Microwave-assisted synthesis of coumarin-based 5,6-dihydro pyrimidin-2(1H)-one derivatives

Damilola V. Aderohunmu¹, Olayinka O. Ajani¹,², Gbolahan O. Oduselu¹ and Ezekiel F. Adebiyi¹,³,*

¹Covenant University Bio-informatics Research Cluster (CUBRe)
²Department of Chemistry, CST, Covenant University, P.M.B. 1023, Ogun State, Nigeria.
³Department of Computer and information Science, CST, Covenant University, P.M.B. 1023, Ogun State, Nigeria.

*Corresponding Author’s E-mail: ezekiel.adebiyi@covenantuniversity.edu.ng;

Abstract. Coumarin is an oxygen-containing heterocyclic compound of great medicinal important and high versatility in electronic and material science research. Incorporation of pyrimidine as a linker on coumarin is a way to provide improved application in solar cell research by extension of unsaturation for improved electronic transition. Convention synthesis approach is common in organic synthesis but have some disadvantages like affecting the eco-system due to discharge of toxic chemical during the process. On the other hand, microwave irradiation is eco-friendly and accelerates synthesis to afford great products following interesting reaction schemes and steps at reduced time. Hence, microwave assisted synthesis of novel coumarin-based 5,6-dihydropyrimidin-2(1H)-one derivatives was herein achieved via a three-step synthetic approach. The reaction was initiated with catalyst supported multicomponent reaction to produce 3-acetylcoumarin 7 which upon condensation with five aromatic aldehydes furnished chalcones 8a-e. Microwave assisted reaction of chalcones 8a-e with lone pair donor, urea led to the formation of the targeted coumarin-based 5,6-dihydropyrimidin-2(1H)-one 9a-e in good-to-excellent yields. The structures were established using spectroscopic data and notable physical properties and the results obtained were consistent with the expected structure of the products. The compounds will be good for further study to authenticate their applications in drug design and material science research.

1. INTRODUCTION

The sustainable form of organic synthesis does not only make use of natural feedstock in catalytic synthesis but also ensure the eco-friendly approach for such laboratory preparation of bioactive compounds. Microwave assisted synthesis is a green, sustainable and eco-friendly method of preparing molecular framework that are organic biomolecule [1] or heterocyclic in nature such as coumarin based-motifs[2]. Green chemistry is an innovative and modern principles of chemistry which eliminate the hazardous chemicals from the chemical reaction [3]. Microwave assisted synthesis is a revolutionized accelerated way of preparing organic compounds with added advantages over the conventional chemical synthesis. The fundamental mechanism This is because, microwave reaction technique less toxic starting material, avoid discharge of harmful chemical, use of minimized steps and contribute immensely to sustainable development [4]. Coumarin is a heterocyclic compound which is also known as the chromen-2-one or benzo-fused lactone. It is naturally occurring in many medicinally important plants such as tonga bean and have also enjoyed preparation on laboratory scale because of the wide pharmacophoric potential of this template. For instance, warfarin, 1 is anticoagulant, armillarisin A, 2 is antibiotic and auraptene, 3 as chemo-preventive agent [5]. They are
also useful in agrochemicals, laser dye, cosmetics and food manufacturing industries as additives. Pyrimidine belong to the family of diazine heterocycle with its nitrogen heteroatom located in positions-1 and 3 of the ring system [6]. Pyrimidine derivatives are the main nitrogenous bases in DNA and essential building block in many existing drug candidates some of which are 5-fluorouracil 4 as anticancer, pyrimethamine 5 as antimalarial and rilpirivine 6 as anti-HIV [7,8]. The structures of commercially available motifs 1 to 6 are as shown in Fig. 1. Various methods have been reported for the synthesis of coumarin and its derivative due to their wide applications. Some of these synthetic routes and methods include microwave assisted synthesis [2] through Knoevenagel approach and preparation via microbial action in the presence of Escherichia coli[9]. Synthetic coupling of coumarin and pyrimidine in one motif could lead to enhancement of bioactivity of the new template and provide novel compound with essential feature for applications in drug discovery, metal complexes, solar cell sensitizer and material science. Therefore, this study deals with microwave-assisted synthesis of novel coumarin-based 5,6-dihydropyrimidin-2(1H)-one derivatives.

Fig. 1: Commercially available drug bearing pyrimidine moieties as active ingredient

2. MATERIAL AND METHODS
2.1. General Conditions
Reagents and the chemicals were supplied by Sigma-Aldrich (USA) except ethyl acetoacetate and piperidine which were manufactured by British Drug House, B.D.H. (UK). The reagents were of analytical grade and they were utilized directly without purification. The products purity was determined using thin layer chromatography. Determination of melting points was carried out with Stuart melting point machine SMP10 (UK). Infrared data were generated with the Bruker FT-IR spectrophotometer (Germany) whereas the ultraviolet-visible analysis was obtained for the ethanolic solution of the synthesized compounds with the aid of Genesys™ 10S UV-Vis. spectrophotometer (Thermo Scientific, USA). Both $^1$H and $^{13}$C nuclear magnetic resonance of the products were analyzed in DMSO-$d_6$ using Bruker NMR machine (Germany). Carlo Erba-1108 elemental analyzer manufactured in Germany was used for C, H, N microanalysis. Microwave irradiative reaction was carried out with LG microwave oven MS2327B (2450 MHz) manufactured in USA.
2.2. Synthetic Procedure

2.2.1. Synthesis of 3-acetylcomunarin, 7

This precursor was synthesized via microwave irradiated technique according to our previously reported method[2]. The spectral data were in consistent with earlier reported value for the proposed structures[2].

2.2.2. General procedure for synthesis of chalcones 8a-e

Catalytic amount of piperidine (5 drops) was added to 3-acetyl coumarin (3.0 g, 16 mmol), followed by benzaldehyde derivatives (16 mmol). The mixture was swirled and was transferred into microwave oven where it was irradiated for 1 to 3 minutes. The completion of reaction was monitored using TLC (eluting solvent: Dichloromethane). The product was recrystallized from ethanol to afford chalcones 8a-e in diverse yield. The spectral data were as reported in our earlier findings [10].

2.2.3. General Procedure for the coumarin-based 5,6-dihydropyrimidin-2(1H)-one, 9a-e.

A solution of urea (0.41 g, 6.8 mmol) in 5 mL of ethanol was added to each of the chalcones 8a-e (6.8 mmol) in a sealed tube and the mixture was irradiated in microwave oven for the required period of time. The reaction completion was monitored using TLC plates (eluting solvent: hexane: ethyl acetate, 3:1). The spectral data were as reported in our earlier findings.

2.2.3.1. Microwave assisted synthesis of 6-(3-hydroxyphenyl)-4-(2-oxo-2H-chromen-3-yl)-5,6-dihydropyrimidin-2(1H)-one 9a.

Treatment of urea (0.41 g, 6.8 mmol) with 8a (2.0 g, 6.8 mmol) for 1½ min, produced 9a (1.51 g, 75.82%). UV-Visible data → $\lambda_{\text{max}}$ (log $\varepsilon_{\text{max}}$): 218 (3.30), 254 (3.32), 386 (4.01), 445 (3.58). Infrared data: 3436 (N–H). 3339 (–OH of phenol), 3030 (CH aromatic), 2950 (CH aliphatic), 1737 (C=O of ester), 1674 (C=O of amide), 1504 (C=N), 1453 (CH$_2$). 1H-NMR (DMSO-d$_6$, 400 MHz) $\delta_{\text{H}}$: 11.15-11.13 (d, $J = 7.92$ Hz, 1H, CH$_2$-CH), 8.88 (s, 1H, Ar–OH), 8.61 (s, 1H, Het-H), 7.95-7.93 (d, $J = 8.00$ Hz, 1H, Ar-H), 7.76-7.72 (m, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.47-7.45 (m, 2H, Ar-H), 7.31-7.29 (d, $J = 8.16$ Hz, 1H, Ar-H), 7.12-7.10 (d, $J = 8.22$ Hz, 1H, Ar-H), 3.36-3.31 (m, 1H, CH), 2.60-2.58 (d, $J = 5.76$ Hz, 2H, CH$_2$-CH).

2.2.3.2. Microwave assisted synthesis of 6-(4-hydroxyphenyl)-4-(2-oxo-2H-chromen-3-yl)-5,6-dihydropyrimidin-2(1H)-one, 9b.

Treatment of urea (0.41 g, 6.8 mmol) with 8b (2.0 g, 6.8 mmol) for 1 min, produced 9b (1.78 g, 89.10 %). UV-Visible data → $\lambda_{\text{max}}$ (log $\varepsilon_{\text{max}}$): 209 (3.49), 248 (3.11), 272 (3.19), 315 (3.36), 356 (3.89). Infrared data: 3292 (–OH of phenol), 2823 (CH aliphatic), 1742 (C=O of ester), 1674 (C=O of amide), 1553 (C=N), 1453 (CH$_2$). 1H-NMR (DMSO-d$_6$, 400 MHz) $\delta_{\text{H}}$: 8.80 (s, 1H, Ar–OH), 8.64 (s, 1H, Het-H), 7.96-7.94 (d, $J = 8.00$ Hz, 1H, Ar-H), 7.77-7.73 (m, 1H, Ar-H), 7.63-7.60 (d, $J = 8.58$ Hz, 2H, Ar-H), 7.47-7.42 (m, 2H, Ar-H), 7.25-7.22 (d, $J = 8.42$ Hz, 2H, Ar-H), 6.84-6.82 (d, $J = 7.96$ Hz, 1H, NH–CH), 3.41-3.36 (m, 1H, CH), 2.59-2.57 (d, $J = 5.18$ Hz, 2H, CH$_2$-CH)$_2$. 13C-NMR (DMSO-d$_6$, 100 MHz) $\delta_{\text{C}}$: 195.38 (C=O), 173.50 (C=O), 157.04, 154.90, 151.26, 146.98, 140.44 (2× CH), 142.93, 137.72, 130.71, 127.77, 121.66 (2× CH), 118.01, 116.04, 113.50, 59.26 (CH$_3$), 47.18 (CH$_2$) ppm.

2.2.3.3. Microwave assisted synthesis of 6-(3-methoxyphenyl)-4-(2-oxo-2H-chromen-3-yl)-5,6-dihydropyrimidin-2(1H)-one, 9c.

Treatment of urea (0.39 g, 6.5 mmol) with 8c (2.0 g, 6.5 mmol) for 1 min, produced 9c (1.39 g, 69.73 %). UV-Visible data → $\lambda_{\text{max}}$ (log $\varepsilon_{\text{max}}$): 248 (2.89), 278 (2.92), 287 (2.85), 326 (3.37). Infrared data: 3340 (N–H), 2930 (CH aliphatic), 1738 (C=O of ester), 1604 (C=C aromatic), 1352 (C=O of ester), 754 (Ar-H). 1H-NMR (DMSO-d$_6$, 400 MHz) $\delta_{\text{H}}$: 8.64 (s, 1H, Het-H), 7.95-7.93 (d, $J = 8.00$ Hz, 1H, Ar-H), 7.75-7.72 (m, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.46-7.43 (m, 2H,
Ar-H), 7.96-7.94 (d, J = 8.00 Hz, 1H, Ar-H), 7.31-7.29 (d, J = 8.42 Hz, 1H, Ar-H), 7.15-7.13 (d, J = 7.88 Hz, 1H, Ar-H), 6.84-6.82 (d, J = 7.96 Hz, 1H, NH-CH), 3.36-3.31 (m, 1H, CH), 2.60-2.57 (d, J = 5.18 Hz, 2H, CH$_2$-CH), 2.25 (s, 3H, Ar-OC$_3$H$_3$). $^{13}$C-NMR (DMSO-$d_6$, 100 MHz) $\delta$: 194.99 (C=O), 173.45 (C=O), 154.32, 150.91, 146.76, 143.34, 140.79, 138.07, 136.44, 134.41, 127.25, 124.86, 123.09, 118.09, 116.04, 113.84, 111.71, 58.57 (CHs), 46.31 (CH$_3$), 29.48 (CH$_3$) ppm.

2.2.3.4. Microwave assisted synthesis of 6-(4-methoxyphenyl)-4-(2-oxo-2H-chromen-3-yl)-5,6-dihydropyrimidin-2(1H)-one, 9d. Treatment of urea (0.39 g, 6.5 mmol) with 8d (2.0 g, 6.5 mmol) for 1 min. produced 9d (1.76 g, 87.76 %). UV-Visible data $\rightarrow \lambda_{\text{max}}$ (log $\varepsilon_{\text{max}}$): 209 (3.44), 236 (2.76), 269 (3.02), 300 (2.94s), 335 (3.67). Infrared data: 3340 (N-H), 2931 (CH aliphatic), 1730 (C=O of ester), 1604 (C=C aromatic), 1575 (C=N), 1353 (C-O of ester), 755 (Ar-H).$^1$H-NMR (DMSO-$d_6$, 400 MHz) $\delta$: 8.64 (s, 1H, Het-H), 7.95-7.93 (d, $J = 8.48$ Hz, 1H, Ar-H), 7.77-7.74 (m, 1H, Ar-H), 7.60-7.58 (d, $J = 8.00$ Hz, 2H, Ar-H), 7.46-7.40 (m, 2H, Ar-H). Visible data $\rightarrow \lambda_{\text{max}}$: 209 (3.44), 236 (2.76), 269 (3.02), 300 (2.94s), 335 (3.67). NMR (DMSO-$d_6$, 100 MHz) $\delta$: 194.45 (C=O), 173.55 (C=O), 154.73, 151.60, 147.06, 143.86, 140.96, 138.59, 134.44, 134.41, 127.25, 124.86, 122.69, 118.20, 116.21, 113.49, 111.11, 58.57 (CHs), 46.31 (CH$_3$), 29.97 (CH$_3$) ppm.

2.2.3.5. Microwave assisted synthesis of 6-(4-(diethylamino)phenyl)-4-(2-oxo-2H-chromen-3-yl)-5,6-dihydropyrimidin-2(1H)-one, 9e. Treatment of urea (0.81 g, 13.0 mmol) with 8e (2.30 g, 13.0 mmol) for 2 min. produced 9e (1.61 g, 80.03 %). UV-Visible data $\rightarrow \lambda_{\text{max}}$ (log $\varepsilon_{\text{max}}$): 248 (2.92), 269 (3.04), 338 (3.94), 410 (2.64). Infrared data: 3340 (N-H), 2974 (CH aliphatic), 1746 (C=O of ester), 1600 (C=C aromatic), 1580 (C=N), 1353 (C-O of ester), 755 (Ar-H).$^1$H-NMR (DMSO-$d_6$, 400 MHz) $\delta$: 8.69 (s, 1H, Het-H), 7.95-7.93 (d, $J = 8.58$ Hz, 1H, Ar-H), 7.75-7.73 (m, 1H, Ar-H), 7.58-7.56 (d, $J = 8.00$ Hz, 2H, Ar-H), 7.46-7.42 (m, 2H, Ar-H). Visible data $\rightarrow \lambda_{\text{max}}$: 209 (3.44), 236 (2.76), 269 (3.02), 300 (2.94s), 335 (3.67). NMR (DMSO-$d_6$, 100 MHz) $\delta$: 195.38 (C=O), 173.53 (C=O), 157.96, 154.89, 151.99, 146.97, 142.93, 140.62, 138.25 (2 × CH), 131.01, 127.96, 122.17 (2 × CH), 118.53, 116.37, 109.86, 59.26 (CHs), 50.83 (2 × CH$_2$), 47.18 (CH$_3$), 19.46 (2 × CH$_3$) ppm.

3. RESULT AND DISCUSSION

3.1. Chemistry

From time immemorial, heterocyclic compounds have been involved in many importance processes valuable to man and his environment not only in drug design but in other areas of sustainable developmental applications such as material science, agrochemical, renewable energy, food, solar cell among others. Thus, this present study deals with the synthesis of coumarin-based 5,6-dihydropyrimidin-2(1H)-one derivatives for possible application in sustainable development. The first stage involved the piperidine-catalyzed microwave reaction of ethyl acetoacetate and salicylaldehyde for achieving 3-acetylcoumarin 7 in high yield (Scheme 1). The oxygen-containing heterocycle 7 was reacted with five different aromatic aldehydes according to our earlier established technique [10] under microwave irradiation to produce five corresponding chalcones 8a-e in very encouraging yields (Scheme 2). The precursor 8a-e were then used as reactive intermediates and reacted with urea under the influence of microwave heating to afford the targeted coumarin-based 5,6-dihydropyrimidin-2(1H)-one derivatives 9a-e as shown in Scheme 3. The physical properties and spectroscopic characteristic showed that the data obtained were in agreement with that expected for the proposed structure, hence, the synthesized compounds 9a-e which were the final products (targeted motifs) have been authenticated to be correct and novel. For the sake of brevity, compound 9a will be used as the representative of this class of targeted compounds 9a-e in this study. The compound 6-(3-ydroxyphenyl)-4-(2-oxo-2H-chromen-3-yl)-5,6-dihydropyrimidin-2(1H)-one 9a, also referred to as the
first member of the coumarin-based 5,6-dihydropyrimidin-2(1H)-one derivative, was achieved in 75.82% via microwave irradiation of an equimolar mixture of chalcone 8a and urea in ethanol for 1½ min. after purification by recrystallization (Table 1). Compound 9a was red crystalline heterocycle with a melting point of 95-96°C and had R_f of 0.62 in TLC using hexane: ethyl acetate (v/v→9:1) as eluting solvent.

Scheme 1: Synthetic route for the preparation of 3-acetylcoumarin, 7

Scheme 2: Synthetic path for the preparation of final products 9a-e

Furthermore, the structural elucidation of 9a was further supported using IR, UV and NMR spectral data (See Experimental). The uv-visible analysis revealed that 9a possessed three noticeable transitions and a shoulder at λ_max of 218 nm, 254 nm, 386 nm and 445 nm and log ε_max of 3.30, 3.32, 4.01 and 3.58 respectively (Fig. 1). This indicated that the peak at wavelength of 386 nm had the highest absorbance. The λ_max at 218 nm was as a result of π→π* depicting the presence of C=C. The λ_max at 254 nm was due to n→π* electronic transition peculiar to C=O from coumarin ring and C=N from pyrimidin-2(1H)-one nucleus. Other bathochromic shifts at λ_max 386 nm and 445 nm resulted from the combination of effect of extensive conjugation, lone pair availability and presence of auxochromes. The FT-IR analysis was run between 400 cm⁻¹ and 4000 cm⁻¹ (Fig. 2) The result of IR unveiled that the stretching absorption bands at 3436 cm⁻¹, 3339 cm⁻¹, 3030 cm⁻¹, 2950 cm⁻¹ which depicted the presence of N-H, O-H, CH aromatic and CH aliphatic functionalities respectively. This was in conformity with the recent report which stated the CH stretching vibration to between 2951 and 2920 cm⁻¹ [11]. Although, the C=O of ester absorbed at 1737 cm⁻¹ while that of amide appeared at 1674 cm⁻¹, but C=O was doubly confirmed by the appearance of C=O of its alkoxy at 1352 cm⁻¹. The C=N of pyrimidine was found at stretching frequency of 1553 which was confirmed by it bending
Table 1. Structures and the Physical Properties of the Synthesized Compound 9a-e

| Sample Code | R          | Product | Melting point (°C) | Yield (%) | Colour | R_f |
|-------------|------------|---------|-------------------|-----------|--------|-----|
| 9a          | 3-OH       | 9a      | 95-96             | 75.82     | Red    | 0.62|
| 9b          | 4-OH       | 9b      | 67-68             | 89.10     | Brown  | 0.60|
| 9c          | 3-OCH_3    | 9c      | 97-99             | 69.73     | Brown  | 0.74|
| 9d          | 4-OCH_3    | 9d      | 100-105           | 87.76     | Brown  | 0.71|
| 9e          | 4-N(CH_3)_2| 9e      | 94-96             | 80.25     | Red    | 0.70|

vibration frequency at 1229 cm\(^{-1}\). According to \(^1\)H-NMR analysis of 9a ran in DMSO-d_6, the most downfield signal was one proton doublet of NH at \(\delta_H\) 11.15-11.13 ppm followed by one proton singlet of OH at \(\delta_H\) of 8.88 ppm. All the aromatic protons were found at the expected region ranging from 8.61 ppm to 7.12-7.10 ppm. This was supported by the recent finding from El-Naggar and co-workers who reported that the aromatic protons resonated between 6.50 ppm to 8.50 ppm [12]. The CH and CH\(_2\) in pyrimidin-2(1H)-one were responsible for the two highly de-shielded signals at 3.36-3.31 ppm (multiplet) and 2.60-2.58 (doublet) respectively.
4. CONCLUSION
In conclusion, microwave-assisted approached was herein established as sustainable and eco-friendly approach for the preparation of coumarin-based 5,6-dihydropyrimidin-2(1H)-one derivatives 9a-e. The presence of NH and OH which are lone pair donors suggested that these compounds could be highly dependable in the design of corrosion inhibitors while extensive conjugation and high wavelength values in their uv spectral data confirmed some of these compounds to be good materials in dye application and sola cell sensitizing formulations.

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