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DESIGN, SYNTHESIS AND EVALUATION OF COUMARIN DERIVATIVES

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ABSTRACT

Only a few of the many qualities that coumarin possesses include antibacterial, antiviral, antifungal, anti-inflammatory, anti-cancer, and antimalarial effects. In this class of chemical compounds, an aromatic ring and a pyrone nucleus are both present. The tonka bean (Dipteryx odorata Willd, Fabaceae), which provided coumarin prior to its isolation in 1820, is known by the colloquial name "coumarou," from whence the word "coumarin" is derived. It is referred to as coumarinor 2H- chromen-2-one and has the chemical formula C9H6O2. According to the definition, it has a benzene molecule as its molecule. The potential for their antibacterial action is being examined while several coumarin analogues are being synthesized as part of the current study. Currently, efforts are concentrated on developing and synthesizing coumarin derivatives, describing such derivatives, and determining the antibacterial efficacy of those compounds.

KEYWORDS: Coumarin , Antibacterial, Antimicrobial, Antioxidant

INTRODUCTION

The word "coumarin" comes from the word "coumarou," which is the common name for the tonka bean (Dipteryx odorata Willd, Fabaceae), which was the source of coumarin until it was isolated in 1820. The chemical molecule with the formula C9H6O2 is called coumarinor 2H-chromen-2-one. Its structure can be described as a benzene molecule with two adjacent hydrogen atoms primarily substituted by a lactone-like chain - (CH)=(CH)-(C=O)-O-, generating a second 6-membered heterocycle that typically shares two carbons with the benzene ring. It might be categorized as a lactone or a benzopyrone molecule. 1 The colorless, crystalline substance known as coumarin has a bitter taste and a sweet, vanilla-like scent. 2 It can also serve as a chemical defence against predators in a variety of

plants where it is found. An anticoagulant medicine called warfarin, which prevents the formation of blood clots, deep vein thrombosis, and pulmonary embolism, uses a similar chemical that inhibits the manufacture of vitamin K where it is present. The four primary subtypes of coumarin are as follows: [5-7]

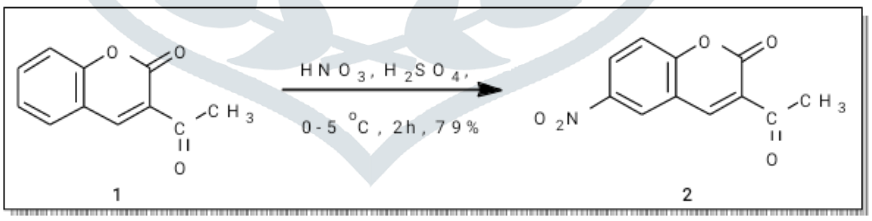
There are four types of coumarins: simple coumarins, furanocoumarins, pyranocoumarins, and coumarins replaced with pyrone. After being isolated for the first time in 1822, the Coumarins was first synthesized in 1868. Because they were believed to be category 1 hepatotoxin and carcinogens, the Food and Drug Administration outlawed them in the 1950s. This decision was based on animal testing. Till the subsequent animal data were obtained, nevertheless, this might need to be revised. A variety of coumarin compounds were thought to have anticoagulant, immune-stimulating, and tumor-suppressing properties. [8-19]

Material and Method

The ingredients used in this are 2-oxo-2H-1-benzopyran-3-carboxylic acid, sulfuric acid, tetrahydrofuran (THF), nitric acid, methanol, diethyl ether, dichloromethane, tri ethylamine, N, N-dimethyl formamide, hexanes, palladium on carbon (Pd/C), hydrochloric acid, sodium sulphate, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-\striazolo[4,5b] Hexafluorophosphate with pyridinium-3-oxide Azabenzotriazole Tetramethyl Uranium (HATU) compound's observed IR spectrum. Compounds are recorded and analysed using 1H NMR. The Agar diffusion method has been used to assess manufactured substances. Agar cup, paper disc, and agar ditch methods are the three different forms of agar diffusion techniques. Agar cup technique was employed in the current study. As a standard, tobramycin was employed. [20-24]

1 Series 1: 3-acetyl-6-(substituted amino)-2H-chromen-2-one derivatives

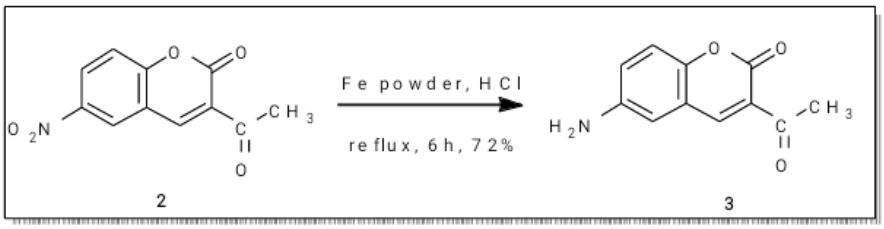
Step- 1



3-Acetyl-6-nitro-2H-chromen-2-one (2) Synthesis: 15 minutes at 0 oC were spent stirring a solution of concentrated sulfuric acid (1.10 ml) and 3-acetyl coumarin (1.188 gm, 1 mmole). Then, 0.06 ml (d 1.4) of concentrated nitric acid and 0.20 ml (98%) of sulphuric acid were added. During the addition process, the temperature was kept between 0 and 5 oC. After that, the mixture was constantly stirred for 2 hours at the same temperature. Then, a conical flask containing 25 ml of ice water was filled with the mixture. The chemical 3-acetyl-6-nitro-2H-chromen-2-one 2 (yield 79%) was isolated after a solid precipitated out of the water layer, was filtered, dried, and refined using silica gel column chromatography (petroleum ether/benzene 1:1 v/v).[25]

1H NMR (400 MHz, DMSO-d6) : δ 2.45 (3H, s), 7.44 (1H, dd, J = 7.9, 0.4 Hz), 8.51 (1H, dd, J = 7.9, 1.9 Hz),8.78 (1H, s), 8.84 (1H, dd, J = 1.9, 0.4 Hz). MS (ESI) calcd for C18H13NO4 [M+1]+ 308.08, obtained m/z 308.10

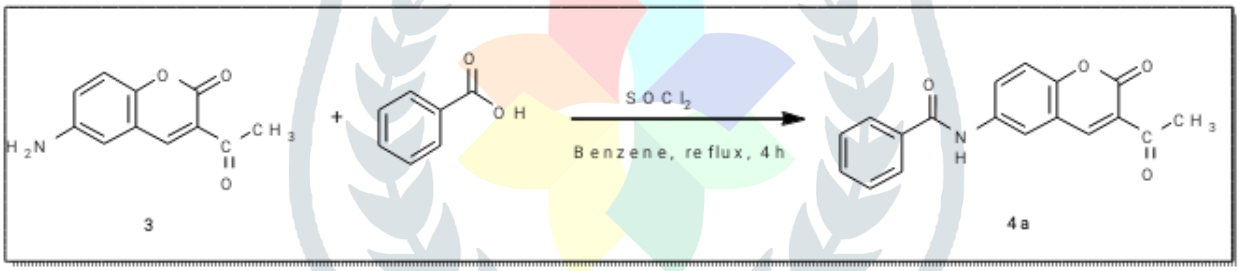
Step-2



3-Acetyl-6-amino-2H-chromen-2-one (3) Synthesis: Compound 2 3-acetyl-6-nitro-2H- chromen-2-one (0.233 g, 1 mmol, 3.14 gm, 0.01 mole), iron powder (0.296 g), strong hydrochloric acid (1.11 ml), and ethanol (10 ml) were combined and refluxed for six hours. Cool the reaction mixture after which the precipitate was filtered off, thoroughly wet, and dried. By recrystallizing the crude product with ethanol, the chemical 3-acetyl-6-amino-2H-chromen-2-one 3 was produced, yielding a 72% purity rate.[26]

1H NMR: 2.44 (3H, s), 6.77 (1H, dd, J = 8.5, 1.7 Hz), 7.20 (1H, dd, J = 8.5, 0.5 Hz), 7.51 (1H, dd, J = 1.7, 0.5 Hz), 8.65 (1H, s). MS (ESI) calculated for C11H9NO3 [M+1]+ 226.04 and Obtained m/z 226.17.

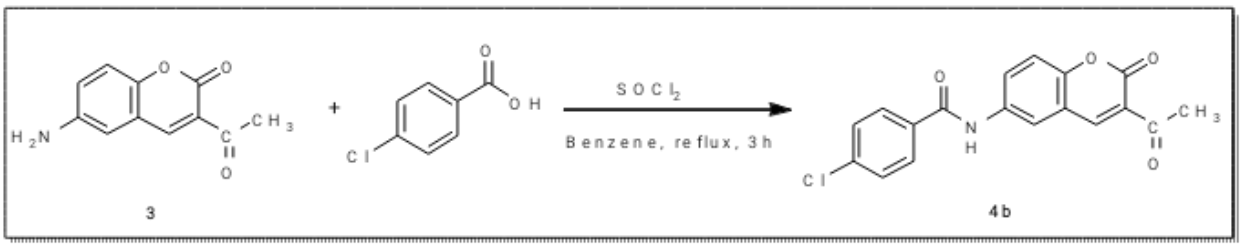
Step- 3 Synthesis of Coumarin derivatives through the various benzoic acids Synthesis of Compound- 4a



Synthesis of N-(3-acetyl-2-oxo-2H-chromen-6-yl)benzamide (4a): To a mixture of 3-acetyl-6- aminocoumarin (0.203 g, 1 mmol) and benzoic acid (0.122 g, 1 mmol) was added thionyl chloride (0.141 g, 1.2 mmol, 1.2 equiv) and benzene (1.5 ml) and refluxed for 2 hr. Then the mixture was poured into a conical flask contained 25 ml of an ice water. Solid precipitated out of the water layer, filtered and dissolved in 1.25 ml of 2N sodium hydroxide solution and filtered again. The solution was acidified with 2N hydrochloric acid, filtered by Buchner funnel and washed with a copious amount of cold water and concentrated in vacuo to give the crude product which was purified by re-crystallization from ethanol and gave compound N-(3-acetyl-2-oxo-2H-chromen-6-yl)benzamide (4a) (yield 65%).[27-32]

3314(N-H str), 3082 (C-H str), 3056(aromatic C-H str), 1744 (lactone ester), 1693 (CONH amide), 1680 (C=O str), 1537 (C=C aromatic), 1424 (C-O-C str). 1H NMR: δ 2.51 (3H, s), 8.32-8.49 (2H, 7.46 (dd, J = 8.6, 1.5 Hz), 7.43 (dd, J = 8.6, 0.5 Hz)), 7.53-7.63 (3H, m), 7.58 (dd, J = 8.5, 7.5 Hz)), 7.64 (1H, dd, J = 1.5,0.5 Hz), 8.00 (2H, dd, J = 8.5, 1.9 Hz), 8.71 (1H, s). MS (ESI) calcd for C18H13NO4 [M+Na]+ 330.07, found m/z 330.18.

Synthesis of Compound- 4b



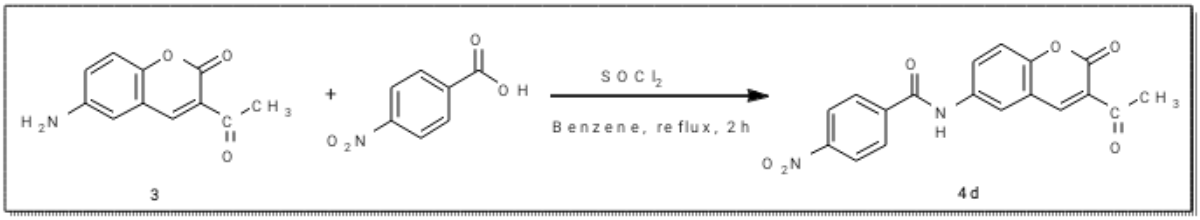
N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-chlorobenzamide (4b) synthesis: Benzene (1.5 ml) and thionyl chloride (0.141 g, 1.2 mmol, 1.2 equiv) were added to a combination containing 3-acetyl-6-amino coumarin (0.203 g, 1 mmol) and 4-chlorobenzoic acid (0.156 g, 1 mmol), and the mixture was refluxed for two hours. The mixture was then added to a conical flask that held 25 ml of ice water. Solid separated from the water layer and was filtered before being dissolved in 1.25 ml of 2N sodium hydroxide solution and filtered once more. The solution was treated with 2N hydrochloric acid, filtered using a Buchner funnel, thoroughly washed with cold water, and concentrated in vacuum to produce the crude product, which was then cleaned up by re-crystallizing ethanol to produce the compound N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-chlorobenzamide (4b), which had a yield of 68%.[33-35]

A lactone ester is a compound with the following formula: 3320(N-H str), 3050(C-H str), 3067(aromatic C-H str), 1766(lactone ester), 1681(CONH amide), 1686(C=O str), 1528(C=C aromatic), 1421(C-O-C str), 800. (C-Cl). 1H NMR: 2.54 (3 H, s), 8.63 (2 H, s), 7.43 (dd, J = 8.6, 0.5 Hz), 7.53 (2 H, dd, J = 8.7, 1.4 Hz), 7.64 (1 H, dd, J = 1.5, 0.5 Hz), 7.75 (2 H, dd, J = 8.7, 1.8 Hz), and 8.71 (1H, s). For C18H12ClNO4 [M+Na]+ 364.03, found m/z 364.19 using MS (ESI) calculation.

Synthesis of Compound-4c

N- (3-acetyl-2-oxo-2H-chromen-6-yl) -4-fluorobenzamide (4c) Synthesis: Benzene (1.5 ml) and thionyl chloride (0.141 g, 1.2 mmol, 1.2 equiv) were added to a mixture of 3-acetyl-6- aminocoumarin (0.203 g, 1 mmol) and 4-fluorobenzoic acid (0.140 g, 1 mmol) and refluxed for two hours. The mixture was then poured into a conical flask that held 25 ml of ice water. Out of the water, a solid precipitated layer, filtered, then dissolved in 1.25 ml of 2N sodium hydroxide solution and filtered once more.[36-38] The solution was treated with 2N hydrochloric acid, filtered using a Buchner funnel, thoroughly washed with cold water, and concentrated in vacuum to produce the crude product, which was then purified by re-crystallization from ethanol to produce the compound N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-fluorobenzamide (4c) (yield 71%). 3330 (N-H str), 3056 (C-H str), 3047 (aromatic C-H str), 1746 (lactone ester), 1689 (CONH amide), 1680 (C=O str), 1538 (C=C aromatic), 1429 (C-O-C str), and 1155 (lactone ester) (C-F). 1H NMR: 2.16 (3H, s), 7.67–7.70 (4H, 7.46 (dd, J = 8.6, 1.5 Hz), 7.47 (dd, J = 8.7, 1.1 Hz), 7.43 (dd, J = 8.6, 0.5 Hz), 7.64 (1H, dd, J = 1.5, 0.5 Hz), 7.90 (2H, dd, J = 8.7, 1.8 Hz), and 8.71 (1H, s). MS (ESI) calculated for C18H12FNO4 [M+Na]+ 348.22, finding m/z 348.22.

Compound-4d Synthesis



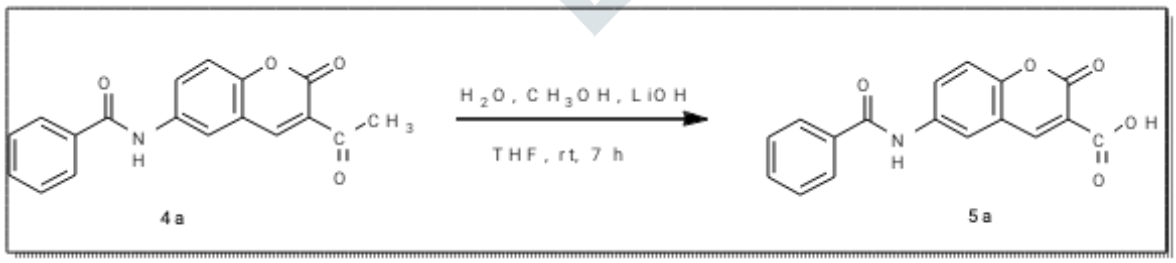
The synthesis of N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-nitrobenzamide (4d): 3-acetyl-6- aminocoumarin (0.203 g, 1 mmol), 4-nitrobenzoic acid (0.167 g, 1 mmol), thionyl chloride (0.141 g, 1.2 mmol, 1.2 equiv), and benzene (1.5 ml) were added to the mixture and refluxed for two hours. The mixture was then added to a conical flask that held 25 ml of ice water. Solid separated from the water layer and was filtered before being dissolved in 1.25 ml of 2N sodium hydroxide solution and filtered once more. The mixture was treated with 2N hydrochloric acid, filtered using a Buchner funnel, thoroughly washed with cold water, and concentrated in vacuum to produce the crude product, which was then cleaned up using re-crystallization of ethanol to produce the compound N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-nitrobenzamide (4d) (yield 66%).[39]

In addition to the following numbers: 3342 (N-H str), 3060 (C-H str), 3052 (aromatic C-H str), 1748 (lactone ester), 1692 (CONH amide), 1689 (C=O str), 1530 (C=C aromatic), 1516 (NO2), 1436 (C-O-C str), and 1355. (NO2). 2.46 (3H, s), 8.30–8.19 (2H, 7.46 (dd, J = 8.6, 1.5 Hz), 7.43 (dd, J = 8.6, 0.5 Hz), 7.64 (1H, dd, J = 1.5, 0.5 Hz), 7.89 (2H, dd, J = 8.6, 1.4 Hz), 8.14 (2H, dd, J = 8.6, 1.8 Hz), and 8.71 (1H, s). For C18H12N2O6 [M+Na]+ 375.05, MS (ESI) calculated, m/z 375.23 was obtained.

Synthesis Compound- 4e

Series 2: Hydrolysis of 4 derivatives of compounds

Compound-5a's Synthesis

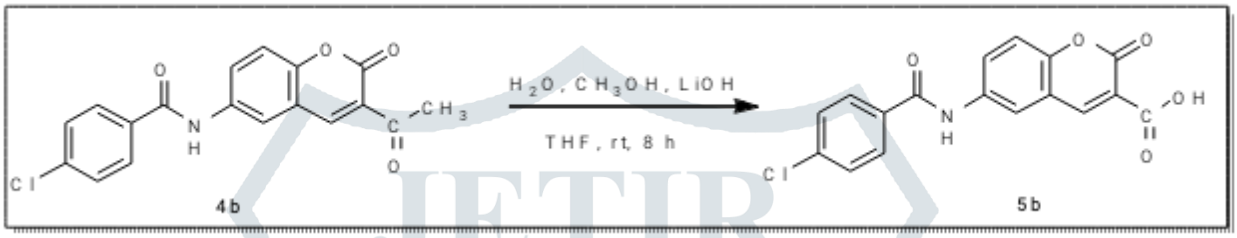


6-Benzamido-2-oxo-2H-chromene-3-carboxylic acid (5a) synthesis: The previously created N-(3-acetyl-2-oxo-2H-chromen-6-yl)benzamide (4a) molecule was combined with mixes of water, methanol, and THF (1.5 ml), then LiOH monohydrate (1.13 g, 3.69 mmol) was added, and the reaction mixture was agitated at room temperature for 6 hours. After the reaction mass had gone through all of the starting components, it was extracted with ethyl acetate after being acidified with 3M HCl solution until a pH of 2.0 was attained. Using silica gel chromatography (hexane: ethylacetate

8:2 v/v), the crude product, 6-benzamido-2-oxo-2H-chromene-3-carboxylic acid (5a) (yield 58%), was refined from the organic layer that had been dried over sodium sulphate and distilled off under vacuum.[40-41]

3314 (N-H str), 3056 (aromatic C-H str), 2841 (carboxylic acid OH str), 1744 (lactone ester), 1693 (CONH amide), 1537 (C=C aromatic), and 1424 (lactone ester) are some of the other structural elements (C-O-C str).1H NMR: 7.40–7.48 (2H, 8.10(dd, J = 8.6, 1.5 Hz), 7.42 (dd, J = 8.6, 0.5 Hz), 7.53–7.63 (3H, m), 7.58(dd, J = 8.5, 7.5 Hz), 7.64(1H, dd, J = 1.5, 0.5 Hz), 8.00(2H, dd, J = 8.5, 1.9 Hz), and 8.81 (1H, s). MS (ESI) calculated for C17H11NO5 [M+1]+ 310.07 and discovered m/z 310.18

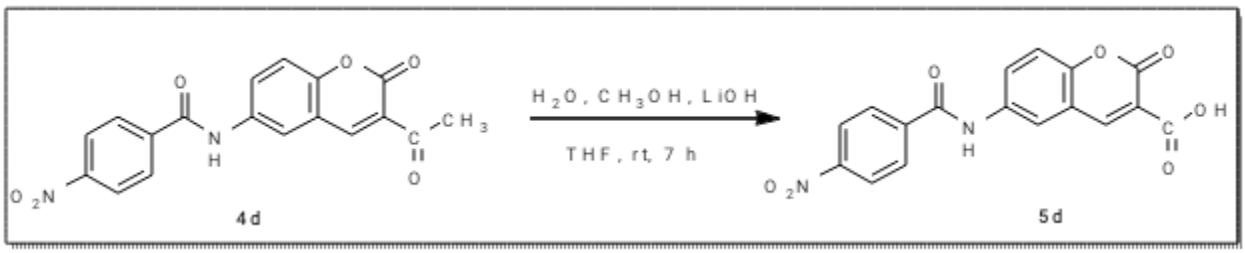
Compound-5b's synthesis



Synthesis of 6- (4-chlorobenzamido)2-Oxo-2H-Chromene-3-Carboxylic Acid (5b): N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-chlorobenzamide (4b), which had previously been created, was combined with mixes of water, methanol, and THF. LiOH monohydrate (1.26 g, 3.69 mmol) was then added, and the reaction mixture was agitated at room temperature for six hours. When all of the initial ingredients had been used, the reaction mass was extracted with ethyl acetate after being acidified with 3M HCl solution until a pH of 2.0 was attained. The organic layer was dried over sodium sulphate and vacuum-distilled to obtain the crude product, which was then refined using silica gel chromatography (hexane: ethylacetate 8:2 v/v) to produce compound 6-(4-chlorobenzamido)-2-oxo-2H-chromene-3-carboxylic acid (5b) (yield 56%).[42]

3391 (Amide-NH), 3055 (Aromatic-CH), 2596 (Carboxylic acid-OH), 1760 (lactone ester), 1669 (Amide CO), 1618 (Amide-NH), 1573 (Aromatic C-C), and 800 (C-Cl). 1H NMR: 8.40-8.48 (2H, 7.45 (dd, J = 8.6, 1.5 Hz), 7.42 (dd, J = 8.6, 0.5 Hz), 7.53 (2H, dd, J = 8.7, 1.4 Hz), 7.64 (1H, dd, J = 1.5, 0.5 Hz), 7.71 (2H, dd, J = 8.7, 1.8 Hz), and 8.81 (1H, s). MS (ESI) calculated for wes C17H10ClNO5 [M+1]+ 344.03 and discovered m/z 344.22

Compound- 5C Synthesis



Synthesis of 6- (4-nitrobenzamido)-2-oxo-2H-chromene-3-carboxylic acid (5C): N-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-nitrobenzamide (4d), a previously synthesised compound, was combined with mixes of water, methanol, and THF. LiOH monohydrate (1.30 g, 3.69 mmol) was then added, and the reaction mixture was agitated at room

temperature for six hours. When all of the initial ingredients had been used, the reaction mass was extracted with ethyl acetate after being acidified with 3M HCl solution until a pH of 2.0 was attained. The organic layer was dried over sodium sulphate and vacuum-distilled to obtain the crude product, which was then refined using silica gel chromatography (hexane: ethylacetate 8:2 v/v) to produce compound 6-(4-nitrobenzamido)-2-oxo-2H-chromene-3-carboxylic acid (5C) (yield: 57%).[43]

3390 (Amide-NH), 3058 (Aromatic-CH), 2591 (Carboxylic acid-OH), 1756 (lactone ester), 1678 (Amide CO), 1631 (Amide-NH), 1561 (Aromatic C-C), 1520 (NO2), and 1361 (nitrogen dioxide) (NO2). 1H NMR: 7.40-7.49 (2H, dd, J = 8.6, 1.4 Hz), 7.43 (dd, J = 8.6, 0.5 Hz), 7.64 (1H, dd, J = 1.4, 0.5 Hz), 7.89 (2H, dd, J = 8.6, 1.4 Hz), 8.14 (2H, dd, J = 8.6, 1.8 Hz), and 8.81 (1H, s). MS (ESI) calculated for C17H10N2O7 [M+1]+ 355.05 and discovered m/z 355.34

Antimicrobial Evaluation

For an in-vitro investigation, the following microorganisms were chosen.

1).Gram-positive organisms include Staphylococcus aureus ATCC 25923 and Bacillus subtilis ATCC 14579.

2).Pseudomonas aeruginosa ATCC 27853 and Escherichia coli ATCC 25922 are gram-negative bacteria. preparation of the culture media.

Peptone, NaCl, Meat Extracts, and Agar are all used to produce the culture medium (2.0 gm). The medium's pH was adjusted to 7.6 after all ingredients, with the exception of agar, were dissolved in distilled water (100 ml). Agar was then added to the medium and distributed in 25 ml portions in several test tubes. The test tubes were sealed with cotton wool and sterilised for 20 minutes at 121.5°C.Testing for antibacterial susceptibility: Nutrient agar broth was inoculated with 0.5 ml of culture medium that had been sitting for 24 hours. The mixture was shaken thoroughly before being poured onto the sterile Petri dish (25 ml each). After letting the liquid set for a while, the "cups" were created by using a sterile cup borer to punch holes into the agar's surface. A previously sterilised micropipette was used to inject the test solution to these "cups." It was noted that the plates. At a concentration of 1000 ppm, all synthetic compounds' antibacterial activity was examined in vitro and measured in percentages (%) of inhibition, as shown in Tables 1 and 2.[44-45]

After five days, the above formula was used to calculate the % inhibition for bacteria.

Where ,

X = Colony area on control plate. Y = Test plate colony area.

Tables 6 and 7 include percentage (%) data that are displayed as follows:

- (+): Slightly active, small cleaning zone (50%)
- (++) Indicates Moderately active, medium clearing zone (51–55% of the sky is clear),

- (+++) Indicates A sizable clearing zone (56–60%), a lot of activity, and
- Very high activity and a very sizable clearance zone (>60%)

Table 6: Antibacterial activity of compounds (4a-e)

Compounds (4a-e)	% Zone of Inhibition			
	Gram +Ve		Gram –Ve	
	Bacillus Subtilis	Staphylococcus Aureus	Pseudomonas aeruginosa	E-Coli
4a	+	++	+	++
4b	++	+	++	++
4c	+++	+	+++	++
4d	++	+++	++	+++
4e	++	++	++	++
Tobramycin	++++	+++	++++	++++

Table 7: Antibacterial activity of compounds (5a-c)

Compounds (5a-e)	% Zone of Inhibition			
	Gram +Ve		Gram –Ve	
	Bacillus subtilis	Staphylococcus Aureus	Pseudomonas aeruginosa	E-Coli
5a	++	++	++	++
5b	+	+	++	++
5c	++++	+++	++++	+++
Tobramycin	++++	+++	++++	++++

The Synthesized compounds that have been tested for antibacterial activity display a percentage (%) of the zone where bacterial growth of both Gram-positive and Gram-negative bacteria is inhibited. Four compounds from Series 1 (4a-e) and two from Series 2 (5a-b) were evaluated for antibacterial activity against the bacterial strains B. subtilis and S. aureus, which are Gram-positive, and P. aeruginosa and E. coli, which are Gram-negative.[46]

A promising action against the bacterial strains S. aureus and E. coli was discovered in Series 1 Compound 4d. B. subtilis and P. aeruginosa bacterial strains were discovered to have promising action against chemical 5c in Series 2.[47-48]

CONCLUSION:

The compound six (4-nitrobenzamido) 2 Oxo-2H Chromene-3 Carboxylic Acid, N- (3-acetyl-2-oxo-2H- chromen-6-yl)There is a need for more investigation because -4-nitrobenzamide exhibits the highest antibacterial activity.identify the molecular mechanism.

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