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Application of Suzuki Coupling in the Synthesis of Some Novel Coumarin Derivatives as Potent Antibacterial Agents

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ABSTRACT

In this paper, we report the synthesis of some novel coumarin derivatives by Palladium catalyzed Suzuki cross-coupling and evaluation of their antibacterial potency. Most of the compounds exhibited exceptional antibacterial activity as compared with the respective standard, Ciprofloxacin.

Keywords: Coumarin, Suzuki coupling, Antibacterial activity

INTRODUCTION

Bacterial infections are an increasing problem in present-day medicine, yet only a few antibacterial agents are used in clinical practice. Even though a lot of drugs as potent antibacterial agents have been identified and developed hitherto, the increase of resistance among microorganisms or the development of multi drug resistance in pathogens still persist as a major challenge [1,2]. Therefore, there is a significant need for the development of new and definite antibacterial agents for defying this hazard [3].

Coumarins are an essential class of benzopyrones found in green plants and display a large spectrum of pharmacological properties [4-6]. Coumarins are broadly reported to be potent as antibacterial [7], antiinflammatory [8] and antiviral agents [9,10]. The coumarin if is present as a core moiety within the chemical structure of various pharmaceutical drugs such as warfarin and acenocoumarol and in antibiotics such as novobiocin, clorobiocin and coumermycin A1 [11,12]. Owing to these remarkable applications and the versatility in its synthesis, the investigation of natural or synthetic coumarin derivatives has attracted chemists for decades.

The Suzuki–Miyaura cross-coupling reaction between organoboranes and organic halides or pseudohalides has materialized as one of the foremost methods for the creation of carbon–carbon bonds [13]. The reaction offers an efficient pathway to a range of pharmaceuticals, herbicides, and liquid crystalline materials [14]. The prominent features of these reactions are the availability, stability and non-toxicity of a variety of boronic acids and extensive functional group tolerance [15]. These features clearly reveal its importance in synthetic chemistry and hence this reaction has found extensive use in Pharma industries. Although the Suzuki cross-coupling of bromomethyl coumarins at 4^{th} position has been reported by Shah et al., the examples with heterocyclic boronic acids as substrates are still less and challenging [16]. In view of these varied applications of coumarins, we were interested in the synthesis of a series of novel coumarin derivatives coupled with different heterocycles of substantial pharmacological importance. In this paper, we report the synthesis and antibacterial evaluation of some novel coumarin derivatives.

MATERIALS AND METHODS

All solvents and reagents were obtained from commercial suppliers and used without any further purification unless otherwise noted. Analytical TLC was performed on pre-coated aluminum sheets of silica ($60F_{254}$ nm) and visualized by short-wave UV light at λ=254. Melting points were determined on an EZ-Melt automated melting point apparatus. ^{1}H-NMR spectra were recorded at 400 MHz using an internal deuterium lock. Chemical shifts were measured in δ (ppm). Data is presented as follows: chemical shift, multiplicity, coupling constant (*J*) in Hz, and integration. The following abbreviations are used for the splitting patterns: s for singlet, d for doublet, t for triplet, m for multiplet and br for broad. ^{13}C-NMR spectra were recorded at 100 MHz using an internal deuterium lock.

Procedure for the synthesis of 4-methyl coumarin intermediate (2)

To the weighed quantity of phenol (1 equiv.) and ethyl acetoacetate (1.1 equiv.), the ionic liquid [bmim] $Cl{\cdot}2AlCl_3$ (1.1 equiv.) was added and the reaction mixture was stirred at 30°C for 20 min. All additions were carried out in an inert atmosphere. The reaction was quenched by adding

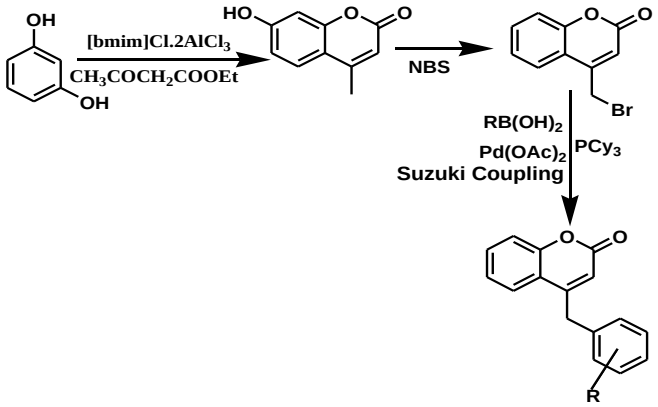
6 M HCl in cold conditions. The resultant product was filtered and further purified by column chromatography to obtain the titled compound 2 as off white solid in 88% yield. mp: 70-72°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.49, d, *J*=1.68 Hz, 3H, CH_3; δ=6.1, s, 1H, ArH; δ=6.69, d, *J*=2.32 Hz, 1H, ArH; δ=6.77-6.80, dd, J_1=2.24 Hz, J_2=8.6 Hz, 1H, ArH; δ=7.57, d, *J*=8.68 Hz, 1H, ArH; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=18.67, CH_3; δ=103.07, δ=110.81, δ=112.6, δ=113.24, δ=125.75, δ=153.22, δ=155.24, δ=161.32; HRMS: 199.0371 (M+Na).

Procedure of bromination reaction for the synthesis of intermediate (3)

The synthesis of intermediate 3 was carried out by the procedure previously reported by Belluti et al [17].

General procedure for the synthesis of compounds (4a-j)

To the weighed quantity of intermediate 3 (1 equiv.) in Dimethyl Formamide (DMF), were added boronic acid (1.2 equiv.), Pd $(OAc)_2$ (0.1 equiv.), PCy_3 (0.2 equiv.) and cesium carbonate (2 equiv.) and the reaction mixture was heated for 10 h. at 100°C. The reaction mixture was filtered through celite and distilled in reduced pressure to obtain the crude product. The crude product was further purified by column chromatography and eluted in varying polarities to obtain the titled compounds (4a-j).



Scheme 1: Synthesis of various coumarins

4-((Pyridin-4-yl)methyl)-2H-chromen-2-one (4a): Brown solid. m.p: 168-170°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.47, (s, 2H, CH_2), 6.28, (d, *J*=1.16 Hz, 1H, ArH), 7.43-7.53, (m, 4H, ArH), 7.60-7.64, (d, *J*=7.28 Hz, 2H, ArH), 8.85, (d, *J*=7.28 Hz, 2H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$), δ=18.64, 115.21, 115.28, 119.59, 122.89, 123.82, 125.39, 128.47, 128.58, 131.96, 131.99, 132.09, 134.47, 134.73, 141.35, 148.18, 149.49, 151.99, 153.96, 160.56, CO; HRMS: 260.0687 (M+Na).

4-((Pyridin-3-yl)methyl)-2H-chromen-2-one(4b): Light brown solid. m.p: 167-169°C; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=2.45, (s, 2H, CH_2), 6.29, (d, *J*=1.12 Hz, 1H, ArH), 7.40-7.52, (m, 3H, ArH), 7.61-7.69, (m, 2H, ArH), 7.88-7.91, (m, 1H, ArH), 8.62-8.63, (dd, J_1=1.16 Hz, J_2=4.64 Hz, 1H, ArH), 8.85, (d, *J*=1.80 Hz, 1H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$), δ=18.61, 115.19, 115.27, 119.57, 122.88, 123.80, 125.38, 128.43, 128.55, 131.95, 131.98, 132.08, 134.46, 134.70, 141.31, 148.14, 149.47, 151.98, 153.93, 160.52, CO; HRMS: 260.0687 (M+Na).

4-((Furan-2-yl)methyl)-2H-chromen-2-one (4c): Brown solid. m.p: 155-157°C;^{1}H-NMR (400 MHz, $CDCl_3$), δ=2.42, (s, 2H, CH_2), 6.23, (s, 1H, ArH), 6.51-6.52, (m, 1H, ArH), 6.79, (d, *J*=3.32 Hz, 1H, ArH), 7.52-7.56, (m, 5H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.56, 107.74, 111.46, 112.15, 114.47, 118.77, 119.57, 124.97, 125.51, 133.98, 143.43, 152.07, 152.10, 153.98, 160.85, CO; HRMS: 249.0528 (M+Na).

4-((Thiophen-2-yl)methyl)-2H-chromen-2-one(4d): Black solid. mp: 193-195°C; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=2.43, (s, 2H, CH_2), 6.25, (s, 1H, ArH), 6.52-6.56, (m, 1H, ArH), 6.80, (d, *J*=4.08 Hz, 1H, ArH), 7.54-7.58, (m, 5H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.64, 107.86, 111.58, 112.22, 114.67, 118.92, 119.62, 124.99, 125.58, 133.99, 143.47, 152.27, 152.18, 153.99, 160.89, CO; HRMS: 265.0299 (M+Na).

4-((Pyrimidin-2-yl)methyl)-2H-chromen-2-one (4e): Yellow solid. mp: 189-191°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.49, (s, 2H, CH_2), 6.30, (d, *J*=1.16 Hz, 1H, ArH), 7.41-7.49, (m, 3H, ArH), 7.57-7.61, (m, 2H, ArH), 8.89, (d, *J*=6.80 Hz, 2H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.62, 115.24, 115.29, 119.55, 122.86, 123.84, 125.35, 128.44, 128.56, 131.93, 131.95, 132.06, 134.46, 134.71, 141.33, 149.42, 153.91, 160.59, CO, δ=169.82; HRMS: 261.064 (M+Na).

4-((2-Methylpyridin-4-yl)methyl)-2H-chromen-2-one (4f): White solid. mp: 210-212°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.49 (s, 2H, CH_2), 2.66 (s, 3H, CH_3), 6.35 (s, 1H, ArH), 7.34 (d, *J*=4.12 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.55-7.58, (m, 2H, ArH), 7.64-7.70, (m, 2H, ArH), 8.60, (d, *J*=4.68 Hz, 1H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.62, 24.56, 115.35, 115.62, 122.81, 125.28, 128.43, 128.55, 131.95, 132.03, 132.12, 149.86, 160.68, CO; HRMS: 274.0844 (M+Na).

4-((5-Chloropyridin-3-yl)methyl)-2H-chromen-2-one (4g): Light brown solid. mp: 203-205°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.49, (s, 2H, CH_2), 6.36, (d, *J*=1.24 Hz, 1H, ArH), 7.50-7.54, (m, 2H, ArH), 7.72, (d, *J*=8.08 Hz, 1H, ArH) 7.92-8.16, (m, 2H, ArH), 8.62, (d, *J*=2.28 Hz, 1H, ArH) 8.76, (d, *J*=1.92 Hz, 1H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): 18.61, 115.42, 115.64, 122.96, 123.17, 125.57, 134.28, 136.23, 139.07, 145.82, 148.19, 160.70, CO; HRMS: 274.0844; HRMS: 294.0298 (M+Na).

4-((Pyridin-2-yl)methyl)-2H-chromen-2-one (4h): White solid. mp: 146-148°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.49, (s, 2H, CH_2), 6.26, (d, *J*=1.24 Hz, 1H, ArH), 7.44-7.52, (m, 3H, ArH), 7.63-7.67, (m, 2H, ArH), 7.84-7.87, (m, 1H, ArH), 8.64-8.68, (dd, J_1=2.24 Hz, J_2=6.48 Hz, 1H, ArH), 8.89, (d, *J*=3.16 Hz, 1H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.62, 115.20, 115.25, 119.56, 122.87, 123.81, 125.36, 128.43, 128.54, 131.92, 131.94, 132.06, 134.41, 134.70, 141.33, 148.16, 149.45, 151.96, 153.92, 160.51, CO; HRMS: 260.0687 (M+Na).

4-((3-Methylfuran-2-yl)methyl)-2H-chromen-2-one(4i): Yellow solid. mp: 190-192 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.43, (s, 2H, CH_2), 2.71, (s, 3H, CH_3), 6.26, (s, 1H, ArH), 6.53-6.57, (m, 1H, ArH), 6.81, (d, *J*=3.56 Hz, 1H, ArH), 7.44-7.51, (m, 4H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.56, 24.48, 107.76, 111.48, 112.18, 114.46, 118.79, 124.92, 125.55, 133.94, 143.47, 152.08, 152.16, 153.90, 160.88, CO; HRMS: 263.0684 (M+Na).

4-((3-Methylthiophen-2-yl)methyl)-2H-chromen-2-one(4j): Light yellow solid. mp: 158-160°C; δ=2.44, (s, 2H, CH_2), 2.73, (s, 3H, CH_3), 6.28, (s, 1H, ArH), 6.55-6.59, (m, 1H, ArH), 6.82, (d, *J*=3.76 Hz, 1H, ArH), 7.46-7.53, (m, 4H, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$): δ=18.58, 24.49, 107.77, 111.49, 112.20, 114.48, 118.82, 124.95, 125.59, 133.97, 143.48, 152.10, 152.18, 153.904, 160.68, CO; HRMS: 279.0456 (M+Na).

Biology

Antibacterial activity

The antibacterial potency of the newly synthesized compounds (4a-j) was determined by well plate method in nutrient agar media. The compounds were tested against a group of pathogenic microorganisms, including *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*. Microorganism strains were preserved on nutrient agar medium at 37°C. The cultures were inoculated in fresh 10 ml nutrient broth to furnish an initial suspension of approximately 10-100 cfu/ml. All broths were then developed statically at the above mentioned temperatures for microorganisms for 18-24 h so that all cells were in the stationary phase. Susceptibility of the test organism to the compounds was determined by employing in the well plate method. The bacterial suspensions were diluted tenfold in sterilized distilled water and 0.1 ml from the appropriate dilution was spread plated on nutrient agar so as to give a population approximately 10^6 cfu/plate. Six millimeter diameter well was then punched carefully using a sterile cork borer and 30 µl of test solutions of varied concentrations were added into each labeled well. The same procedure was replicated for different micro-organisms. Each experiment was done in triplicate. After the incubation, the inhibition zone was measured and the values for DMSO were subtracted to get the real values. Ciprofloxacin was used as the standard drug.

Determination of Minimum Inhibitory Concentration (MIC)

The MIC of the organic compounds was analyzed with the broth dilution method using nutrient broth. The MIC value, representing the lowest concentration that totally inhibited the formation of visible growth, was determined after 18 h. of incubation at 37°C.

RESULTS AND DISCUSSION

Chemistry

The synthetic route accessing the coumarin derivatives has been summarized in Scheme 1. The modified Pechmann cyclisation of phenol 1 with ethylacetoacetate procured the 4-methylcoumarin intermediate 2 which was further brominated at 4th position by treating it with N-bromosuccinimide in dibenzoyl peroxide [17-19]. The bromomethyl coumarin intermediate 3 thus obtained was then subjected to the palladium catalyzed Suzuki cross-coupling reaction with various heterocyclic boronic acids to furnish an assortment of novel coumarin derivatives (4a-j).

As a model reaction, we took the pyridine-4-boronic acid as the substrate and Cs_2CO_3 as the base and various catalyst ligand combinations in various solvents were screened. $Pd(OAc)_2$ in PCy_3 was found to be crucial for effective conversions. The required coupled product was obtained in better yield when DMF was used as the solvent. The optimization studies are detailed in Table 1. The best yield (90% isolated yield) was obtained when 1.2 equivalent pyridine-4-boronic acid, 2 equivalent Cs_2CO_3, 10 mol % $Pd(OAc)_2$ and 20 mol % PCy_3 was heated at 100°C for 10 h.

Table 1: Effect of various catalysts and solvents in the Suzuki coupling of 3 with pyridine-4-boronic acid

Entry	Catalyst	Ligand	Base	Solvent	Yield[b] 4 (%)
1	$Pd_2(dba)_3$	PCy_3	Cs_2CO_3	Dioxane	traces
2	$Pd(dppf)Cl_2$	PCy_3	Cs_2CO_3	Dioxane	10
3	$PdCl_2.(CH_3CN)_2$	PCy_3	Cs_2CO_3	Dioxane	15
4	$Pd(dppf)CH_2Cl_2$	PCy_3	Cs_2CO_3	Dioxane	20
5	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	Dioxane	50
6	$Pd(OAc)_2$	BINAP	Cs_2CO_3	Dioxane	30
7	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Dioxane	40
8	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	DME	60
9	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	DCE	75
10	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	DMF	90

Reaction conditions: 4-bromomethyl coumarin (1 mmol), pyridine-4-boronic acid (1.2 mmol), catalyst (10 mol %), Ligand (20 mol %), Base (2 mmol), solvent, heated at 100°C for 10 h; [b]Isolated yield

Once the optimization studies are carried out, a comparative study of the various bases was also done by keeping all the other parameters constant (Table 2). The bases like KOH and NaOH gave moderate yields of the coupled product whereas cesium bases like cesium fluoride and cesium acetate gave better yields. Cesium carbonate was found to be the best base for this particular coupling reaction.

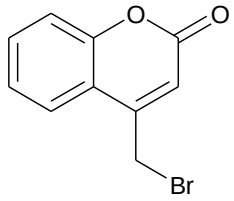
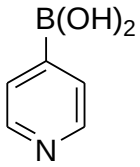
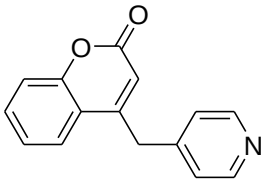
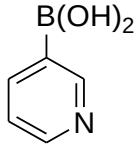
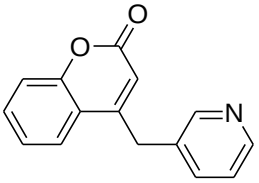
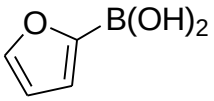
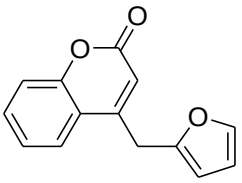
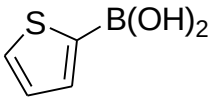
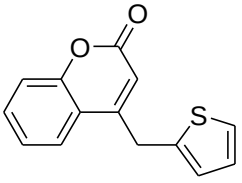
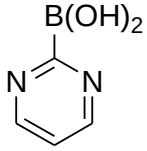
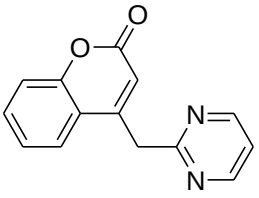
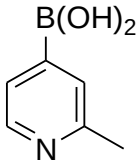
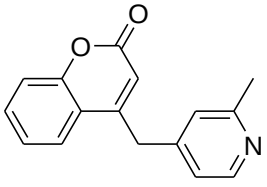
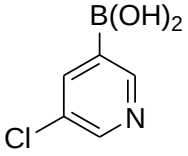
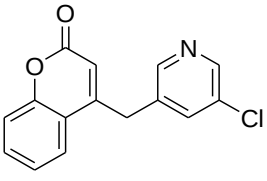
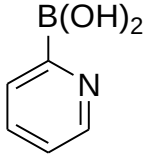
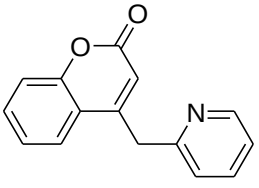
Table 2: Effect of various bases in the Suzuki coupling of intermediate 3 with pyridine-4-boronic acid

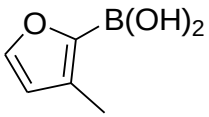
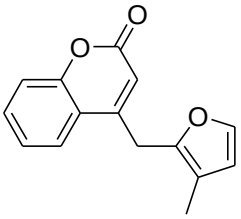
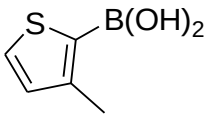
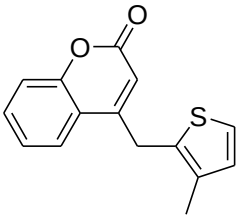
Entry	Base	Yield[b] 4d (%)
1	K_2CO_3	15
2	NaOH	traces
3	Na_2CO_3	18
4	K_3PO_4	48
5	CsF	65
6	CsOAc	60
7	Cs_2CO_3	90

Reaction conditions: 4-bromomethyl coumarin (1 mmol), pyridine-4-boronic acid (1.2 mmol), Pd $(OAc)_2$ (10 mol %), PCy_3 (0.2 mmol), base (2 mmol), DMF at 100°C for 10 h; [b]Isolated yield

Our immediate attention was to elaborate the substrate scope by coupling the reaction with a wide variety of heterocyclic boronic acids (Table 3). Almost all the boronic acids procured the coupling product in exceptional yields.

Table 3: Suzuki coupling reaction of bromointermediate 3 with various boronic acids

Entry	Bromo intermediate (3)	Boronic acid	Product (4a-j)	Yield[b] (%)
1			 4a	90
2	3		 4b	88
3	3		 4c	92
4	3		 4d	90
5	3		 4e	88
6	3		 4f	91
7	3		 4g	92
8	3		 4h	95

9	3		 4i	89
10	3		 4j	96

Reaction conditions: 4-bromomethyl coumarin (1 mmol), boronic acid (1.2 mmol), $Pd(OAc)_2$ (10 mol %), PCy_3 (0.2 mmol), Cs_2CO_3 (2 mmol), DMF at 100 °C for 10 h; [b]Isolated yield

Biology

The clinical relevance of bacterial diseases has increased over the past 30 years due to an increasing population of patients who suffer from various diseases. The development of multidrug resistance among pathogens could be a major reason for this issue [20]. In view of these facts and stimulated by the profound activity profile of coumarins and heterocycles, we carried out the analysis of antibacterial activities of the newly synthesized compounds (4a-j) against two Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633) and two Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922). The results from the evaluation of antibacterial activities are illustrated in Table 4.

As evident from Table 4, some of the compounds showed promising antibacterial activity when compared to the standard drug, Ciprofloxacin. Compounds 4a, 4d, 4g and 4e showed good and comparable activity with the standard while the compounds 4b, 4c, 4f and 4h exhibited moderate activity whereas the compounds 4i and 4j failed to show any activity against the tested strains.

Table 4: Determination of antibacterial activity of the synthesized organic compounds[a]

Compounds	***Escherichia coli***		***Staphylococcus aureus***		***Pseudomonas aeruginosa***		***Bacillus subtilis***	
Concentration (mg/ml)	**1**	**0.5**	**1**	**0.5**	**1**	**0.5**	**1**	**0.5**
Control	**00**		**00**		**00**		**00**	
Ciprofloxacin	18 ± 0.2	13 ± 0.1	17 ± 0.2	14 ± 0.2	17 ± 0.2	15 ± 0.2	20.8 ± 0.3	11.2 ± 0.2
4a	12 ± 0.2	09 ± 0.1	09 ± 0.2	07 ± 0.1	10 ± 0.2	08 ± 0.1	07 ± 0.4	04 ± 0.2
4b	03 ± 0.4	01 ± 0.2	05 ± 0.6	03 ± 0.6	07 ± 0.3	04 ± 0.4	08 ± 0.2	05 ± 0.3
4c	07 ± 0.3	05 ± 0.2	08 ± 0.2	06 ± 0.4	05 ± 0.3	03 ± 0.3	10 ± 0.5	08 ± 0.3
4d	13 ± 0.1	10 ± 0.2	12 ± 0.3	10 ± 0.2	13 ± 0.2	11 ± 0.3	13 ± 0.4	10 ± 0.1
4e	14 ± 0.1	10 ± 0.2	14 ± 0.3	12 ± 0.2	16 ± 0.2	13 ± 0.3	15 ± 0.4	12 ± 0.1
4f	08 ± 0.5	06 ± 0.3	08 ± 0.2	05 ± 0.1	10 ± 0.4	08 ± 0.2	10 ± 0.3	08 ± 0.3
4g	12 ± 0.1	9 ± 0.2	12 ± 0.3	10 ± 0.2	12 ± 0.2	10 ± 0.3	11 ± 0.4	8 ± 0.1
4h	04 ± 0.5	02 ± 0.3	03 ± 0.2	02 ± 0.1	05 ± 0.4	03 ± 0.2	05 ± 0.3	03 ± 0.3
4i	00	00	00	00	00	00	00	00
4j	00	00	00	00	00	00	00	00

The MIC of the more active compounds was evaluated by broth dilution method using nutrient broth (Table 5). From the results, it was recognized that *S. aureus* (5 µg MIC) and *P. aeruginosa* (5 µg MIC) was the most susceptible, and *E. coli* (10 µg MIC) and *B. subtilis* (10 µg MIC) were the most insensitive strain among all the bacteria used in this study. The compound 4e was found to be potent against all the bacterial strains. All the other compounds exhibited moderate to comparable potency against all the tested bacterial strains.

Table 5: Minimum inhibitory concentration of organic compounds[a]

Compounds (µg/ml)	***Escherichia coli***	***Staphylococcus aureus***	***Pseudomonas aeruginosa***	***Bacillus subtilis***
4a	---	100	100	75
4d	50	25	50	25
4e	10	10	10	25
4g	---	50	50	50
Ciprofloxacin	6	2	2	4

[a]The experiment was performed in triplicate and the values are expressed as Mean ± SD

Structure-activity relationships

The presence of two nitrogen atoms of pyrimidine attached to the coumarin in 4e is presumed to be the sole reason for the comparable antibacterial activity of that compound. The presence of already active heterocyclic thiazole ring was found to be beneficial for the enhanced activity of compound 4d. The presence of nitrogen atom in the ring and electron withdrawing chlorine atom might be the reason for the moderate antibacterial activity of 4a and 4g. The electron withdrawing-groups are anticipated to increase the lipophilicity and thereby increasing the cell

permeability of the molecule and hence enhanced its activity [21]. In general, it can be described that in the present study, the presence of ring nitrogen or an electron withdrawing group or a heterocyclic group at 4^{th} position of coumarins is an essential feature for the increased antibacterial effect of the synthesized compounds.

CONCLUSION

We have achieved an efficient access for the synthesis of an array of 4-substituted coumarins via Suzuki cross-coupling and evaluated their antibacterial properties. The compounds 4d and 4e exhibited comparable antibacterial activity with Ciprofloxacin against all the tested bacteria. The present study paved the way for the synthesis of various coumarin derivatives with significant pharmacological properties.

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