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# Synthesis and Characterisation of Coumarin Analogues Using Palladium Catalyst and their Free Radical Scavenging Activity

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## Abstract

Coumarins are naturally and synthetically derived compounds containing oxygen. In this work, coumarin analogues were synthesised by Suzuki cross-coupling reaction using boronic acid in the presence of a palladium catalyst with a base. The synthesised compounds were screened for free radical scavenging activity by the DPPH method. The synthesised compound Ethyl 6-(4-fluorophenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate showed a better inhibition percentage than ethyl 6-(3,5-dimethylphenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate. The compound Ethyl 6-(4-fluorophenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate showed 80% inhibition while Ethyl 6-(3,5-dimethylphenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate showed 75% inhibition.

**Keywords:** Antioxidant Activity, Coumarin, Palladium Catalyst

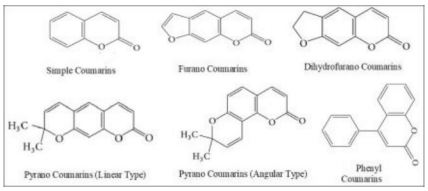
## 1.0 Introduction

Coumarins also known by the name 2H-Chromen-2-one are secondary metabolites with the molecular formula $C_9H_6O_2$. Coumarin has a sweet odour like the scent of vanilla. It occurs naturally as a constituent of the name coumarin originating from the French word "*Coumarou*" which means tonka beans plants and essential oils. It is a white or colourless crystalline and volatile compound. The molecular weight of coumarin is 146.15gmol[1]. It exists as glistening and colourless with a pleasant and characteristic odour. The melting point of coumarin is 68-70$^0$C andthe boiling point is 303$^0$C. Coumarin has an Ultra Violet (UV)-visible absorption maximum of 272nm in chloroform[1,2].

Due to their structural versatility and pharmacological properties, coumarins have been extensively used in biological food and pharmacological industries. Coumarins have been reported to possess antiviral, anticancer, antioxidant, anticoagulant and anti-inflammatory properties. Many coumarins containing parent moieties are used as Food and Drug Authority

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(FDA) approved drugs such as warfarin, dicumarol, phenprocoumon, acenocoumarol and clover leaf. Coumarin has been reported to exhibit antioxidant, analgesic, anti-inflammatory, and antimutagenic properties (Hoult and Paya, 1996). There are six basic groups of natural coumarins namely, simple coumarins, furan coumarins, pyrano coumarins (linear and angular type), dihydrofurano coumarins, phenyl coumarins and bicoumarins[3].




Here is a brief history of the synthesis of coumarin. In 1820, coumarin was first extracted from tonka beans by A. Vogel (German Chemist). It was mistaken for benzoic acid. In 1820, a French pharmacist named Jean Baptiste Gaston Guibourt independently isolated coumarin. He had mistaken coumarin for benzoic acid. In 1835 a French pharmacist A. Guillemette proved that Vogel and Guibourt had isolated the same substance. In the mid-19$^{th}$ century, W.H. Perkins first synthesised coumarin in his famous synthesis of vegetable perfume. Back in 1883, Hans Von Pechmann, a German chemist synthesised coumarins from their action phenols with a carboxylic acid or ester containing a β-carbonyl group. Perkin reaction, also known as the even reaction, Baylis-Hillman reaction, Wittig reaction and Michael addition reaction are different methods of synthesis of coumarin as indicated in Figure 1[3].

Antioxidants are found in foods commonly fruits and vegetables and can also be accessible in dietary supplements. In recent years, the research on antioxidants has grown because of their benefits in the prevention of diseases ultimately leading to the promotion of health. Many versions or models are being developed to study the mechanisms of action of antioxidants and also to identify new antioxidants from natural sources. Fruits, vegetables, spices, grains and herbs are the sources of almost all the natural antioxidants. They help in the protection of cellular damage from oxidative stress. The risk of diseases such as chronic disease has also been reduced. Positive features and statistics were reported for a sequence of these agents[4].

Coumarin has many pharmacological activities as shown in Figure 3. It can act as an anti-depressant, anti-HIV, anti-microbial, anti-cancer, anti-inflammatory, anti-coagulant, anti-convulsant and antioxidant. Because of all these, coumarins have a high pharmaceutical potential. Here, the focus will be given tothe antioxidant activity of coumarins. Coumarins being developed as an antioxidant have drawn attention in recent years. Coumarins allow the discovery of new antioxidants with truly novel mechanisms of action. Antioxidants can protect cellular organelles from the damage caused by free radical-induced oxidative stress. Free radicals and other reactive oxygen species are derived from normal essential metabolic processes in the human body or external sources. Most of the organic radicals have a short lifetime and are spontaneously dimerised. Free radicals are often derived from nitrogen, oxygen and sulphur-containing molecules in the biological system. These radicals are a part of groups of molecules known as Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS) and Reactive Sulphur Species (RSS). Antioxidants can be natural or man-made substances that help in the prevention or the delay of some types of cell damage.

Coumarin and its derivatives constitute one of the active classes of compounds possessing a wide range of

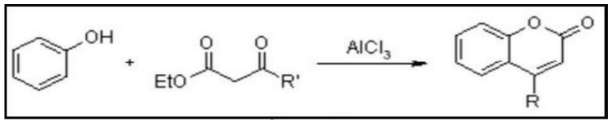



**Figure 1.** Pechmann reaction.

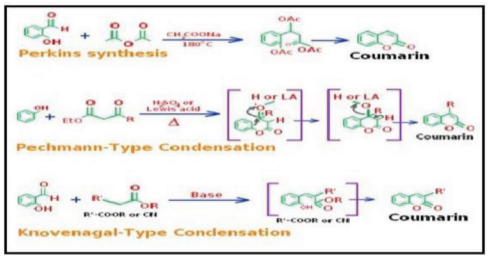



**Figure 2.** Types of synthesis of coumarin.

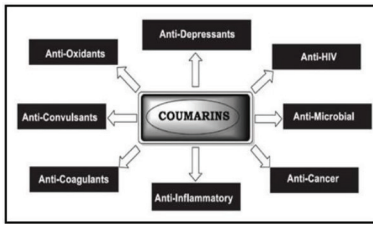



**Figure 3.** Various pharmacological properties of coumarin.

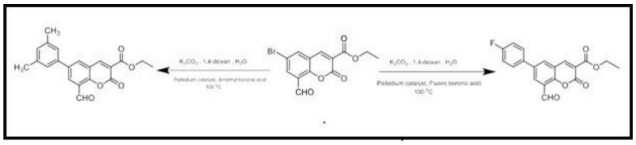
biological activities. The application of coumarin can be found in many fields. They are used as additives in food. It also has applications and benefits for industries such as the perfumery industry, cosmetic industry and pharmaceutical industry. It is used as an optical brightener. Coumarins have superthermal stability and outstanding optical properties including extended spectral response, superior photostability and higher quantum yields[4].

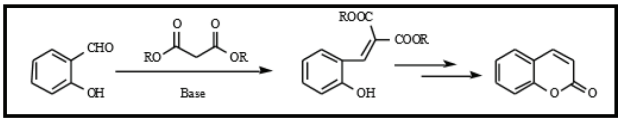
## 2.0 Materials and Methodology

### 2.1 Formylation of 4-Bromophenol

6 grams of 4-bromophenol was taken alongwith 102.04ml of Trifluoroacetic Acid (TFA) and was poured into the Round Bottom (RB) flask. It was allowed to cool down to room temperature. Now, the RB was kept in an ice bath and stirred continuously at about 400 rpm for 3 to 4 hours until there was a formation of crystals. After the formation of crystals, the stirring was stopped and kept for a few hours until there was the formation of plenty of crystals. The crystals were then filtered using Buchner filtration. The crystals were kept for drying after which they were ready for cyclisation[5].

#### *2.1.1 When Dimethyl Boronic Acid is Used as Reagent*






**Scheme 1:** Knoevenagel Reaction

### 2.2 Knoevenagel Reaction

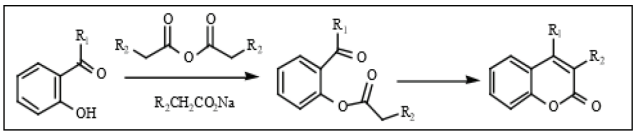
Knoevenagel is a reaction that occurs when aldehydes react with active methylene compounds in the presence of ammonia or amines. Under homogeneous conditions, the reaction is usually catalysed by weak bases or suitable combinations of amines and carboxylic or Lewis acids. Isofraxidin (7-hydroxy-6,8-dimethoxy coumarin), a well-known natural coumarin, was synthesised quickly using a syringaldehyde derivative and Meldrum's acid in the presence of ZnO, which promoted a Knoevenagel type reaction. The resulting 3-carboxylic acid coumarin was further decarboxylated with copper. Another process that yielded substituted 3-carboxy coumarins used a solid-phase method. Following thermal decarboxylation, these intermediates were used to make other coumarins. Meldrum's acid was also used in a solvent-free one-pot process to obtain 3-3-carboxy coumarins. When malonic acid and pyridine are combined, with or without traces of piperidine, the reaction is known as the Doebner modification[6].

### 2.3 Kostanecki-Robinson Reaction

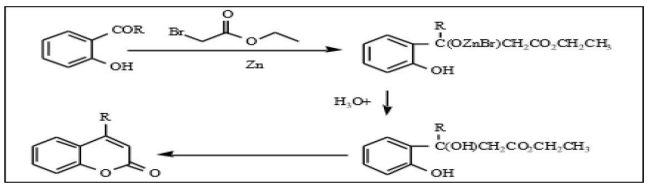
The formation of coumarins, usually 3- and 4-substituted coumarins, by this reaction, occurred by acylation of ortho–hydroxyaryl ketones with aliphatic acid anhydrides, followed by cyclisation (Figure 2 and Scheme 2)[6-9].

### 2.4 Reformatsky Reaction

This approach was used to synthesise 3-ureido derivatives of 4-phenyl coumarin by condensation of aldehydes or ketones with organozinc derivatives of -halo esters to generate -hydroxy esters. Condensation of the 2-hydroxy benzophenones with diethyl malonate in the presence of base is required for the synthesis of the intermediates for 3 coumarin carboxylates (piperidine or 1,8-diazabicyclo under-7-ene). Using Meldrum's acid and natural clays, high yields of carboxy coumarins were produced from the necessary acetophenones. By cathodic reduction of trichloroacetyl esters of ortho-hydroxyketones and salicylaldehydes in an aprotic medium, Batanero and Barba introduce the Reformatsky reaction, an original




**Scheme 2:** Kostanecki-Robinson Reaction

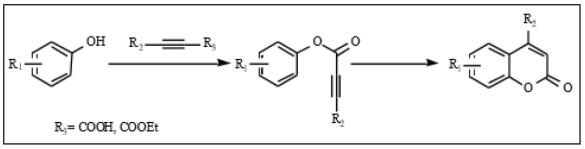



**Scheme 3:** Reformatsky Reaction

one-pot method of producing 3-chlorocoumarins and styrenes[9-13] (Scheme 3).

## 2.5 Miscellaneous

A stereo- and regioselective hydroarylation with palladium catalysed could also be used to synthesise coumarins. This reaction takes place between functionalised alkynes and aryl halides at room temperature, followed by a fast intramolecular reaction (Scheme 4)[13,14].




**Scheme 4:**

## 2.6 DPPH Free Radical Scavenging Method

For DPPH free radical scavenging method, 2mg of the Suzuki product is taken in a beaker. To this beaker, 20ml of methanol is added and shaken well. 10ml of this solution is poured into a test tube and another 10ml of methanol is added to this 10ml solution and shaken well. Now amounts of 2ml, 3ml and 4ml of this mixed solution are added to three different test tubes respectively. 3ml of DPPH solution is added to each of these three test tubes. The three test tubes are covered with aluminium foil. It is allowed to rest for 30 minutes for incubation. Characterisation is done by UV spectroscopy[15-17].

# 3.0 Results and Discussion

## 3.1 $^1$HNMR

All compounds which were synthesized and obtained in each of the objectives were characterized by Proton Nuclear Magnetic Resonance ($^1$HNMR) spectroscopy. The two coumarin derivatives which were synthesised were also screened for their free radical scavenging activity.

In the above $^1$HNMR results, two peaks were observed. The two peaks obtained are10.118δppm and 8.138δppm. The peak at 10.118 δppm corresponds to the aldehydic protons and the peak at 8.138 corresponds tothe phenylic protons. It is to be noted that both Carbon Hydrogen Oxygen (CHO) groups have similar environments and so they both correspond to a similar chemical shift value.

Four peaks are obtained in the above $^1$HNM result. The peak at 10.116δ ppm corresponds to aldehydic protons. The peak at 7 to 7.7 corresponds to the three coumarin protons.

4.100 and 4.092δ ppm corresponds to the methylene group ($CH_2$ group) while the peak at 1 to 1.206δ ppm corresponds to the methyl group ($CH_3$ group).

The peak at 10.116 δppm corresponds to the aldehydic proton, while the peak at 7.359 δppm corresponds to phenylic protons and the coumarin protons (3 protons) corresponds to 7.612 δppm. Peak at 4.295 δppm corresponds to the methylene ($CH_2$) group. 2.370 δ ppm corresponds to the methyl ($CH_3$) groups of the phenylboronic acid. 1.293 δ ppm corresponds to the methyl ($CH_3$) groups.

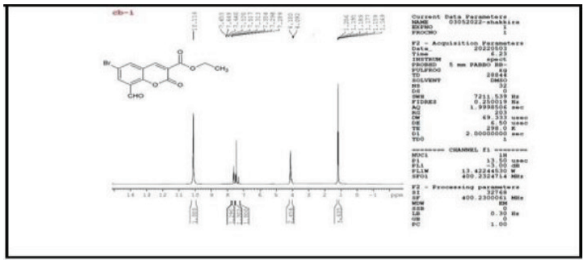


**Figure 5.** $^1$HNMR pattern of coumarin from formylated bromo phenol.
**IUPAC Name:** ethyl6-bromo-8-formyl-2-oxo-2Hchromene-3-carboxylate

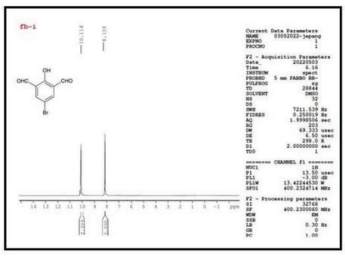


**Figure 4.** $^1$HNMR pattern of formylated bromophenol.
**IUPAC Name**: 5-bromo-2-hydroxyisophthalaldehyde

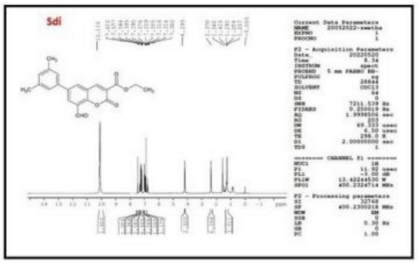


**Figure 6.** $^1$HNMR pattern of ethyl 6-(3,5-dimethyl phenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate.
**IUPAC NAME:** ethyl 6-(3,5-dimethylphenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate

10.116 $\delta$ppm corresponds to the aldehydic protons. 7.462 $\delta$ppm corresponds to the coumarin protons (3 protons). 4.197 $\delta$ppm corresponds to the methylene ($CH_2$) group and methyl groups correspond to 1.615 $\delta$ppm.

### 3.2 Free Radical Scavenging Activity by DPPH Method

Free radical scavenging activity was screened by the DPPH method. The two synthesized compounds displayed good percentage inhibition. Out of the two synthesised compounds fluorine substituted compound showed an inhibition percentage of 80% while dimethyl substituted compound showed 75% inhibition. This indicates that the fluorine-substituted compound (ethyl6-(4-fluorophenyl)-8-formyl-2-oxo-2H-chromene-3- carboxylate) showed better percentage inhibition than dimethyl substituted compound (ethyl6-(3,5-dimethylphenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate).

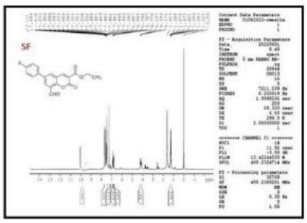


**Figure 7.** $^1$HNMR pattern of ethyl 6-(4-fluorophenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate.
**IUPAC NAME:** ethyl 6-(4-fluorophenyl)-8-formyl-2- oxo-2H-chromene-3-carboxylate

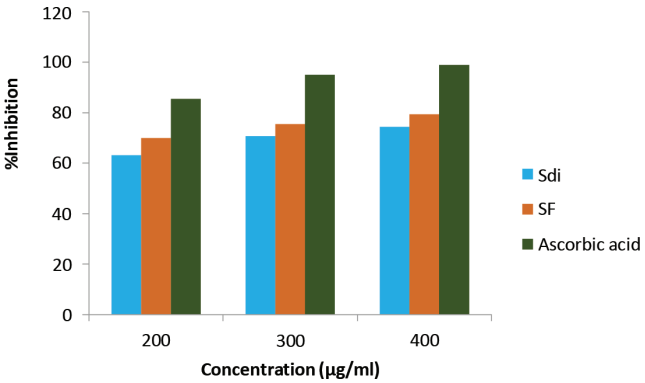



**Figure 8.** DPPH graph for ethyl 6-(3,5-dimethyl phenyl)-8-formyl-2-oxo-2H- chromene-3-carboxylate, ethyl 6- (4-fluorophenyl)-8-formyl-2-oxo-2H-chromene-3-carboxylate and ascorbic acid with different levels of concentration.

## 4.0 Conclusion

Coumarins have made a remarkable display of their importance in biological and pharmacological applications thus making researchers eager to find out more and discover more of its applications and capabilities. Coumarins are naturally derived and can also be synthetically derived. Their existence in nature has brought benefits in multiple fields. The applications of coumarin and its derivatives have been discussed in this work. The first procedure starts with the formulation of 4-bromophenol followed by cyclization of the formylated bromophenol and then a Suzuki cross-coupling reaction with a boronic acid and palladium catalyst in the presence of a base. While carrying out the reactions certain conditions have to be maintained to achieve the desired products. Fluoro boronic acid and dimethyl boronic acid were the two boronic acids used in the Suzuki cross-coupling reaction.

The synthesised compounds were confirmed by 1HNMR and screened for free radical scavenging activity by the DPPH method at 517nm. Among the two synthesised compounds, fluorine substituted compound showed a better percentage of inhibition than dimethyl substituted compound. Fluorine fluorine-substituted compound showed 80% DPPH inhibition compared to 75% inhibition of dimethyl substituted compound.

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