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A novel synthesis and antimicrobial activity of new coumarin derivatives

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ABSTRACT

A series of new coumarine derivatives (**6a-h**) were synthesized from N-(6-bromo-2-oxo-2H-chromen-3-yl) acetamide (**1**). The synthetic stages involved condensation of phenylboronic acid (**2**) with N-(6-bromo-2-oxo-2H-chromen-3-yl)acetamide (**1**) (**Suzuki coupling**) yielded N-(2-oxo-6-phenyl-2H-chromen-3-yl)acetamide (**3a-c**) followed by the deportation in presence of base (or) acid media gives 3-amino-6-phenyl-2H-chromen-2-one (**4a-c**), finally compound (**4a-c**) coupling with the Aldehydes to get coumarine derivatives of Schiff-bases (**6a-h**) and characterized through IR, ¹H-NMR, ¹³C-NMR, Mass spectral data and elemental analysis. The synthesized compounds (**6a-h**) have been screened for antimicrobial activity.

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KEYWORDS

N-(6-bromo-2-oxo-2H-chromen-3-yl)acetamide (**1**);
Suzuki coupling products
(**3a-c**);
3-amino-6-phenyl-2H-chromen-2-one (**4a-c**);
Schiff-bases (**6a-h**).

INTRODUCTION

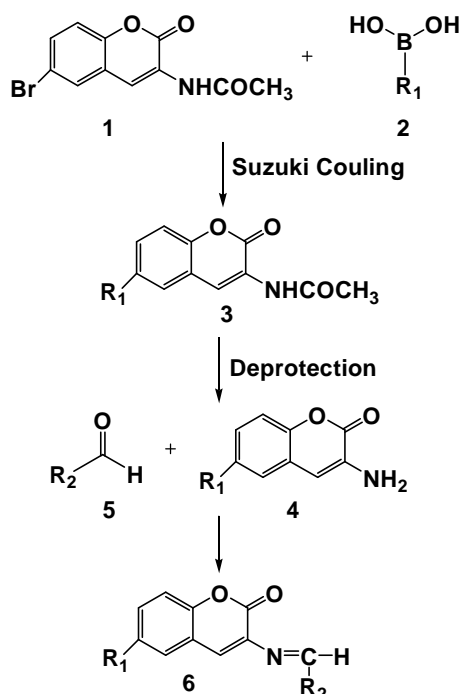
Coumarin and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. Many of these compounds have proved to be active as antimicrobial^[1-5], antitumor^[6-7], anticoagulant^[8] and antiinflammatory^[9]. In addition, these compounds are used as additives to food and cosmetics^[10]. Dispersed fluorescent and laser^[11]. Various analogues of 3-substituted coumarins such as 3-aminocoumarins exhibit antimicrobial activity^[12-13]. From the above line of reasoning we directed this paper towards synthesis of various coumarine derivatives of biological interest using N-(6-bromo-2-oxo-2H-chromen-3-yl)acetamide (**1**) as a key starting material.

RESULTS AND DISCUSSION

The reaction sequences employed for the synthesis of title compound is shown in Scheme 1. The key inter-

mediates N-(2-oxo-6-phenyl-2H-chromen-3-yl) acetamide (**3a-c**), 3-amino-6-phenyl-2H-chromen-2-one (**4a-c**) required for the preparation of the target compound. The new coumarin derivatives was obtained by the condensation of phenylboronic acid (**2**) with N-(6-bromo-2-oxo-2H-chromen-3-yl) acetamide (**1**) in THF into that added triethyl amine and PdCl₂(PPh₃)₂ and allowed the reaction to heat under reflux for 1hrs. Cooled the reaction mass, into that added water adjust pH-7 product isolated by ethyl acetate and dried Na₂SO₄ and concentrated up to 2vol into that charged heptanes, N-(2-oxo-6-phenyl-2H-chromen-3-yl) acetamide (**3a-c**) isolated by filtration with good yields(76%). The compound (**3a-c**) treated with acids (or) base at 20-25°C to give 3-amino-6-phenyl-2H-chromen-2-one (**4a-c**). Finally free amine coumarin compound (**4a-c**) react with appropriate aldehyde in absolute ethanol, containing a catalytic amount of piperidine offered good yields of coumarine derivatives of Schiff-Bases (**6a-h**).

The structural elucidation of new compounds were



Scheme 1 : The synthesis of the title compounds

Sr.No.	R ₁	R ₂
a		
b		
c		
d		
e		
f		
g		
h		

based on their elemental analysis and spectral (IR, ¹H-NMR and mass) data. The characterization data of all the new compounds are summarized in the TABLE 1 and their spectral data are given below.

N-(2-oxo-6-phenyl-2H-chromen-3-yl)acetamide (3a)

Yield 78%. M.p.: 191-192°C. ¹H NMR (300 MHz,

TABLE 1 : Antimicrobial activity of the title compounds (3a-c) and (6a-h)

Compd.	Zone of inhibition in mm					
	Antibacterial activity		Antifungal activity			
	<i>E.-coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>A. terreus</i>
3a	16	16	15	18	23	15
3b	15	18	19	16	24	13
3c	18	16	15	21	22	15
6a	14	18	17	15	20	14
6b	17	16	18	17	21	12
6c	19	19	19	15	19	15
6d	14	22	15	21	28	15
6e	16	15	21	16	18	17
6f	15	21	14	15	29	14
6g	14	17	15	16	17	15
6h	17	18	16	17	18	17
Getamycine	20	24	22	-	-	-
Fluconazole	-	-	-	22	30	18
DMSO	Nil	Nil	Nil	Nil	Nil	Nil

DMSO) δ 9.91(s, 1H, -NH), 8.7(d, 1H, J = 9Hz, H-5), 8.01(d, 1H, J = 9Hz, H-7), 7.9-7.5(m, 5H, Ar-H), 7.31(d, 1H, H-8), 7.12 (s, 1H, H-4), 2.12(s, 3H, -CH₃). ¹³C-NMR (75 MHz, DMSO) δ 166.21, 159.33, 148.90, 135.52, 134.23, 133.21, 130.19, 128.90, 129.41, 127.61, 127.32, 126.11, 125.33, 123.52, 122.04, 115.7, 23.82. Elemental analysis: Calcd. (%) for C₁₇H₁₃NO₃: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.56; H, 4.88; N, 5.20. LC-MS (m/z): 280.12 (M, 100%).

N-(2-oxo-6-p-tolyl-2H-chromen-3-yl)acetamide (3b)

Yield 77%. M.p.: 199-201°C. ¹H NMR (300 MHz, DMSO) δ 9.93(s, 1H, -NH), 8.67(d, 1H, J = 9Hz, H-5), 8.11(d, 1H, J = 9Hz, H-7), 7.89-7.65(m, 4H, Ar-H), 7.31(d, 1H, H-8), 7.12(s, 1H, H-4), 2.36(s, 3H, -CH₃), 2.12(s, 3H, -CH₃). ¹³C-NMR (75 MHz, DMSO) δ 165.91, 158.33, 149.90, 135.52, 135.23, 134.21, 131.19, 129.10, 129.45, 127.61, 127.12, 127.11, 125.33, 123.52, 122.04, 117.7, 24.52, 23.98. Elemental analysis: Calcd. (%) for C₁₈H₁₅NO₃: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.66; H, 4.98; N, 4.69. LC-MS (m/z): 294.19 (M, 100%).

N-(2-oxo-6-(4-(trifluoromethyl)phenyl)-2H-chromen-3-yl)acetamide (3c)

Yield 75%. M.p.: 202-204°C. ¹H NMR (300

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MHz, DMSO) δ 9.89(s, 1H, -NH), 8.77(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75 (m, 4H, Ar-H), 7.41(d, 1H, H-8), 7.22(s, 1H, H-4), 2.12 (s, 3H, -CH₃). ¹³C-NMR (75 MHz, DMSO) δ 166.41, 161.33, 148.90, 135.52, 134.23, 133.21, 130.19, 128.90, 129.41, 127.61, 127.32, 126.11, 125.33, 123.52, 122.04, 115.7, 23.42. Elemental analysis: Calcd. (%) for C₁₈H₁₂F₃NO₃: C, 62.25; H, 3.48; N, 4.03. Found: C, 61.98; H, 3.56; N, 4.13. LC-MS (m/z): 348.19 (M, 100%).

3-(benzylideneamino)-6-phenyl-2H-chromen-2-one (6a)

Yield 75%. M.p.: 212-214°C. IR (KBr, cm⁻¹) 1705 (C = O), 1622 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.59(s, 1H, -H), 8.47(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75 (m, 5H, Ar-H), 7.41(d, 1H, H-8), 7.32-7.15(m, 5H, Ar-H), 7.12 (s, 1H, H-4), ¹³C-NMR (75 MHz, DMSO) δ 163.41, 156.23, 148.90, 135.52, 134.23, 134.11 133.21, 131.1, 130.19, 129.90, 129.51, 129.41, 128.76, 127.61, 127.32, 126.11, 125.33, 124.55, 123.52, 122.04, 115.7, 115.64. Elemental analysis: Calcd. (%) for C₂₂H₁₅NO₂: C, 81.21; H, 4.65; N, 4.30. Found: C, 81.35; H, 4.66; N, 4.53. LC-MS (m/z): 326.19 (M, 100%).

3-(p-tolylideneamino)-6-p-tolyl-2H-chromen-2-one (6b)

Yield 78%. M.p.: 222-224°C. IR (KBr, cm⁻¹) 1745 (C = O), 1632 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.52(s, 1H, -H), 8.43 (d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 4H, Ar-H), 7.41 (d, 1H, H-8), 7.38-7.15(m, 4H, Ar-H), 7.12 (s, 1H, H-4), 2.31(s, 3H, -CH₃), 2.27 (s, 3H, CH₃) ¹³C-NMR (75 MHz, DMSO) δ 164.41, 157.23, 148.60, 135.52, 134.23, 134.11 133.21, 131.1, 130.19, 129.90, 129.51, 129.41, 128.76, 127.61, 127.32, 126.11, 125.33, 124.55, 123.52, 122.04, 115.7, 115.64, 24.54, 23.54. Elemental analysis: Calcd. (%) for C₂₄H₁₉NO₂: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.65; H, 5.21; N, 4.23. LC-MS (m/z): 354.40 (M, 100%).

3-(thiophen-2-ylmethyleneamino)-6-(4-(trifluoromethyl)phenyl)-2H-chromen-2-one (6c)

Yield 76%. M.p.: 216-218°C. IR (KBr, cm⁻¹) 1745 (C = O), 1622 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.52(s, 1H, -H), 8.43(d, 1H, J = 9Hz, H-5), 8.21(d,

1H, J = 9Hz, H-7), 7.99-7.75(m, 4H, Ar-H), 7.41(d, 1H, H-8), 7.22(s, 1H, H-4), 7.21-7.01(m, 3H), ¹³C-NMR (75 MHz, DMSO) δ 166.41, 156.23, 148.60, 134.52, 134.23, 134.11 133.21, 131.1, 130.19, 129.90, 129.51, 127.61, 127.32, 126.11, 125.33, 124.55, 123.52, 122.04, 120.55, 115.7, 115.64. Elemental analysis: Calcd. (%) for C₂₁H₁₂NO₂S: C, 63.15; H, 3.03; N, 3.51. Found: C, 63.55; H, 3.21; N, 3.61. LC-MS (m/z): 400.36 (M, 100%).

6-phenyl-3-(thiophen-2-ylmethyleneamino)-2H-chromen-2-one (6d)

Yield 78%. M.p.: 219-221°C. IR (KBr, cm⁻¹) 1735 (C = O), 1632 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.51(s, 1H, -H), 8.43(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 5H, Ar-H), 7.41(d, 1H, H-8), 7.22(s, 1H, H-4), 7.21-7.01(m, 4H, Ar-H), 2.31(s, 3H, CH₃), ¹³C-NMR (75 MHz, DMSO) δ 166.41, 156.23, 148.60, 134.52, 134.23, 134.11, 133.21, 131.1, 130.19, 130, 129.98, 129.90, 129.51, 126.45, 127.61, 127.32, 126.11, 125.33, 124.55, 123.52. Elemental analysis: Calcd. (%) for C₂₀H₁₃NO₂S: C, 72.49; H, 3.95; N, 4.23. Found: C, 72.66; H, 4.01; N, 4.56. LC-MS (m/z): 332.36 (M, 100%).

3-(thiophen-2-ylmethyleneamino)-6-p-tolyl-2H-chromen-2-one (6e)

Yield 76%. M.p.: 225-227°C. IR (KBr, cm⁻¹) 1745 (C = O), 1638 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.51(s, 1H, -H), 8.43(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 4H, Ar-H), 7.41(d, 1H, H-8), 7.22(s, 1H, H-4), 7.21-7.01(m, 3H), 2.31(s, 3H, CH₃), ¹³C-NMR (75 MHz, DMSO) δ 166.41, 156.23, 148.60, 134.52, 134.23, 134.11, 133.21, 131.1, 130.19, 130, 129.98, 129.90, 129.51, 126.45, 127.61, 127.32, 126.11, 125.33, 120.55, 115.7, 24.32. Elemental analysis: Calcd. (%) for C₂₁H₁₅NO₂S: C, 73.02; H, 4.38; N, 4.06. Found: C, 73.12; H, 4.11; N, 4.21. LC-MS (m/z): 346.36 (M, 100%).

3-(p-tolylideneamino)-6-(4-(trifluoromethyl)phenyl)-2H-chromen-2-one(6f)

Yield 75%. M.p.: 225-227°C. IR (KBr, cm⁻¹) 1745 (C = O), 1638 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.51(s, 1H, -H), 8.43(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 4H, Ar-H), 7.41(d, 1H, H-8), 7.22(s, 1H, H-4), 7.21-7.01(m, 4H, Ar-

H), 2.31(s,3H, CH₃), ¹³C-NMR (75 MHz, DMSO) δ 166.41, 156.23, 148.60, 134.52, 134.23, 134.11, 133.21, 131.1, 130.19, 130, 129.98, 129.90, 129.51, 128.41, 128.11, 126.91, 126.45, 127.61, 127.32, 126.11, 125.33, 120.55, 115.7, 24.32. Elemental analysis: Calcd. (%) for C₂₄H₁₆NO₂F₃: C, 70.76; H, 3.96; N, 3.44. Found: C, 71.10; H, 4.11; N, 3.65. LC-MS (m/z): 408.4 (M, 100%).

3-(4-methoxybenzylideneamino)-6-p-tolyl-2H-chromen-2-one(6g)

Yield 75%. M.p.: 235-237°C. IR (KBr, cm⁻¹) 1745 (C = O), 1638 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.51(s, 1H, -H), 8.43(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 4H, Ar-H), 7.41(d, 1H, H-8), 7.22(s, 1H, H-4), 7.21-7.01(m, 4H, Ar-H), 3.79(s, 3H, -O-CH₃), 2.31(s, 3H, CH₃), ¹³C-NMR (75 MHz, DMSO) δ 166.41, 156.23, 148.60, 134.52, 134.23, 134.11, 133.21, 131.1, 130.19, 130, 129.98, 129.90, 129.51, 128.41, 128.11, 126.91, 126.45, 127.61, 127.32, 126.11, 125.33, 120.55, 56.34, 24.32. Elemental analysis: Calcd. (%) for C₂₄H₁₉NO₃: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.10; H, 5.18; N, 3.65. LC-MS (m/z): 370.4 (M, 100%).

6-phenyl-3-(p-tolylideneamino)-2H-chromen-2-one (6h)

Yield 78%. M.p.: 222-224°C. IR (KBr, cm⁻¹) 1745 (C = O), 1632 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.52(s, 1H, -H), 8.43(d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 5H, Ar-H), 7.41(d, 1H, H-8), 7.38-7.15(m, 4H, Ar-H), 7.12(s, 1H, H-4), 2.31(s, 3H, -CH₃), ¹³C-NMR (75 MHz, DMSO) δ 164.41, 157.23, 148.60, 135.52, 134.23, 134.11, 133.21, 131.1, 130.19, 129.90, 129.51, 129.41, 128.76, 127.61, 127.32, 126.11, 125.33, 124.55, 123.52, 122.04, 115.7, 115.64, 23.54. Elemental analysis: Calcd. (%) for C₂₃H₁₇NO₂: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.65; H, 5.21; N, 4.23. LC-MS (m/z): 340.29 (M, 100%).

Antibacterial and antifungal activity

The *in vitro* antimicrobial activity was carried out against 24hrs old cultures of three bacteria and three fungi by cup-plate method^[14]. Compounds (3a-c) & (6a-h) has been tested for their antimicrobial activity against *E.coli*, *P.aeruginosa* and *S.aureus* and

antifungal activity against *A.niger*, *A.flavus* and *A.terrus* at a concentration of 1000µg/ml in distilled DMSO using cup plate diffusion method. Nutrient agar and potato dextrose agars were used to culture the bacteria and fungus respectively. The solution of Getamycine 1000µg/ml and Fluconazole 1000µg/ml were prepared in sterilized water and used for standards for comparison of antibacterial and antifungal activities respectively the results were discussed in TABLE 1.

The Compounds (3c) and (6c) exhibiting good activity against *E.coli* and compounds (6d) and (6f) showing good activity of against *P.aeruginosa*, and compounds (6e) showing good activity against *S.aureus*. All remaining compounds exhibited moderate activity against all the organisms used for screening.

In anti-fungal activity the compounds (3c) and (6d) exhibited excellent activity against *A.niger* and compounds (6d) and (6f) exhibiting good activity against *A.flavus* and compounds (6e) and (6h) showed a good activity *A.terrus* and all remaining compounds exhibiting moderate activity against all the three organisms used for screening.

EXPERIMENTAL

The melting points were determined in open capillaries. The purity of the compound was checked by the thin layer chromatography (TLC) on a silica-coated aluminium sheet (silica gel 60F₂₅₄) using dichloromethane and methanol (8:2, v/v). The IR spectra were recorded on a Nicolet Avatar 330-FTIR spectrometer. The ¹H- and ¹³C-NMR (3a-c) & (6a-h) spectra was recorded on a Varian 300 MHz NMR spectrometer using TMS as the internal standard the chemical shift (δ) are reported in ppm and the signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) and multiplet (m). The FAB mass spectra were recorded on Jeol SX 102/DA-6000 spectrophotometer/data system using argon/xenon (6 KV, 10mA) FAB gas, at 70eV. Elemental analysis was carried out a flash EA 1112 Series, CHNSO analyzer (Thermo). The solvent and reagents were purchased from commercial vendors in the appropriate grade and were used without purification.

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General procedure for the preparation of N-(2-oxo-6-phenyl-2H-chromen-3-yl) acetamide (3a-c)/ Suzuki coupling reaction

To solution of phenylboronic acid (**2**) (0.0011 mole) with N-(6-bromo-2-oxo-2H-chromen-3-yl)acetamide (**1**) (0.001 mol), triethyl amine (3 eq.) in a dry THF. Into that added PdCl₂(PPh₃)₂, stirred for 4-5hrs at reflux temperature, reaction monitored by TLC technique upto completion. After the reaction completion, into that charged ice water and adjust pH-6 to 7 by using diluted acid product extracted with ethyl acetate and dried Na₂SO₄ and distill completely, purified by silica column chromatography technique with methanol & dichloromethane with good yield (78%). The ¹H-NMR (300 MHz) spectra of N-(2-oxo-6-phenyl-2H-chromen-3-yl) acetamide (**3a**) recorded in DMSO-d₆ shows δ 9.91(s, 1H, -NH), 8.7(d, 1H, J=9Hz, H-5), 8.01(d, 1H, J=9Hz, H-7), 7.9-7.5(m, 5H, Ar-H), 7.31(d, 1H, H-8), 7.12(s, 1H, H-4), 2.12(s, 3H, -CH₃).

General procedure for the preparation of 3-amino-6-phenyl-2H-chromen-2-one (4a-c)

To solution of N-(2-oxo-6-phenyl-2H-chromen-3-yl) acetamide (**3a**) in a 20% IPA in HCl (or) Methanolic sodium hydroxide solution stirred at 20-25°C for 1-2hrs, reaction monitored by TLC technique upto completion. After the reaction completion, adjust pH-7 and solvent is removed by vacuum into that charged ice cold water, product extracted with ethyl acetate and dried Na₂SO₄ and distill under vacuum, purified by silica column chromatography technique with methanol & dichloromethane with good yield (96%). The ¹H-NMR (300 MHz) spectra of 3-amino-6-phenyl-2H-chromen-2-one (**4a**) shows disappearance of -CH₃ peak at δ 2.12(s, 3H, -CH₃).

General procedure for preparation of schiff base (6a-h)

To solution of 3-amino-6-phenyl-2H-chromen-2-one (**4a**) (0.001 mol) and benzaldehyde (0.001 mol) in ethanol, into that added catalytic of piperidine. The reaction mixture reflux for 5-6hrs, reaction monitored by TLC technique upto completion. After the reaction completion reaction mixture cooled to 0-5°C and solids collected by filtration technique, with good yield

(76%) and recrystallized by ethanol. The same procedure for the preparation of compounds (**6a-h**). The structure of 3-(benzylideneamino)-6-phenyl-2H-chromen-2-one (**6a**) was conformed by the below analytical data.

IR (KBr, cm⁻¹) 1705 (C = O), 1622 (C = N), ¹H NMR (300 MHz, DMSO) δ 8.59(s, 1H, -H), 8.47 (d, 1H, J = 9Hz, H-5), 8.21(d, 1H, J = 9Hz, H-7), 7.99-7.75(m, 5H, Ar-H), 7.41(d, 1H, H-8), 7.32-7.15 (m, 5H, Ar-H), 7.12(s, 1H, H-4), ¹³C-NMR (75 MHz, DMSO) δ 163.41, 156.23, 148.90, 135.52, 134.23, 134.11 133.21, 131.1, 130.19, 129.90, 129.51, 129.41, 128.76, 127.61, 127.32, 126.11, 125.33, 124.55, 123.52, 122.04, 115.7, 115.64. Elemental analysis: Calcd. (%) for C₂₂H₁₅NO₂: C, 81.21; H, 4.65; N, 4.30. Found: C, 81.35; H, 4.66; N, 4.53. LC-MS (m/z): 326.19 (M, 100%).

CONCLUSION

The successful synthesis of series of title compounds and evaluation of the antimicrobial activity of Coumarine derivatives of schiff-bases were reported. From the results of the antimicrobial activity is due to the presence of both coumarines and Schiff-bases in the structure.

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