C-NMR (DMSO-d6): 19.7 (Me), 112.6 (Coumarin-C3), 119.8, 125.7, 126.6, 128.8, 133.7 and 150.1 (benzene), 161.8 (C=O). Ms: m/z 190 (M+, 70%). Anal. Calcd for C10H10N2O2 (190.20): C 63.15, H 5.30, N 14.73%. Found: C 63.01, H 5.12, N 14.54%.

3.2.6. General Procedure for Microwave-Assisted Synthesis of Spiro Compounds 8a and 8b, Method A

An equimolar amount of hydroxycoumarin (1, 1 mmol), cyclopentanone (6a, 1 mmol) or cyclohexanone (6b, 1 mmol) and malononitrile (7, 1 mmol) were reacted according to the general procedure 3.2.1 (Method A) to give 8a,b, in 98% and 95% yields respectively.

3.2.7. General Procedure for Conventional Synthesis of Spiro Compounds 8a and 8b, Method B

An equimolar amount of hydroxylicoumarin (1, 1 mmol), cyclopentanone(6a, 1 mmol) or cyclohexanone (6b, 1 mmol) and malononitrile (7, 1 mmol) were reacted according to the general procedure 3.2.2 (Method B) to give 8a,b, in 78% and 82% yields respectively.

2'-Amino-10'-methyl-8'-oxo-5'H-spirocyclopentane-1,1'-pyrano[3,2-f][chromene]-3'-carbonitrile (8a).
Brown crystals (EtOH/DMF (1:1)); mp 167–169 °C; IR (cm⁻¹): 1695 (C=O), 2210 (CN str), 3363 (NH2 str). H-NMR: 1.00–1.07 (m, 3H, Cy-H), 1.24–1.35 (m, 2H, Cy-H), 1.53–1.70 (m, 5H, Cy-H), 2.43 (s, 3H, CH3), 6.23 (s, 1H, coumarin-H3), 6.82 (br., s, 2H, NH2, D2O-exchangeable), 7.42 (d, 1H, J = 4, Ar-H), 7.53 (d, 1H, J = 4, Ar-H). C-NMR: 23.7 (Me), 20.5, 24.4, 26.4, 35.2 (Cy-C), 112.6 (coumarin-C3), 117.4 (CN), 119.8, 125.7, 126.6, 128.8, 133.7, 150.1 (benzene), 67.1, 175.6 (Py-C), 160.8 (C=O). MS (m/z%) = 308 (M+, 25%). Anal. Calcd for C16H16N2O3 (308.12): C, 70.12; H, 5.23; N, 9.09%. Found: C, 70.02; H, 5.11; N, 8.99%.

3'-Amino-10'-methyl-8'-oxy-8'H-spirocyclohexane-1,1'-pyrano[3,2-f][chromene]-2'-carbonitrile (8b).
Reddish brown crystals (EtOH/DMF (1:1)); mp 151–153 °C; IR (cm⁻¹): 1695 (C=O), 2217 (CN str), 3361 (NH2 str). H-NMR: 1.00–1.05 (m, 3H, Cy-H), 1.53–1.65 (m, 5H, Cy-H), 1.66–1.70 (m, 2H, Cy-H), 2.43 (s, 3H, CH3), 6.43 (s, 1H, coumarin-H3), 6.72 (br., s, 2H, NH2, D2O-exchangeable), 7.42 (d, 1H, J = 4, Ar-H), 7.53 (d, 1H, J = 4, Ar-H). C-NMR: 23.7 (Me), 20.5, 24.4, 26.4, 35.2 (Cy-C), 112.6 (coumarin-C3), 117.4 (CN), 119.8, 125.7, 126.6, 128.8, 133.7, 150.1 (benzene), 67.1, 175.6 (Py-C), 160.8 (C=O). MS (m/z%) = 322 (M+, 57%). Anal. Calcd for C19H18N2O3 (322.36): C, 70.69; H, 5.63; N, 8.69%. Found: C, 70.72; H, 5.46; N, 8.76%.
3.2.8. Microwave-Assisted Synthesis of 5-(2-(6-Hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11)

An equimolar amount of 6-hydroxy-2-oxo-2H-chromene-4-carbaldehyde (2, 1 mmol), 5-amino-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (9, 1 mmol) and thioglycolic acid (10, 1 mmol) was reacted according to the general procedure 3.2.1 (Method A) to give 11.

3.2.9. Conventional Synthesis of Compound 11

An equimolar amount of 6-hydroxy-2-oxo-2H-chromene-4-carbaldehyde (2, 1 mmol), 5-amino-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (9, 1 mmol) and thioglycolic acid (10, 1 mmol) were reacted according to the general procedure 3.2.2 (Method B) to give 11 as a yellow solid, mp 251–253 °C; IR (cm⁻¹): 1681–1708 (3 C=Oatr), 3156 (br, N-Hatr), 3480 (O-Hatr); ¹H-NMR: 2.43 (s, 3H, CH₃), 3.97 (s, 2H, CH₂ of thiazolidine), 6.46 (s, 1H, thiophene methine), 6.51 (s, 1H, Coum-H3), 6.61 (s, 1H, thiazolidine-H2), 7.03–7.51 (m, 3H, Ar-H), 12.21 (s, br., 1H, -NH), 12.50 (s, 1H, OH). ¹³C-NMR: 21.8 (CH₃), 33.8 (C-5-thiazolidine), 117.4 (C-2-thiophene), 124 (C-3-thiophene), 126 (C-4-thiophene), 152.8 (C-5-thiophene), 161.2 (C-2-thiazolidine), 154.8 (C-2-pyrimidine), 161.0, 162.4, 171.2 (3C=O) and 119.8, 125.7, 126.6, 128.6, 133.7 and 150.1 (Ph). MS (m/z%) = 427 (M⁺, 60%). Anal. Calcd for C₁₉H₁₃N₅O₅S₂ (427.45): C, 53.39; H, 3.07; N, 9.83%. Found: C, 53.21; H, 3.01; N, 9.67%.

3.2.10. Microwave-Assisted Synthesis of 3-((4-Methyl-2-oxo-2H-chromen-6-yl)amino)-2-phenylthiazolidin-4-one (13)

An equimolar amount of 6-hydrazinyl-4-methyl-2H-chromen-2-one (5, 1 mmol), benzaldehyde (12, 1 mmol), and thioglycolic acid (10, 1 mmol) were reacted according to the general procedure 3.2.1 (Method A) to give 13.

3.2.11. Conventional Synthesis of Compound 13

Equimolar amounts of 6-hydrazinyl-4-methyl-2H-chromen-2-one (5, 1 mmol), benzaldehyde (12, 1 mmol), and thioglycolic acid (10, 1 mmol) were reacted according to the general procedure 3.2.2 (Method B) to give 13 as a brown solid, mp 278–280 °C; IR (cm⁻¹): 1681-1708 (2 C=Oatr), 3280 (br, N-Hatr); ¹H-NMR: 2.43 (s, 3H, CH₃), 3.95 (s, 2H, CH₂ of thiazolidine), 6.23 (s, 1H, Coum-H3), 5.91 (s, br., 1H, -NH), 5.91 (s, 1H, thiazolidine-H2), 7.03–7.51 (m, 8H, Ar-H). ¹³C-NMR: 19.1 (CH₃), 36.0 (C-5-thiazolidine), 58.2 (C-2-thiazolidine), 160.1, 170.4 (2C=O) and 119.8, 125.7, 126.6, 128.6 and 133.7, 150.1 (Ph). MS (m/z%) = 352 (M⁺, 65%). Anal. Calcd for C₁₉H₁₆N₂O₃S (352.41): C, 64.76; H, 4.58; N, 7.95%. Found: C, 64.56; H, 4.32; N, 7.87%.

3.2.12. General Procedure for Microwave-Assisted Synthesis of Thiazolo[5,4-d]isoxazole Derivatives 16 and 17, Method A

Equimolar amounts of 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11, 1 mmol) or 3-(4-methyl-2-oxo-2H-chromen-6-ylamino)-2-phenylthiazolidin-4-one (13, 1 mmol), dimethylformamide-dimethylacetal (DMF-DMA) (14, 1 mmol),
and hydroxylamine (15, 1 mmol) were reacted according to the general procedure 3.2.1 (Method A) to afford pure products 16 and 17, respectively.

3.2.13. General Procedure for Conventional Synthesis of Synthesis of Thiazolo[5,4-d]isoxazole Derivatives 16 and 17, Method B

Equimolar amounts of 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11, 1 mmol) or 3-(4-methyl-2-oxo-2H-chromen-5-ylamino)-2-phenylthiazolidin-4-one (13), dimethylformamide-dimethylacetal (DMF-DMA) (14, 1 mmol), and hydroxylamine (15, 1 mmol) were reacted according to the general procedure 3.2.2 (Method B) to obtain pure products 16 and 17, respectively.

5-((5-(6-Hydroxy-2-oxo-2H-chromen-4-yl)thiazolo[5,4-d]isoxazol-6(5H)-yl)-2-methylthieno-[3,4-d]pyrimidin-4(3H)-one (16). Pale brown solid, mp 210–213 °C; IR (cm⁻¹): 1681, 1696 (2 C=Ostr), 3263 (br, N-Hstr), 3453 (O-Hstr); ¹H-NMR: 2.71 (s, 3H, CH₃), 4.95 (s, 1H, thiazole-H2), 6.42 (s, 1H, methine of thiophene-H5), 7.28–7.80 (m, 3H, Ar-H), 8.14 (s, 1H, isoxazole-H3), 10.56 (s, br., 1H, -NH), 12.52 (s, 1H, OH). ¹³C-NMR: 21.4 (CH₃), 70.71 (C-2-thiazole), 100.0 (C-5-thiazole), 125.0 (C-4-thiophene), 129.4 (C-5-thiophene), 137.0 (C-2-thiophene), 142.0 (C-3-thiophene), 150.0 (C-3-isoxazole), 154.5 (C-2-pyrimidine), 160.8, 161.0 (2C=O) and 109.8, 125.7, 126.6, 128.6 and 133.7, 150.1 (Ph). MS (m/z %) = 452 (M⁺, 25%). Anal. Caled for C₂₀H₁₂N₄O₄S₂ (452.46): C, 53.09; H, 2.67; N, 12.38%. Found: C, 53.01; H, 2.56; N, 12.23%.

4-Methyl-6-((5-phenylthiazolo[5,4-d]isoxazol-6-ylamino)-4a,8a-dihydro-2H-chromen-2-one (17). Brown solid, mp 182–184 °C; IR (cm⁻¹): 1681 (C=Ostr), 3263 (br, N-Hstr); ¹H-NMR: 2.43 (s, 3H, CH₃), 4.95 (s, 1H, thiazole-H2), 6.43 (s, 1H, Coum-H3), 5.93 (s, br., 1H, -NH-), 7.03–7.51 (m, 8H, Ar-H), 8.17 (s, 1H, isoxazole-H3). ¹³C-NMR: 19.1 (CH₃), 72.4 (C-2-thiazole), 100.0 (C-5-thiazole), 150.0 (C-3-isoxazole), 160.8 (C=O) and 119.8, 125.7, 126.6, 128.6 and 133.7, 150.1 (Ph). MS (m/z %) = 377 (M⁺, 35%). Anal. Caled for C₂₀H₁₅N₅O₄S (377.42): C, 63.65; H, 4.01; N, 11.13%. Found: C, 63.53; H, 3.98; N, 11.02%.

3.2.14. General Procedure for Microwave-Assisted Synthesis of Thiazolo[4,5-d]pyrimidine Derivatives 19 and 20, Method A

An equimolar amount of 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11, 1 mmol) or 3-(4-methyl-2-oxo-2H-chromen-6-ylamino)-2-phenylthiazolidin-4-one (13), benzaldehyde 12 (1 mmol) and thiourea 18 was reacted according to the general procedure 3.2.1 (Method A) to give pure products 19 and 20, respectively.

3.2.15. General Procedure for Conventional Synthesis of Thiazolo[5,4-d]isoxazole Derivatives 19 and 20, Method B

Equimolar amount of 5-(2-(6-hydroxy-2-oxo-2H-chromen-4-yl)-4-oxothiazolidin-3-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (11, 1 mmol) or 3-(4-methyl-2-oxo-2H-chromen-6-ylamino)-2-phenylthiazolidin-4-one (13), benzaldehyde (12) and thiourea (18) was reacted according to the general procedure 3.2.1 (Method A) to afford pure products 19 and 20, respectively.
5-(2-(6-Hydroxy-2-oxo-2H-chromen-4-yl)-7-phenyl-5-thioxo-5,6,7,7a-tetrahydrothiazolo[4,5-d]pyrimidin-3(2H)-yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (19). Yellow solid, mp 198–200 °C; IR (cm⁻¹): 1378 (C=Σw), 1684 (C=Ow), 3250–3486 (br, 2NHw); ¹H-NMR: 2.41 (s, 3H, CH₃), 3.20 (d, 1H, thiazole-H5), 3.41 (d, 1H, NH-CS-), 4.21 (d, 1H, pyrimidine-H6), 6.46 (s, 1H, thiophene-H5), 6.51 (s, 1H, Coum-H3), 6.71 (s, 2H, thiazole-H2), 7.03-7.51 (m, 8H, Ar-H), 12.20 (s, br., 1H, pyrimidine-NH), 12.52 (s, 1H, OH). ¹³C-NMR: 21.4 (CH₃), 33.8 (C-5-thiazole), 117.4 (C-2-thiophene), 124 (C-3-thiophene), 126 (C-4-thiophene), 152.8 (C=O-thiazole), 154.8 (C-2-pyrimidine), 160.8, 161.0 (2C=O) and 119.8, 125.7, 126.6, 128.6, 133.7, 150.1 (Ph), 187.0 (C=S). MS (m/z%) = 498 (M⁺, 70%). Anal. Calcd for C₂₂H₁₅N₆O₃S (573.67): C, 56.53; H, 3.21; N, 11.89; S, 16.46%.

6-(2,7-Diphenyl-5-thioxo-5,6,7,7a-tetrahydrothiazolo[4,5-d]pyrimidin-3(2H)-ylamino)-4-methyl-2H-chromen-2-one (20). Yellow crystals, mp 217–219 °C; IR (cm⁻¹): 1378 (C=Σw), 1684 (C=Ow), 3250–3486 (br, 2NHw); ¹H-NMR: 2.43 (s, 3H, CH₃), 3.20 (d, 1H, thiazole-H5), 3.41 (d, 1H, pyrimidine-NH), 4.2 (d, 1H, pyrimidine-H6), 4.95 (s, 2H, thiazole-H2), 6.23 (s, 1H, Coum-H3), 5.91 (s, br., 1H, -NH-), 7.03–7.51 (m, 13H, Ar-H). ¹³C-NMR: 19.4 (CH₃), 68.0 (C-2-thiophene), 164.0 (C-5-thiazole), 160.8 (C=O) and 119.8, 125.7, 126.6, 128.6 and 133.7, 150.1 (Ph), 187.0 (C=S). MS (m/z%) = 498 (M⁺, 70%). Anal. Calcd for C₂₁H₁₄N₆O₃S (489.62): C, 65.04; H, 4.45; N, 11.24; S, 12.86%. Found: C, 64.86; H, 4.34; N, 11.12; S, 12.67%.

3.3. Antimicrobial Evaluation

Some strains of bacteria and fungi were obtained from Assiut University Mycological Center (AUMC) and other strains were obtained from Aswan Teaching Hospital, Aswan, Egypt. All the synthesized compounds were screened for their in vitro antimicrobial activity, against three Gram positive bacteria; (BS): B. subtilis (MTCC 443); (CT): C. tetani (MTCC 449); (SP): S. pneumoniae (MTCC 1936); three Gram negative bacteria; (EC): E. coli (MTCC 440); (ST): S. typhi (MTCC 98); (VC): V. cholerae (MTCC 3906); and two fungal strains; (AF): A. fumigates (MTCC 3008); (CA): C. albicans (MTCC 227). The results are presented in Table 1, expressed in the form of MIC in µg mL⁻¹. The antibacterial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/mL) as previously mentioned by broth dilution method [33] with A: ampicillin; B: ciprofloxacin; C: norfloxacin; D: chloramphenicol as control drugs. The antifungal study was carried out by the standard agar dilution method with E: nystatin and F: griseofulvin as control drugs, DMSO, which exhibited no activity against any of the used organisms, was used as a blank, (Table 2).

An examination of the data prescribed in Table 1 revealed that, some of the compounds were more potent or equipotent to the standard drugs against the Gram-positive bacteria C. tetani and a few against S. pneumoniae and B. subtilis. Against the Gram-positive bacteria B. subtilis, compound 17 (MIC = 65.5 µg·mL⁻¹) was found to be more potent, whereas 2, 4, 8b, 13, and 20 (MIC = 250 µg·mL⁻¹) shows comparable activity to ampicillin (MIC = 250 µg·mL⁻¹). Moreover, compound 17 (MIC = 65.5 µg·mL⁻¹) was found to more active as compared to norfloxacin (MIC = 100 µg·mL⁻¹). Against C. tetani, compounds 3, 11, 17 and 19 (MIC = 100 µg/mL), and 4, 5, 8a and 13 (MIC = 200 µg mL⁻¹) were found to be more potent, whereas 20 (MIC = 250 µg·mL⁻¹) showed comparable activity to
ampicillin (\(MIC = 250 \mu g \cdot mL^{-1}\)), while compounds 3, 11, 17 and 19 (\(MIC = 100 \mu g \cdot mL^{-1}\)) were equally potent as compared to ciprofloxacin (\(MIC = 100 \mu g \cdot mL^{-1}\)). Against \textit{S. pneumoniae}, compound 16 (\(MIC = 50 \mu g \cdot mL^{-1}\)) showed comparable activity to chloramphenicol and ciprofloxacin (\(MIC = 50 \mu g \cdot mL^{-1}\)).

| Compound | Gram-Positive Bacteria | Gram-Negative Bacteria | Fungal Species |
|----------|------------------------|------------------------|---------------|
|          | (BS) (CT) (SP)         | (EC) (ST) (VC)         | (AF) (CA)     |
| 1        | 500 500 500            | 250 500 500            | 1000 >1000    |
| 2        | 250 500 250            | 500 500 100            | 500 100       |
| 3        | 1000 100 500           | 250 500 200            | 250 100       |
| 4        | 250 200 250            | 500 250 200            | 500 250       |
| 5        | 500 200 500            | 250 250 200            | 500 500       |
| 8a       | 500 200 500            | 100 500 250            | 250 250       |
| 8b       | 250 500 250            | 100 100 250            | 1000 500      |
| 11       | 500 100 500            | 250 65.5 250           | 1000 1000     |
| 13       | 250 200 250            | 250 250 200            | 500 250       |
| 16       | 500 500 50             | 250 500 500            | 1000 500      |
| 17       | 65.5 100 250           | 100 65.5 200           | 1000 1000     |
| 19       | 500 100 500            | 200 500 200            | 500 500       |
| 20       | 250 250 500            | 100 65.5 250           | 250 250       |
| A        | 250 250 100            | 100 100 100            | 0 0           |
| B        | 50 100 50              | 25 25 25              | 0 0           |
| C        | 100 50 10              | 10 10 10              | 0 0           |
| D        | 50 50 50               | 50 50 50              | 0 0           |
| E        | 0 0 0                  | 0 0 0                 | 100 100       |
| F        | 0 0 0                  | 0 0 0                 | 100 500       |

A: ampicillin; B: ciprofloxacin; C: norfloxacin; D: chloramphenicol; E: nystatin; F: griseofulvin. “0” represents “not tested”.

Towards the Gram-negative strain \textit{E. coli}, compounds 8a, 8b, 17 and 20 (\(MIC = 100 \mu g \cdot mL^{-1}\)) showed comparable activity to ampicillin (\(MIC = 100 \mu g \cdot mL^{-1}\)). Compounds 11, 17 and 20 (\(MIC = 65.5 \mu g \cdot mL^{-1}\)) were more potent, whereas 8b (\(MIC = 100 \mu g \cdot mL^{-1}\)) showed comparable activity to ampicillin (\(MIC = 100 \mu g \cdot mL^{-1}\)) towards \textit{S. typhi}. Also the compound 20 (\(MIC = 100 \mu g/mL^{-1}\)) show comparable activity, to ampicillin (\(MIC = 100 \mu g/mL^{-1}\)) towards \textit{V. cholerae}.

Against the fungal pathogen \textit{C. albicans}, compounds 3 (\(MIC = 100 \mu g \cdot mL^{-1}\)) 4, 8a, 13 and 20 (\(MIC = 250 \mu g \cdot mL^{-1}\)) showed good to excellent activity, whereas 2, 5, 8b, 16 and 19 (\(MIC = 500 \mu g \cdot mL^{-1}\)) were equipotent to griseofulvin (\(MIC = 500 \mu g \cdot mL^{-1}\)). Compound 3 (\(MIC = 100 \mu g \cdot mL^{-1}\)) was found equipotent to nystatin towards \textit{C. albicans}. The remaining compounds showed moderate to good activity in the inhibition of the growth of bacterial pathogens and were all less effective than the standard drugs.

4. Conclusions

In summary, an efficient synthesis of some new 2H-chromene derivatives 1–20 bearing the phenylthiazolidinone nucleus via a facile one-pot three-component reaction under microwave irradiation
as well as conventional chemical synthesis processes has been reported. Most of the synthesized compounds showed mild to moderately active against the *C. tetani*, a gram positive strain and *E. coli*, a gram negative strain. The antifungal activity of the compounds shows that most of the compounds were more potent against *C. albicans* than against *A. fumigatus*. Compounds 3, 4, 8a, 13 and 20 exhibited remarkable antifungal activity against *C. albicans*.

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Author Contributions

IE designed research; IE, MY and MA performed research and analyzed the data; IE, MY and MA wrote the paper. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Domling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* 2006, 106, 17–89.

2. Lafitte, D.; Lamour, V.; Tsvetkov, P.; Markov, A.A.; Deprez, M.; Klich, P.; Moras, D.; Briand, C.; Gilli, R. DNA gyrase interaction with coumarin-based inhibitors-the role of the hydroxyl benzoate isopentenyl moiety and the 5’-methyl group of the novoise. *Biochemistry* 2002, 41, 7217–7223.

3. Hurry, R.G.; Cortz, C.; Ananthanaraxan, T.P.; Schmolka, S. A new coumarin synthesis and its utilization for the synthesis of polycyclic coumarin compounds with anticarcinogenic properties. *J. Org. Chem.* 1998, 53, 3936–3943.

4. Hafez, E.A.A.; Elnagdi, M.H.; Elagamey, A.G.A.; EL-Taweel, F.M.A.A. Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[c]Coumarin and of Benzo[c]Pyranopyrano[3,2-c]Quinoline Derivatives. *Heterocycles* 1987, 26, 903–907.

5. Tanabe, A.; Nakashima, H.; Yoshida, O.; Yamamoto, N.; Tenmyo, O.; Oki, T. Inhibitory Effect of New Antibiotic, Pradimicin A on Infectivity, Cytopathic Effect and Replication of Human Immunodeficiency Virus in Vitro. *J. Antibiot.* 1988, 41, 1708–1710.

6. Shijay, G.; Cheng, H.T.; Chi, T.; Ching-Fa, Y. Fluoride Ion Catalyzed Multicomponent Reactions for Efficient Synthesis of 4H-Chromene and N-Arylquinoline Derivatives in Aqueous Media. *Tedrahedron* 2008, 64, 9143–9149.

7. Balaji, P.N.; Lakshmi, L.K.; Mohan, K.; Revathi, K.; Chamundeswari, A.; Indrani, P.M. In-vitro anti-inflammatory and antimicrobial activity of synthesized some novel pyrazole derivatives from coumarin chalcones. *Der Pharmacia Sinica* 2012, 3, 685–689.

8. Bayer, T.A.; Schafer, S.; Breyh, H.; Breyhan, O.; Wirths, C.; Treiber, G.A. A Vicious Circle: Role of Oxidative Stress, Intraneuronal Aβ and Cu in Alzheimer’s Disease Multhaup. *Clin. Neuropathol.* 2006, 25, 163–171.
9. Fokialakas, N.; Magiatis, P.; Chinou, L.; Mitaka, S.; Tillequin, F.; Megistoquinones, I, II. Two Quinoline Alkaloids with Antibacterial Activity from the Bark of Sarcomelicope megistophylla. *Chem. Pharm. Bull.* **2002**, *50*, 413–414.

10. Beagley, P.; Blackie, M.A.L.; Chibale, K.; Clarkson, C.; Meijboon, R.; Moss, J.R.; Smith, P.; Su, H. Synthesis and Antiplasmodial Activity *in Vitro* of New Ferrocene-Chloroquine Analogues. *Dalton Trans.* **2003**, *3046–3051*.

11. Morgan, L.R.; Jursic, B.S.; Hooper, C.L.; Neumann, D.M.; Thangaraj, K.; Leblance, B. Anticancer Activity for 4,4-Dihydroxybenzophenone-2,4-Dinitrophenylhydrazone (A-007) Analogues and Their Abilities to interact with Lymphoendothelial Cell Surface Markers. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3407–3411.

12. Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. Synthesis and Pharmacological Activity of 2-oxo-(2H)-1-Benzopyran-3-Carboxamide Derivatives. *Eur. J. Med. Chem.* **1993**, *28*, 517–520.

13. Cannon, J.G.; Khonji, R.R. Centrally Acting Emetics. 9. Hofmann and Emde Degradation Products of Nuciferine. *J. Med. Chem.* **1975**, *18*, 110–112.

14. Biot, C.; Glorian, G.; Maciejewski, L.A.; Brocard, J.S.; Domarle, O.; Blampain, G.; Blampain, P.; Georges, A.J.; Abessolo, H.; *et al.* Synthesis and Antimalarial Activity *in Vitro* and *in Vivo* of a New Ferrocene-Chloroquine Analogue. *J. Med. Chem.* **1997**, *40*, 3715–3718.

15. Abdel-Galil, F.M.; Riad, B.Y.; Sherif, S.M.; Elnagdi, M.H. Activated Nitriles in Heterocyclic Synthesis: A Novel Synthesis of 4-Azoloyl-2- Aminoquinolines. *Chem. Lett.* **1982**, *11*, 1123–1126.

16. Shaker, R.M. Synthesis and Reactions of Some New 4H-Pyrano[3,2-c]benzopyran-5-One Derivatives and Their Potential Biological Activities. *Pharmazie* **1996**, *51*, 148–151.

17. Balalaie, S.; Abdolmohammadi, S. Novel and Efficient Catalysts for the One-Pot Synthesis of 3,4-Dihydropyran[c]Chromene Derivatives in Aqueous Media. *Tetrahedron Lett.* **2007**, *48*, 3299–3303.

18. Kidwai, M.; Saxena, S. Convenient Preparation of Pyrano Benzopyranes in Aqueous Media. *Synth. Commun.* **2006**, *36*, 2737–2742.

19. Heravi, M.M.; Alimadadi, J.B.; Derikvand, F.; Bamoharram, F.F.; Oskooie, H.A. Three Component, One-Pot Synthesis of Dihydropyran[3,2-c]Chromene Derivatives in the Presence of H$_6$P$_2$W$_{18}$O$_{62}$·18H$_2$O as a Green and Recyclable Catalyst. *Catal. Commun.* **2008**, *10*, 272–275.

20. Seifi, M.; Sheibani, H. High Surface Area MgO as a Highly Effective Heterogeneous Base Catalyst for Three-Component Synthesis of Tetrahydro benzopyran and 3,4-Dihydropyran[c]chromene Derivatives in Aqueous Media. *Catal. Lett.* **2008**, *126*, 275–279.

21. Khurana, J.M.; Kumar, S. Tetra Butyl Ammonium Bromide (TBAB): A Neutral and Efficient Catalyst for the Synthesis of Biscoumarin and 3,4-Dihydopyran[c]Chromene Derivatives in Water and Solvent-Free Conditions. *Tetrahedron Lett.* **2009**, *50*, 4125–4127.

22. Dobaria, A.V.; Patel, J.R.; Padaliya J.V.; Parekh, H.H. Thiazolidinones bearing chloroquinoline nucleus as potential antimicrobial agents. *Indian J. Heterocycl. Chem.* **2001**, *11*, 115–118.

23. Deepak, K.; Bux, F.B.; Varsh P.; Arun, S. Thiazolidinone: Synthesis and biological studies. *Der Pharma Chemica* **2012**, *4*, 538–543.

24. Shweta, T.D.; Pratima R.P.S.; Toraskar, M.P. Synthesis and antimicrobial evaluation of some 4-substituted thiazolidinone derivatives. *Der Pharma Chemica* **2010**, *2*, 17–20.
25. Raghav, M.; Isha, T.; Sachin, S.; Jha, K.K. Facile synthesis of thiazolidinones bearing thiophene nucleus as antimicrobial agents. Der Pharma Chemica 2012, 4, 489–496.

26. Aamer, S.; Naeem, A.; Ulrich, F. Synthesis and Antibacterial Activity of some Novel 2-Aroylimino-3-aryl-thiazolidin-4-ones. J. Braz. Chem. Soc. 2007, 18, 559–565.

27. El Azab, I.H.; El Rady, E.A. Facile and Simple Synthesis of some New Polyfunctionally Heterocyclic Derivatives: Incorporating 2-Imino-2H-Chromene Moiety. J. Heterocycl. Chem. 2012, 49, 135–148.

28. El Rady, E.A.; El Azab, I.H. Reactivity of β-enamino ester of benzo[f]chromene: One pot synthesis of isolated and fused heterocyclic derivatives of benzo[f]chromene. Eur. J. Chem. 2012, 3, 81–86.

29. El Azab, I.H. Synthesis of Some New Benzo[b][1,4]diazepine Based Heterocycles. J. Heterocycl. Chem. 2013, 50, 178–188.

30. Azab, I.H.; kenzy, N.A.A. Synthesis of Fused- Isolated Azoles and N-Heteroaryl Derivatives Based on 2-Methyl-3,4-dihydrothieno[3,4-d]pyrimidin-5-amine. Synth. Commun. 2014, 44, 2692–2714.

31. El Azab, I.H.; El Rady, E.A. Simple Method for Synthesis of Isolated Heterocyclic Compounds: Incorporating 2-(2-Bromoacetyl)-isoindoline-1,3-dione and 2-(2-Cyanoacetyl)isoindo-line-1,3-dione. Indian J. Chem. 2014, 52, 1194–1204.

32. Pal, R.; Handa, R.N.; Pujari, H.K. Heterocyclic systems containing bridgehead nitrogen atom: Part LXIII. Reaction of 1-Methyl-7,8,10,11-tetraazaspiro[5,5]undecane-9-thione with bi functional compounds. Indian J. Chem. Soc. 1992, 31B, 771–777.

33. Cappuccino, J.G.; Sherman, N. Microbiology- A Laboratory Manual, 4th ed.; Addison-Wesley, Longman, Inc.: Ithaca, NY, USA, 1999; pp. 477–487.

Sample Availability: Samples of the compounds 4, 5, 11, 16, 17 and 20 are available from the authors.

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