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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEWER COUMARIN DERIVATIVES AS ANTIMICROBIAL AGENTS

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ABSTRACT: For the synthesis of a series of novel Coumarin derivatives, an efficient and easy approach has been designed. 1H-NMR and Fourier Transformed Infrared (FTIR) characterize the structures of freshly synthesized compounds, which are then evaluated for antibacterial activity in vitro by calculating the zone of inhibition and minimum inhibitory concentration. The antibacterial and antifungal activity of 4-[(2-oxo-2-[5-(2-oxo-2H-chromen-3-yl)-1, 3-thiazol-2-yl] aminoethyl] amino] benzoic acid was comparable to that of ciprofloxacin and fluconazole. The reaming compounds had moderate to good activity.

INTRODUCTION: Antibiotics are among the most often prescribed antibiotics today and their research and commercialization have saved countless lives. Multidrug-resistant bacteria cause various bacterial diseases, including diarrhoea, food poisoning and rheumatic fever. Bacterial resistance to currently available antibiotics is rapidly increasing, posing a serious threat to human health [1]. Coumarin and its derivatives are among the most active chemical classes, with a broad range of biological action. Antibacterial, antifungal, anti-inflammatory, anticoagulant, anti-HIV and anticancer properties have been demonstrated for several of these substances.

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Various substituted coumarin analogues have antibacterial, anticonvulsant, acetylcholinesterase inhibitory and aldehyde reeducate inhibitory properties [2, 3, 4]. The design of novel compounds and their vast range of pharmaceutical and medical uses is a crucial study field for the expanding interest in thiazole chemistry. The thiazole ring is a fundamental structural component in many natural bioactive substances such as marine alkaloids. Penicillin (wide range antibiotics), sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (antifungal drug), and tiazofurin (antifungal drug) all contain the thiazole ring (antineoplastic drug) [5, 6, 8, 9].

MATERIAL AND METHODS: Merck, Germany and Loba Company supplied all chemicals and solvents. A Bruker Advance, 500 MHZ equipment, was used to obtain 1HNMR spectra. To determine the purity of the, thin-layer chromatography (TLC) was used. The melting points were determined in

an open capillary using a Veego (model: -VMP-D) electronic instrument. The Shimadzu 8400 FT-IR Spectrophotometer was used to get IR spectra of the synthesized compounds.

Synthesis of 3-acetyl-2H-chromen-2-one: The solution was made up of 25.65mL (0.1mol) ethyl acetoacetate and 21.29mL (0.1mol) salicyl-aldehyde. In an ice bath, it was chilled. Rapid stirring was used to add 2ml (0.02mol) of piperidine to the liquid. The reaction mixture was held at a low temperature. The yellowish material was separated after 20 min, filtered, and washed with ethanol thereafter. It was recrystallized from ethanol: water (7:3) [9]. Yield-85%, Melting point-110-114°C, IR Spectra (KBr) - C=O (α, β unsaturated) at 1600 to 1700 cm^{-1} in addition to ketone C=O at 1745 to 1715 $cm^{-1,}$ aliphatic C-H 3000 to 2850 cm^{-1}, aromatic C-H 3150 to 3000 cm^{-1}.

Synthesis of 2-oxo-2H-chromene-3-carbonyl Bromide: 4.7gm (0.025mol) 3-acetycoumarin was taken in a beaker and dissolved in 20 ml of chloroform. 4gm (0.05mol) bromine was taken in round bottom flask. 13 ml of chloroform was added to it. The two mixtures were mixed by slowly stirring and refluxed for 1 h.

After 1hr reaction mixture was cooled, filtered and washed with petroleum ether. It was recrystallized from ethanol: chloroform (2:1) [4]. Yield-78%, Melting point-140-144°C, IR Spectra- C-Br at 756 cm^{-1}, lactone at 1700 to 1600 cm^{-1}, ketone C=O at 1745 to 1715 cm^{-1}, aromatic C=C at 2350 to 2100 cm^{-1}, aromatic C-H 3150 to 3000 cm^{-1}.

Synthesis of 3-(5-amino-1, 3-thiazol-2-yl)-2*H*-chromen-2-one: 1gm of 3-bromo acetylcoumarin (1mol) and 1gm (1mol) of thiourea were taken in 250 ml of the round bottom flask and dissolved in 20 ml of ethanol by slowly stirring for 15min.

After 15 min, 0.5ml of ammonia was added to it. The reaction mixture was heated under the reflux for 30min. After 30min, the reaction mixture was poured into ice-cold water (50ml), filtered and dried. It was recrystallized from ethanol [10]. Yield-85%, Melting point-220-222°C, IR Spectra(KBr) - C-S at 635 to 500 cm^{-1}, aromatic C=N at 1660 to 1340 cm^{-1}, lactone at 1700 to 1600 cm^{-1}, amine N-H at 3500 to 3100 $^{-1}$cm.

Synthesis of 2-chloro-*N*-[2-(2-oxo-2*H*-chromen-3yl)-1, 3-thizol-5-] Acetamide: In round bottom flask, 0.7 gm (0.005mole) of 3-(5-amino-1, 3-thiazol-2-yl) -2H – chromen – 2 - one, 0.5gm of anhydrous potassium carbonate and 1ml of triethylamine were taken and dissolved into 65ml of dry chloroform with slowly stirring. The reaction mixture was refluxed for 4-5 h. After 5hr, the reaction mixture was evaporated. The resulting solid was washed with cold water and dried. It was recrystallized from ethanol: water (80:20) [11]. Yield-85%%, Melting point-230-232°C, IR Spectra (KBr**)** 591 (C-S), 643 (C-Cl), 1249 (C-O), 1319 (C-N), 1556 (C=N), 1651(C=O), 1735 (keto C=O), 1797 (amide N-H), 2327 (Ar C=C), 3078 (C-H), 3140 (Ar C-H), 3371 (amine N-H).

Synthesis of 1-(substituted phenyl)-3-[4-(2-oxo-2*H*-chromen - 3 -yl)-1, 3-thiazol-2-yl]acetamide: 3gm (0.13 mmol) of 2-chloro-N-[2-(2-Oxo-2H-chromen-3yl)-1, 3-thizol-5-] acetamide and substituted aniline were taken into the round bottom flask dissolved it into 40mlof isopropanol). This reaction mixture was heated under reflux for 8-9 h. After 9 h, the reaction mixture was kept in an ice bath, solid was separated, filtered, and dried. It was recrystallized by using ethanol: water (80:20) [2].

(2-(4-chlorophenylamino)-N-(4-(2-oxo-2H-chromen-3-yl) thiazol-2-yl)acetamide):

IR Spectrum (KBr cm^{-1}) -600 (C-S), 832(C-S), 1187(C-O), C=N (1288), 1535 (lactone C=O), 1666 (ketone C=O), 2391(Ar C=C), 2978 (C-H), 3294 (amine N-H), 1424 (Amide N-H)

^{1}H-NMR ($CDCl_3$, δ ppm) - a) 12.7 (NH, *1H*, S), b) 3.4 (CH, 1*H*, S), c) 4.4 (NH, 1*H*,t), d) 8.0 (Ar.CH,1*H*,d), e) 7.8 (Ar.CH,1*H*,d), f) 7.6 (Ar.CH,1*H*,t), g) 7.4 (Ar.CH,1*H*,d), h) 7.5 (Ar.CH,1*H*,t), i) 8.3 (Ar.CH,1*H*,d).

(2-(4-nitrophenylamino) – N - (4 - (2 – oxo - 2H – chromen – 3 - yl) thiazol-2-yl) Acetamide):

IR Spectrum (KBr, cm^{-1}): 640 (C-S), 1126(C-O), 1394 (NO_2), 1464 (Amide N-H), 1558 (C=N), 1651 (lacto C=O), 1712(keto C=O), 2075 (Ar C=C), 3294 (N-H)

^{1}H-NMR ($CDCl_3$, δ ppm): 9.5 (NH, *1H*, S), 3.7 (CH, 1*H*, S), 4.0 (NH, 1*H*,t), 8.3 (Ar.CH,1*H*,s), 7.6 (Ar.CH,1*H*,d), 7.5 (Ar.CH,1*H*,t), 6.6 (Ar.CH,1*H*,d), 7.1 (Ar.CH,1*H*,t), 8.6 (Ar.CH,1*H*,d).

2-(3-nitrophenylamino)-N-(4-(2-oxo-2H-chromen-3-yl) thiazol-2-yl)acetamide):

IR spectrum (KBr, cm^{-1}) 600 (C-S), 1187(C-O), 1300 (NO_2), 1464 (Amide N-H), 1512 (C=N), 1535 (lacto C=O), 1666(keto C=O), 2391 (Ar C=C), 3294 (N-H).

^{1}H-NMR ($CDCl_3$, δ ppm): 9.1 (NH, *1H*, S), 3.7 (CH, 1*H*, S), 4.0 (NH, 1*H*,t), 8.6 (Ar.CH,1*H*,s), 8 (Ar.CH,1*H*,d), 7.6 (Ar.CH,1*H*,t), 7.4 (Ar.CH,1*H*,d), 7.8 (Ar.CH,1*H*,t), 8.6 (Ar.CH,1*H*,d).

4-[(2-oxo-2-{[5-(2 - oxo - 2*H*-chromen – 3 - yl)-1, 3-thiazol-2-yl]amino}ethyl)amino]benzoic Acid:
IR Spectrum (KBr, cm^{-1}): 600 (C-S), 1180(C-O), 1464 (Amide N-H), 1280 (C-N), 1635 (lacto C=O), 1666(keto C=O), 3001 (Ar C=C), 3201 (N-H), 3230(C=O).

^{1}H-NMR ($CDCl_3$, δ ppm): 10.4 (NH, *1H*, S), 3.7 (CH, 1*H*, S), 4.0 (NH, 1*H*,t), 7.4 (Ar.CH,1*H*,s), 7.8 (Ar.CH,1*H*,d), 7.4 (Ar.CH,1*H*,t), 6.6 (Ar.CH,1*H*,d), 7.6 (Ar.CH,1*H*,t), 7.5 (Ar.CH,1*H*,d), 12.3 (COOH, 1*H*,s).

***N*-[5-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]-2-(phenylamino) Acetamide:**
IR Spectrum (KBr, cm^{-1}): 600 (C-S), 1126(C-O), 1303 (C-N), 1335 (lacto C=O), 1712(keto C=O), 2027 (Ar C=C), 3294 (N-H), 3009(C-H).

^{1}H-NMR ($CDCl_3$, δ ppm): 9.5 (NH, *1H*, S), 3.4 (CH, 1*H*, S), 4.0 (NH, 1*H*,t), 8.3 (Ar.CH,1*H*,s), 7.8 (Ar.CH,1*H*,d), 7.5 (Ar.CH,1*H*,t), 6.4 (Ar.CH,1*H*,d), 7.6 (Ar.CH,1*H*,t), 8 (Ar.CH,1*H*,d), 7.5 (COOH, 1*H*,t).

2-[(3-nitrophenyl) amino] -*N*-[5-(2-oxo-2*H*-chromen – 3 -yl) - 1, 3-thiazol – 2 - yl]acetamide:
IR spectrum (KBr, cm^{-1}): 632 (C-S), 1141(C-O), 1581 (C-N), 1435 (lacto C=O), 1563 (AmideN-H) 1743(keto C=O), 1643 (Ar C=C), 3363 (N-H), 2862(C-H), 3101(Ar CH).

^{1}H-NMR ($CDCl_3$, δ ppm): 12.7 (NH, *1H*, S), 4 (CH, 1*H*, S), 4.4 (NH, 1*H*,t), 8.3 (Ar.CH,1*H*,s), 7.8 (Ar.CH, 1*H*,d), 7.4 (Ar.CH, 1*H*,t), 6.5 (Ar.CH, 1*H*,d), 7.6 (Ar.CH,1*H*,t), 8 (Ar.CH,1*H*,d), 3.4 (CH, 1*H*,s).

(2-(4-methoxyphenylamino)-N-(4-(2-oxo-2H-chromen-3-yl) thiazol-2-yl) Acetamide):
IR Spectrum (KBr, cm^{-1}) 594 (C-S), 1180(C-O), 1390 (C=N), 1657 (lacto C=O), 1535 (AmideN-H) 1666(keto C=O), 3201 (N-H), 3001(Ar CH).

^{1}H-NMR ($CDCl_3$, δ ppm): 12.7 (NH, *1H*, S), (OCH_3 3.5), 4.4 (NH, 1*H*,t), 8.3 (Ar.CH,1*H*,s), 7.8 (Ar.CH,1*H*,d), 7.4 (Ar.CH,1*H*,t), 6.5 (Ar.CH,1*H*,d), 7.6 (Ar.CH,1*H*,t), 8 (Ar.CH,1*H*,d), 3.4 (CH, 1*H*,s).

RESULTS: The synthesized compounds were subjected to antimicrobial screening by the Cup plate method for the zone of inhibition and Minimum Inhibitory Concentration. The Antibacterial activity was tested against various gram-positive and Gram-negative bacteria and anti-fungal activity against various fungal strains compared with standard drugs.

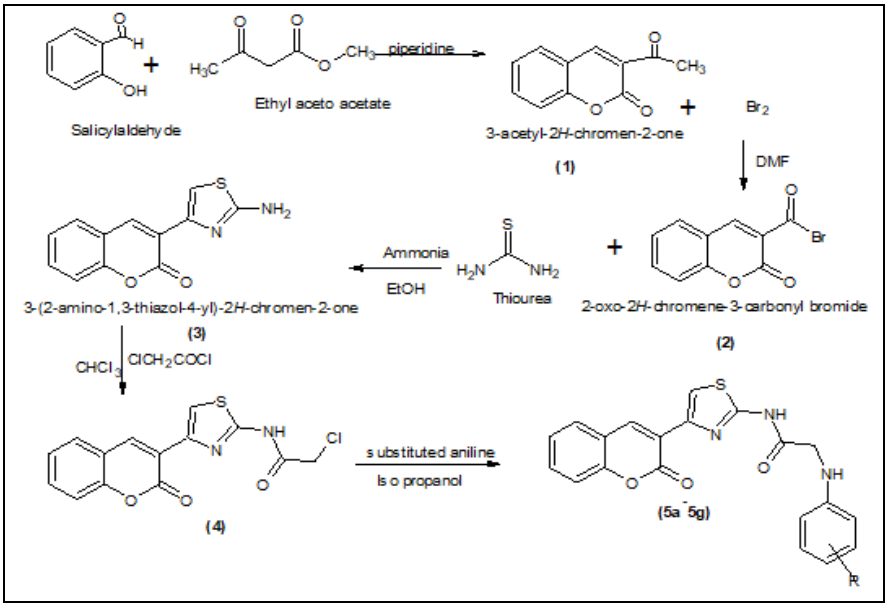

TABLE 1: ZONE OF INHIBITION OF TARGET COMPOUNDS (5A-5G) FOR BACTERIA AND FUNGI

S. no.	Compound	Conc. (µg/ml)	Zone of inhibition (mm)			
			S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
1	5a	50	9±1.73	12±1.68TG	7±1.25	10±1.63
		100	10±1.45	14±1.37	9±1.62	12±1.65
		150	12±1.36	15±1.15	11±1.55	15±1.18
2	5b	50	10±1.32	14±1.18	11±1.18	14±1.34
		100	12±1.67	16±1.17	15±1.27	15±1.16
		150	18±1.06	22±1.19	18±1.51	20±1.45
3	5c	50	8±1.34	12±1.34	10±1.10	12±1.38
		100	12±1.65	14±1.36	12±1.73	13±1.34
		150	14±1.46	15±1.65	14±1.52	15±1.16
4	5d	50	6±1.43	8±1.35	8±1.18	11±1.45
		100	7±1.82	10±1.36	10±1.74	13±1.28
		150	9±1.67	12±1.67	12±1.50	15±1.48
5	5e	50	8±1.43	11±1.48	5±1.45	9±1.84
		100	9±1.32	13±1.17	6±1.34	10±1.67
		150	10±1.10	14±1.04	7±1.72	12±1.47
6	5f	50	7±1.16	11±1.36	6±1.78	9±1.67
		100	10±1.25	13±1.58	18±1.23	12±1.43
		150	12±1.06	14±1.14	10±1.18	13±1.17
7	5g	50	8±1.36	8±1.17	8±1.67	11±1.12
		100	10±1.25	9±1.34	10±1.56	12±1.45
		150	12±1.16	12±1.17	12±1.15	12±1.48
Standard	Ciprofloxacin	150	26±1.36	29±1.54	24±1.35	28±1.33

TABLE 2: ZONE OF INHIBITION OF COMPOUNDS TARGET COMPOUNDS (5A-5G) AGAINST FUNGUS SPECIES

S. no.	Compound	Conc. µg/ml	Zone of inhibition (mm)	
			A. niger	*C. albicans*
1	5a	50	9±1.18	10±1.36
		100	10±1.28	11±1.45
		150	12±1.15	15±1.18
2	5b	50	11±1.36	11±1.17
		100	13±1.39	12±1.23
		150	15±1.11	14±1.18
3	5c	50	14±1.48	10±1.23
		100	15±1.46	12±1.34
		150	17±1.12	14±1.15
4	5d	50	9±1.38	12±1.54
		100	10±1.38	14±1.53
		150	12±1.10	17±1.18
5	5e	50	10±1.30	10±1.36
		100	12±1.63	12±1.52
		150	14±1.72	14±1.17
6	5f	50	11±1.73	12±1.19
		100	12±1.45	13±1.53
		150	14±1.08	14±1.28
7	5g	50	10±1.11	9±1.23
		100	11±1.37	10±1.73
		150	13±1.15	12±1.16
Standard	Fluconazole	150	25±1.35	27±1.33

TABLE 3: MINIMUM INHIBITORY CONCENTRATION (MIC)

S. no.	Compound code	*S. aureus*	*B. subtilis*	*E. coli*	*P. auerginosa*	*A. Niger*	*C. albicans*
1	5a	20	30	40	30	30	40
2	5b	20	20	30	20	30	20
3	5c	40	30	30	40	40	30
4	5d	20	30	30	30	30	40
5	5e	30	20	30	40	30	30
6	5f	40	50	40	40	40	50
7	5g	30	30	30	30	30	40
Standard	Ciprofloxacin	50	50	40	-	-	-
Standard	Fluconazole	-	-	-	40	50	50

The compound 5b has shown good antibacterial activity against *S. aureus* at MIC of 20µg/ml, *B. subtilis* at MIC of 20µg/ml. The compound 5a has shown good antibacterial activity against *E. coli* at MIC 30µg/ml, *P. aeruginosa* at MIC of 20µg/ml. The compound 5b has shown good antifungal activity against *A. niger* and *C. albicans* at MIC of 30 and 20µg/ml, respectively.

DISCUSSION: The antibacterial and antifungal properties of a series of new coumarin derivatives against stevdord medicines were investigated. Compound 5b has proved to be effective against ciprofloxacin at varied concentrations. The actions of the remaining derivatives were moderate. Compounds 5a and 5b have shown good antifungal activities against Fluconazole. The present scheme is innovative, and the derivatives obtained are novel. Few compounds have shown promising antibacterial and antifungal activities. But with suitable molecule modification of the scheme of the derivatives, we may expect the best results**.**

CONCLUSION: The present work describes the synthesis and biological evaluation of antibacterial and antifungal activities of new coumarin derivatives. The compounds' in vitro antimicrobial screening results indicate that 5b, 5c, 5d and 5f showed moderate activity. Compounds 5e and5g showed less activity against bacteria as well as fungus. Compound 5a showed comparable antibacterial and antifungal activity to that of the standard. Thus, we conclude that the synthesized compounds have a new scaffold that can be used as a leader in developing novel antimicrobial agents.

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CONFLICTS OF INTEREST: Nil

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