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Synthesis, Characterization and Anti-bacterial Studies of 4-(arylsulfonyl)methyl-2H-Chromene Derivatives

P. S. HARIKRISHNAN*[1]

[1] Department of Chemistry, The Madura College (Autonomous), Madurai - 625 001, Tamil Nadu, India

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Abstract

A series of novel 4-((arylsulfonyl)methyl)-2H-chromen-2-one has been synthesized by Pechmann condensation of ethyl 3-oxo-4-(arylsulfonyl)butanoate 7, various phenol derivatives using $AlCl_3$ as a Lewis catalyst in the presence of Nitro benzene at 100 - 130°C. The prepared compounds were screened for anti-bacterial activity studies Many of the compounds shown remarkable anti-bacterial activity against the tested organisms.

***Key words*:** Ethyl 3-oxo-4-(arylsulfonyl)butanoate, 4-[(arysulfonyl)methyl]-2H-chromen-2-ones, Anti-bacterial activity

Chromene derivatives are an important group of heterocycles with diverse biological properties and therapeutic application which have attracted many attentions [1]. These heterocycles are prominent natural products, widely distributed among many plants [2]. The natural chromenes also display a wide range of valuable physiological activities [3]. Additionally, fused chromenes are important constituents of pharmacologically active compounds, as these systems have exhibited a broad spectrum of biological activities such as antimicrobial [4], antiviral [5], antitumor [6], antiproliferative [7], sex pheromonal [8], mutagenicity [9], central nervous system (CNS) activities [10], and inhibitors of influenza virus sialidases. Substituted chromenes can bind to 5HT receptors, acting as antagonists [11] and were also reported as MAO and human β-secretase inhibitors [12]. They have striking biological importance, especially as potentially useful pesticides [13] for their anti-hypoxic, hypotensive and antiallergic properties [14] and inhibitors of cell proliferation with potential anticancer effects. Chromene compounds exhibit high antibacterial and antifungal activities [15], in addition, chromenes have been found to possess anti-picornavirus properties and binding to virus capsids [16]. They have strong antioxidant activities [17] and also represent useful synthetic building blocks in organic and medicinal chemistry [18].

The study involves the development of chromene-based compounds bearing arylsulfonylmethyl groups, known for their potential biological activity. These derivatives are synthesized through a multicomponent reaction involving salicylaldehyde, malononitrile, and arylsulfonyl reagents, often catalyzed by green catalysts like Montmorillonite K-10 under eco-friendly conditions. Structural characterization is carried out using FT-IR, NMR, mass spectrometry, and elemental analysis to confirm the formation and purity of the compounds. The antibacterial activity of the synthesized derivatives is evaluated against various Gram-positive and Gram-negative bacterial strains using agar diffusion and MIC methods, revealing that the nature and position of substituents on the aryl ring significantly influence biological efficacy. Compounds with electron-withdrawing groups tend to exhibit stronger antibacterial effects, likely due to enhanced interaction with bacterial enzymes or membranes. Overall, the incorporation of the arylsulfonylmethyl moiety into the chromene scaffold shows promising potential for developing new antibacterial agents.

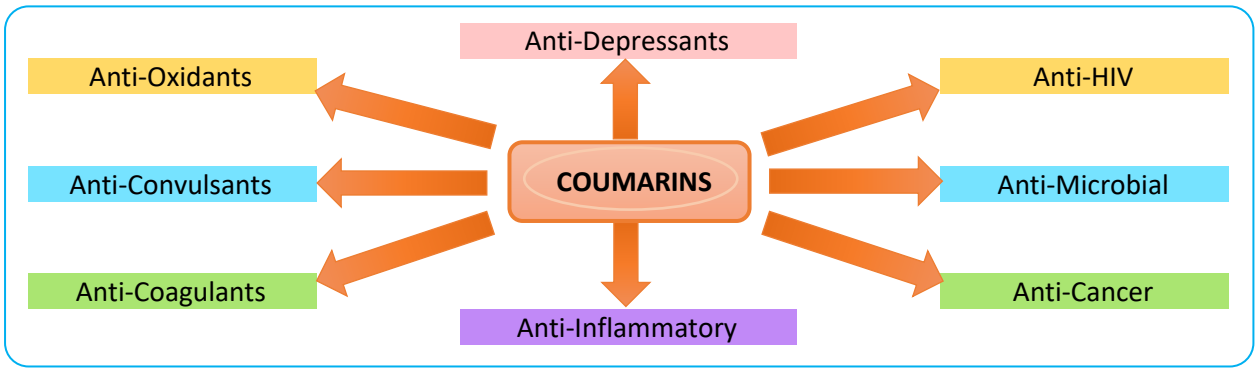

Fig 1 Various biological activities of coumarin (Chromene is the derivative of coumarin)

***Correspondence to:** P. S. Harikrishnan, E-mail: harikimku@gmail.com; Tel: +91 092452 29481

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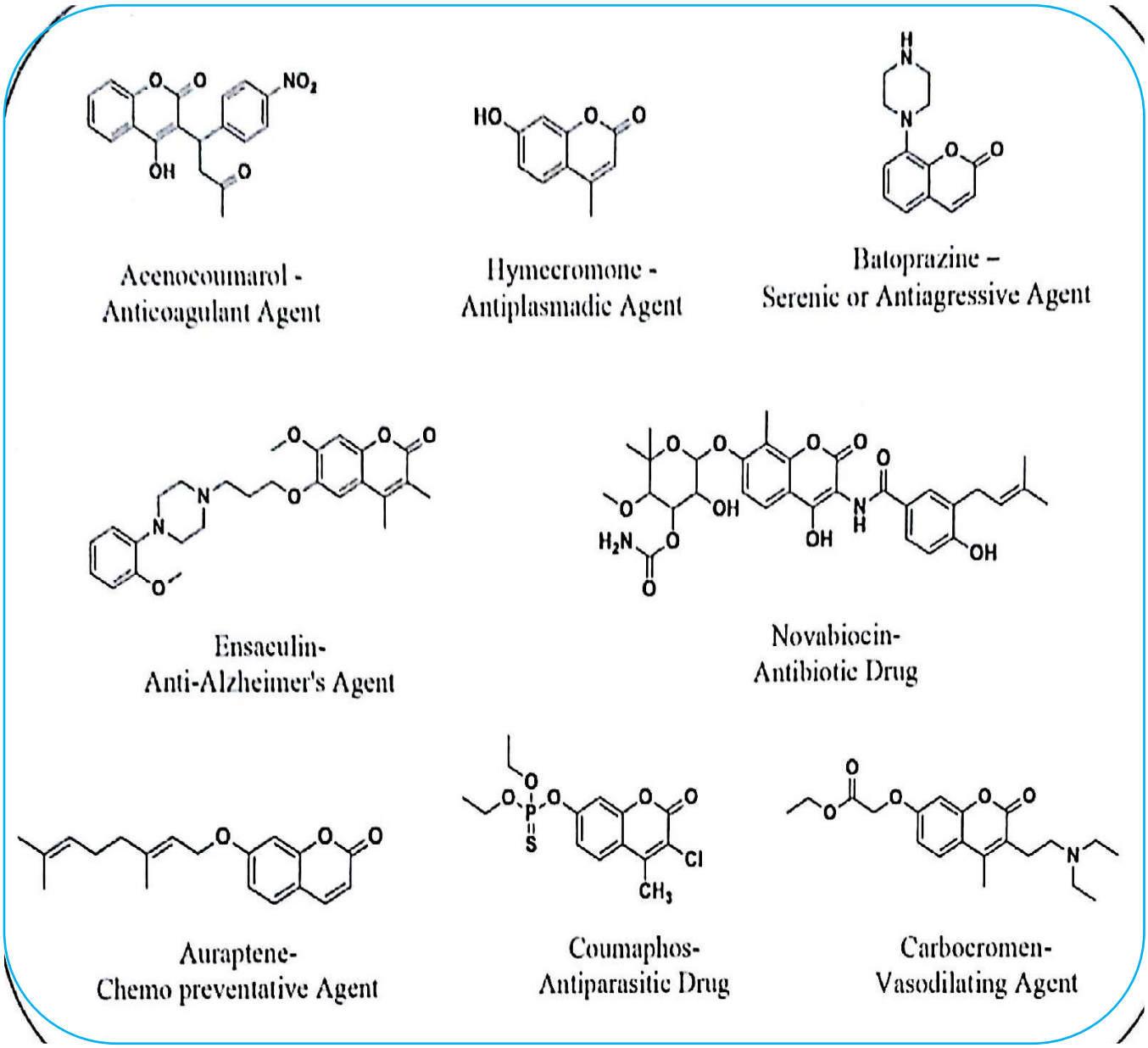
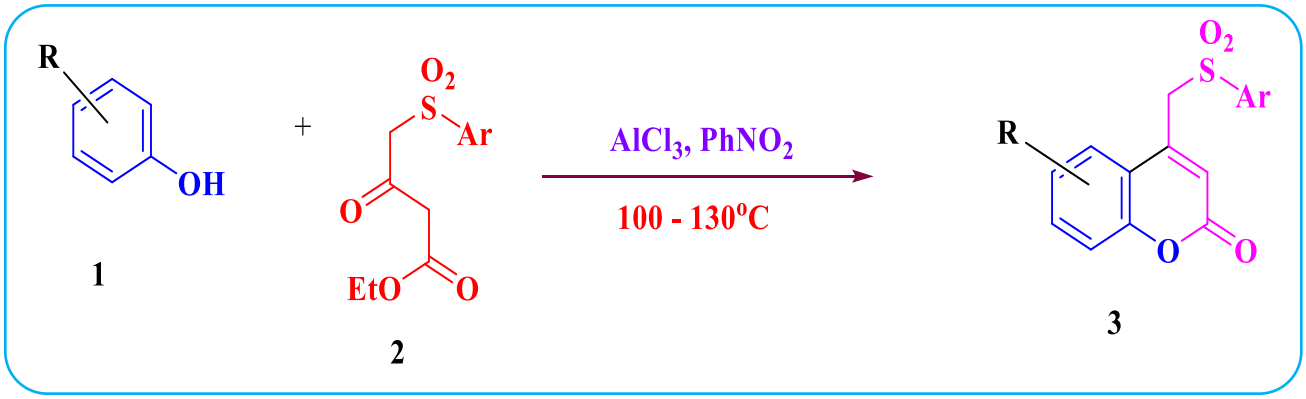


Fig 2 Structures of some commercially available coumarin based drugs

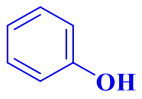
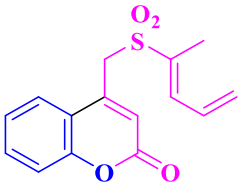
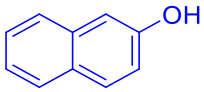
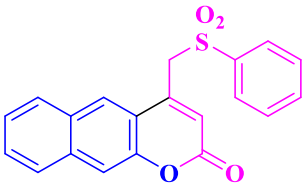
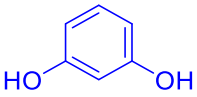
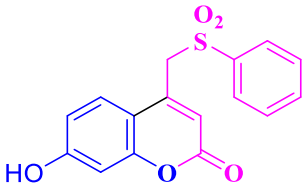
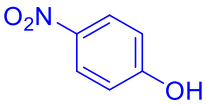
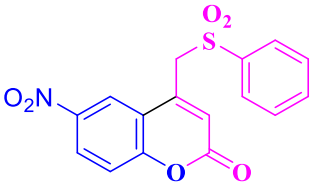
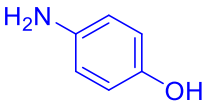
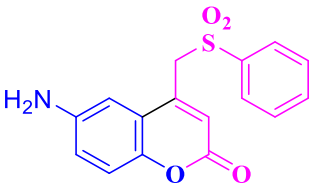
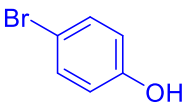
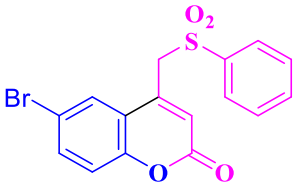
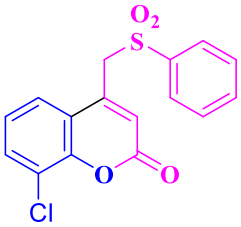
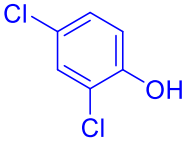
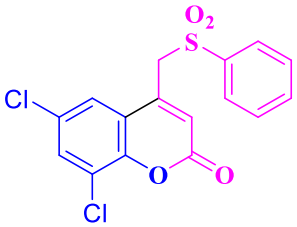
RESULTS AND DISCUSSION

In the present investigation a series of novel 4-((arylsulfonyl)methyl)-2H-chromen-2-one 3 has been synthesized by Pechmann condensation of ethyl 3-oxo-4-(arylsulfonyl)butanoate 2, various phenol derivatives 1 using $AlCl_3$ as a Lewis catalyst in the presence of Nitro benzene at 100 – 130 °C (Scheme 1). The prepared compounds were screened for anti-bacterial activity studies Many of the compounds shown remarkable anti-bacterial activity against the tested organisms.



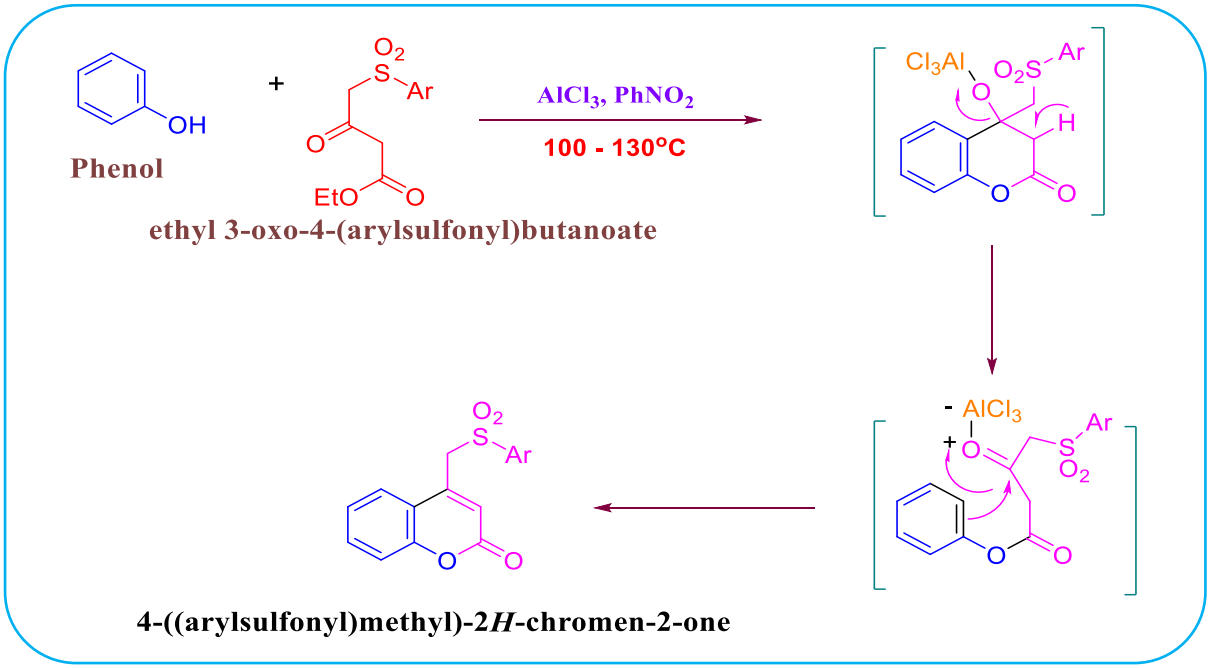
Scheme 1 Synthesis of compound 3

Table 1 The yield and melting point of the synthesized compound 3

S. No.	Phenol Derivative (6)	Ar	Product	Yield %	m.p °C
3a		C_6H_5		88	102-104
3b		C_6H_5		85	124-126
3c		C_6H_5		92	114-116
3d		C_6H_5		95	168-170
3e		C_6H_5		82	165-167
3f		C_6H_5		96	186-188
3g		C_6H_5		86	176-178
3h		C_6H_5		84	125-127

Mechanism of the reaction

Starting from a derivative of phenol and a carboxylic acid or ester containing β-carbonyl group produced substituted chromenes. The condensation is performed under acidic conditions. The mechanism involves an esterification / transesterification followed by attack of the activated carbonyl ortho to the oxygen to generate the new ring. The final step is a dehydration, as seen following aldol condensation.



NMR data of the prepared compounds

4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3a) Pale yellow solid; yield 92%; mp 221 – 224°C, ^{1}H NMR (400 MHz, DMSO-d$_6$)δ_H: 1.64, 1.54 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 1.66, 1.41 (dd, 2H, *J* = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 2.63 (q, 1H, *J* = 7.0 Hz), 2.71 (t, 2H,, *J* = 7.1 Hz), 3.45 (d, 1H, *J* = 7.1 Hz), 3.71 (t, 2H, *J* = 7.1 Hz), 3.81 (s, 3H, -OCH$_3$), 6.93 (dd, 2H, *J* = 7.5 Hz, 1.5 Hz, Ar-H), 7.17-7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

4-((phenylsulfonyl)methyl)-2H-benzo[g]chromen-2-one (3b) Pale yellow solid; yield 92%; mp 221 – 224°C, ^{1}H NMR (400 MHz, DMSO-d$_6$)δ_H: 1.64, 1.54 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 1.66, 1.41 (dd, 2H, *J* = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 2.63 (q, 1H, *J* = 7.0 Hz), 2.71 (t, 2H,, *J* = 7.1 Hz), 3.45 (d, 1H, *J* = 7.1 Hz), 3.71 (t, 2H, *J* = 7.1 Hz), 3.81 (s, 3H, -OCH$_3$), 6.93 (dd, 2H, *J* = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

7-hydroxy-4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3c) Pale yellow solid; yield 92%; mp 221 – 224°C, ^{1}H NMR (400 MHz, DMSO-d$_6$)δ_H: 1.64, 1.54 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 1.66, 1.41 (dd, 2H, *J* = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 2.63 (q, 1H, *J* = 7.0 Hz), 2.71 (t, 2H,, *J* = 7.1 Hz), 3.45 (d, 1H, *J* = 7.1 Hz), 3.71 (t, 2H, *J* = 7.1 Hz), 3.81 (s, 3H, -OCH$_3$), 6.93 (dd, 2H, *J* = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

6-nitro-4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3d) Pale yellow solid; yield 92%; mp 221 – 224°C, ^{1}H NMR (400 MHz, DMSO-d$_6$)δ_H: 1.64, 1.54 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 1.66, 1.41 (dd, 2H, *J* = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 2.63 (q, 1H, *J* = 7.0 Hz), 2.71 (t, 2H,, *J* = 7.1 Hz), 3.45 (d, 1H, *J* = 7.1 Hz), 3.71 (t, 2H, *J* = 7.1 Hz), 3.81 (s, 3H, -OCH$_3$), 6.93 (dd, 2H, *J* = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

6-amino-4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3e) Pale yellow solid; yield 92%; mp 221 – 224°C, ^{1}H NMR (400 MHz, DMSO-d$_6$)δ_H: 1.64, 1.54 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 1.66, 1.41 (dd, 2H, *J* = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, *J* = 7.1 Hz, *J* = 7.0 Hz), 2.63 (q, 1H, *J* = 7.0 Hz), 2.71 (t, 2H,, *J* = 7.1 Hz), 3.45 (d, 1H, *J* = 7.1 Hz), 3.71 (t, 2H, *J* = 7.1 Hz), 3.81 (s, 3H, -OCH$_3$), 6.93 (dd, 2H, *J* = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

6-bromo-4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3f) Pale yellow solid; yield 92%; mp 221 – 224°C, ^{1}H NMR (400 MHz, DMSO-d$_6$)δ_H: 1.64, 1.54 (dd, 2H, *J* = 7.1 Hz,

J = 7.0 Hz), 1.66, 1.41 (dd, 2H, J = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, J = 7.1 Hz, J = 7.0 Hz), 2.63 (q, 1H, J = 7.0 Hz), 2.71 (t, 2H,, J = 7.1 Hz), 3.45 (d, 1H, J = 7.1 Hz), 3.71 (t, 2H, J = 7.1 Hz), 3.81 (s, 3H, -OCH_3), 6.93 (dd, 2H, J = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

8-chloro-4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3g) Pale yellow solid; yield 92%; mp 221 – 224ºC, ^{1}H NMR (400 MHz, DMSO-d_6)δ_H: 1.64, 1.54 (dd, 2H, J = 7.1 Hz, J = 7.0 Hz), 1.66, 1.41 (dd, 2H, J = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, J = 7.1 Hz, J = 7.0 Hz), 2.63 (q, 1H, J = 7.0 Hz), 2.71 (t, 2H,, J = 7.1 Hz), 3.45 (d, 1H, J = 7.1 Hz), 3.71 (t, 2H, J = 7.1 Hz), 3.81 (s, 3H, -OCH_3), 6.93 (dd, 2H, J = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

6,8-dichloro-4-((phenylsulfonyl)methyl)-2H-chromen-2-one (3h) Pale yellow solid; yield 92%; mp 221 – 224ºC, ^{1}H NMR (400 MHz, DMSO-d_6)δ_H: 1.64, 1.54 (dd, 2H, J = 7.1 Hz, J = 7.0 Hz), 1.66, 1.41 (dd, 2H, J = 7.1 Hz, 7.0 Hz), 2.40, 2.30 (dd, 2H, J = 7.1 Hz, J = 7.0 Hz), 2.63 (q, 1H, J = 7.0 Hz), 2.71 (t, 2H,, J = 7.1 Hz), 3.45 (d, 1H, J = 7.1 Hz), 3.71 (t, 2H, J = 7.1 Hz), 3.81 (s, 3H, -OCH_3), 6.93 (dd, 2H, J = 7.5 Hz, 1.5 Hz, Ar-H), 7.17- 7.38 (m, 4H, Ar-H), 7.43 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 10.66 (s, 1H, -NH), 10.68 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 22.5, 25.7, 32.4, 38.0, 40.9, 52.3, 52.7, 55.8, 63.3, 67.5, 89.6, 114.1, 114,5, 121.7, 122.3, 126.1, 129.1, 130.3,, 130.4, 131.4, 134.1, 137.7, 138.2, 139.6, 142.3, 157.8, 172.0 182.1..Anal. Calcd for $C_{30}H_{27}Cl_2N_3O_3$: C, 65.70; H, 4.96; Cl, 12.93; N, 7.66; O, 8.75% Found C, 65.68, H, 4.98, Cl, 12.91, N, 7.647, O, 8.77%

Anti-bacterial studies

The antimicrobial activity of the compounds (3a-3h) were measured *in vitro* against bacteria such as *Streptococcus*, *Staphylococcus, pseudomonas aeruginosa* and *salmonella typhi* by paper disc plate method with Nutient Agar media. The compounds were tested using 25, 50, 75 and 100 mmol solutions in DMSO and compared with that of known antibiotics *viz tetracyclin* (Table 2). For fungicidal activity, compounds were screened *in vitro* against *Aspergillus niger, Trichoderma* and *Candida albicans* by mycelia dry weight method with glucose nitrate media. The activity of the compounds measured at 25, 50, 75 and 100 mmol concentrations in DMSO were compared with that of kanamycin.

It was found that compounds, 3a, 3b and 3f possess a pronounced antibacterial activity against all the tested organisms (Table 2). These compounds 3a, 3b and 3f have shown growth inhibitory action almost equal to the reference drug tetracyclin against *Streptococcus*, *Staphylococcus, pseudomonas aeruginosa* and *Salmonella typhi.*

Table 2 Antibacterial activity of 4-((arylsulfonyl)methyl)-2H-chromen-2-one 3

S. No.	Code	*Strepto coccus*				*Stephylo coccus*				*Pseudomanas aeruginosa*				*Salmonella typhi*			
		25 mM	50 mM	75 mM	100 mM	25 mM	50 mM	75 mM	100 mM	25 mM	50 mM	75 mM	100 mM	25 mM	50 mM	75 mM	100 mM
1	3a	+	++	+++	++++	+	++	++	+++	-	++	++	+++	++	+++	+++	+++
2	3b	++	++++	+++++	++++	-	++	++	++++	+	++	++	++++	+	++	+++	+++
3	3c	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	3d	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-
5	3e	+	++	+++	+++	-	-	-	-	+	++	++	++	+	++	++	++
6	3f	+	+++	+	+	+	++	+	+		-	-	-	++	++	+++	++++
7	3g	-	-	-	-	-	-	-	-	+	+	+	+	+	+	++	+++
8	3h	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28	*Tetracy Cline*	+	++	+++	++++	++	++	+++	++++	+	+	++	++++	++	++	+++	++++

+ mild activity; ++ moderate activity; +++ high activity; ++++ very high activity; - No activity

CONCLUSION

In this article describes synthesis of a series of novel 4-((arylsulfonyl)methyl)-2H-chromen-2-one has been synthesized by Pechmann condensation of ethyl 3-oxo-4-(arylsulfonyl)butanoate 7, various phenol derivatives using $AlCl_3$ as a Lewis catalyst in the presence of Nitro benzene at 100 - 130°C. The prepared compounds were screened for anti-bacterial activity studies Many of the compounds shown remarkable anti-bacterial activity against the tested organisms.

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