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Design, Synthesis And Evaluation Of Antibacterial Activity Of Novel((7-Nitro/Bromo-4-Oxo-4*h*-Chromen-3-Yl)Methyl)-*N*-Phenylsulfonyl-D-Alanine/Leucine/Glycine Derivatives

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Abstract

Introduction: *The main cause of death worldwide is the spread of various infectious diseases. Despite significant advances in infectious disease research and treatment, the control and eradication of these diseases faces major challenges. So, to treat these deadly infectious diseases, a large number of drugs like antibiotics, antiviral and antifungal agents are used but drug resistance is the major problem among them.*

Aims and Objectives: *To avoid these kinds of problems, more attention has been taken towards designing, synthesis and pharmacological evaluation of some novel antimicrobial molecules. There are a large number of methods for the treatment of infectious diseases. But inhibition of DNA gyrase and RNA synthetase is the very effective mechanism for the treatment of microbial infections. Chromones are very effective against microbial agents as these are proven very successful for the inhibition of DNA gyrase and RNA synthetase. The chromone moiety has a wide variety of pharmacological activities such as anticancer antiviral, antioxidant, antifungal, anti HIV, anti-inflammatory. Similarly, Sulfonamides, have bacteriostatic action by inhibiting the conversion of p-aminobenzoic acid to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis. This knowledge inspired towards the designing, synthesis and pharmacological evaluation of chromone based novel sulfonamide derivatives. The present work includes synthesis of substituted 3-Formylchromones, synthesis of chromone based novel sulfonamide derivatives and evaluation of antimicrobial activity of the synthesized derivatives.*

Materials and Methods: *Initially, synthesis of 3-Formylchromones was carried out under ice chilled conditions with continuous stirring by reacting substituted acetophenones with $POCl_3$ and DMF by Vilsmeier Hack reaction. The compounds 3-Formylchromones have been reacted with various substituted sulphonamide derivatives to yield novel chromone-based sulphonamides. The solid and recrystallized over alcohol, filtered and dried. The reaction completion was monitored by TLC (hexane-ethyl acetate, 9:1).*

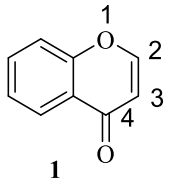
Antibacterial Activity: *All the synthesized compounds were evaluated for their in vitro antibacterial activity.*

Keywords: *Chromone, Sulphonamide, Antibacterial activity, Gram-positive, Gram-negative*

INTRODUCTION

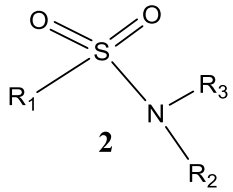
Infectious diseases are the main reason of loss of life worldwide, especially in low earnings countries, specifically in younger children [1,2]. These infectious illnesses are ranked with-inside the top ten reasons of death globally as per the recent survey through the World Health Organization. As in 2013, Infectious

diseases resulted in 9.2 million deaths (about 17% of all deaths) [3]. The development of bacterial infection is highly dependent on the host factors (Genes, nutrition, age, duration of exposure, and co-existing illnesses) and enviroment factor such as environmental pollutants, chemicals, and contaminants which weaken the body's defenses against bacterial infection. It can also spread via vectors such as animals and insects before being passed on to humans. It can affect any organ in the human body [4] There is a tendency for certain bacteria to infect certain organs, but not others. For instance, Neisseria meningitis normally causes meningitis in the meninges (coating) of the central nervous system, and it can cause pneumonia in the lungs and skin infections [5]. There are lots of antibiotic for Infectious microbial disease but it stays a pressing problem worldwide due to the fact microbes have resisted prophylaxis or therapy longer than other life forms. Resistance to a variety of anti-microbial agents (b-lactam antibiotics, macrolides, quinolones, and vancomycin) is becoming an increasingly serious global issue [6,7]. Chromone (**1**) are naturally occurring chemicals which exhibit better anti-microbial activities [8]. The term chromone is derived from the Greek word chroma, which means "color," indicating that many chromone derivatives can exhibit a wide range of colors. It can find all over the world, especially in plants. The core consists of an oxygen-containing heterocycle with a benzoannelated g-pyrone molecule form the core of several flavonoids, such as flavones and isoflavones [9,10]. Chromone system i.e. benzopyran-4-one moiety is basic structure of flavonoids like flavones, flavonols and isoflavones [11]. This moiety is a unit in several drugs as it possesses anti-cancer [12], anti-HIV [13], anti-inflammatory [14] and antibacterial activities [15].



1

Sulfonamides (**2**) are antibacterial drug most widely used in the world, chiefly because of their low cost, low toxicity, and excellent activity against common bacterial diseases [16]. More than 20,000 sulfonamides derivatives have been produced so far [17]. This blocks the synthesis of dihydrofolic acid as well as decreases the amount of metabolically active tetrahydrofolic acid, a co-factor for the synthesis of purines, thymidine, and DNA [18]. The sulphonamides have broad spectrum bacteriostatic activity *Streptococcus pyogenes, Streptococcus pneumoniae, some strains of Bacillus anthracis, Corynebacterium diphtheriae, Haemophilus influenzae, Haemophilus ducreyi,* Brucella species, *Vibrio cholera, Chlamydia trachomatis*, Actinomyces, Nocardia species, protozoans, *Plasmodium falciparum*, *Escherichia coli, Toxoplasma gondii, Enterobacter aerogenes and Pseudomonas aeruginosa* [19]. In this study, we have to prepare chromone of sulphonamide and check the antibacterial activity of it.



2

MATERIALS AND METHOD

MATERIALS

All the chemical and solvent were Acetophenones, $POCl_3$ (Phosphoryl chloride), DMF(Dimethyl formamide), 3-Formylchromones, Sodium carbonate, Amino acids (alanine, leucine and glycine), Benzene sulphonyl chloride, Methanol, DCM (Dichloromethane), HCl, Silica gel, Ethanol, Acetic acid, Benzene sulphonamide.

METHODS

Synthesis of substituted 4-oxo-2-(phenylamino)-4*H*-chromone-3-carbaldehyde (4a-b) from substituted acetophenones (3a-b)

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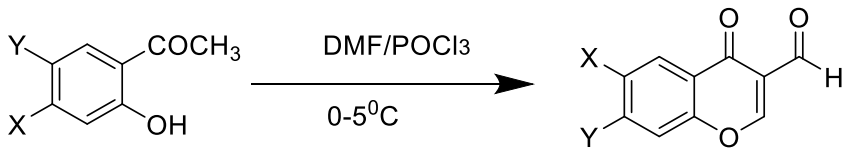
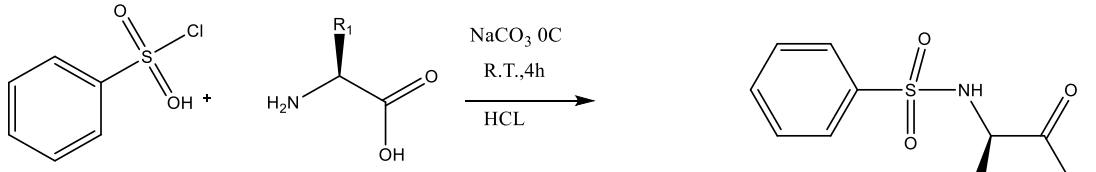
Initially, synthesis of 3-Formylchromones **(4a-b)** was carried out under ice chilled conditions with continuous stirring by reacting substituted acetophenones **(3a-b)** with $POCl_3$ and DMF by Vilsmeier Hack reaction **(Scheme-1)** [20,21,22].



(3a-b) **(Scheme-1)** **(4a-b)**

Compounds (4a-b)	X	Y
a	H	NO_2
b	H	Br

Synthesis of amino acids substituted benzene sulphonamides (7a-c):
Sodium carbonate (NaCO3, 1.59 g, 15 mmol) was added to a solution of various amino acids (alanine, leucine and glycine) (2, 12.5 mmol) in water (15 mL) with continuous stirring until all the solutes dissolved. The solution was cooled to −5°C and the appropriate benzene sulphonyl chloride (1, 15 mmol) was added in four portions over a period of 1 h. The slurry was then stirred at room temperature for another 4 hours. TLC (MeOH/DCM 1:9) was used to monitor the reaction's progress. Upon completion, the mixture was acidified using 20% aqueous hydrochloric acid to pH 2. The products (7a-c) were obtained in their analytical grade after washing with tartaric acid solution of pH 2.2. The products were dried over self-indicating fused silica gel in a desiccator **(Scheme- 2)** [23].



(5) **(6a-c)** **(Scheme-2)** **(7a-c)**

Compounds	R_1
7 a	Alanine
7b	Leucine
7c	Glycine

Synthesis of Novel substituted chromone based sulfonamides or *N*-((7-Nitro/bromo-4-oxo-4*H*-chromen-3-yl)-methyl)-*N*-(phenylsulfonyl)-D-alanine/leucine/glycine (8a-f):
The compounds 3-Formylchromones (4a-b) and Amino acid substituted benzene sulphonamides (7a-c) were refluxed with continuous stirring in dry ethanol at 80° C. After 10 minutes, 1 mL glacial acetic acid was added and the stirring was continued for 1 hour at refluxing temperature. Then, stirring was kept continued, at room temperature, for another 12 hours leading to formation of a solid product (8a-f). The solid (8a-f) and recrystallized over alcohol, filtered and dried **(Scheme-3)**. The reaction completion was monitored by TLC (hexane-ethyl acetate, 9:1).

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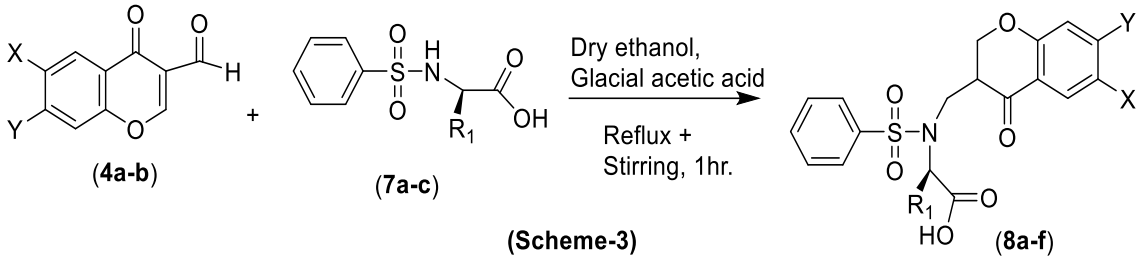


(4a-b) (7a-c) (8a-f)

(Scheme-3)

Compounds	X	Y	R_1
8a	H	NO_2	Alanine
8b	H	NO_2	Leuine
8c	H	NO_2	Glycine
8d	H	Br	Alanine
8e	H	Br	Leucine
8f	H	Br	Glycine

Table-1: %age yield and reaction conditions of compounds (8a-f) are summarized below:

Sr. No.	Compound	X	Y	R_1	Solvent (Dry)	Reaction Condition	Product (%Yield)
1	8a	H	NO_2	Alanine	Ethanol	Reflux,80°C, 1 h, Stirring, R.T., (12h)	70
2	8b	H	NO_2	Leucine			75
3	8c	H	NO_2	Glycine			66
4	8d	H	Br	Alanine			74
5	8e	H	Br	Leucine			76
6	8f	H	Br	Glycine			74

Structural characterization of all the titled compounds was done through spectral analysis (^{1}HNMR).

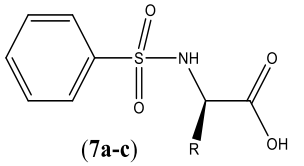
EXPERIMENTAL

Identification and characterization of the compounds synthesized is done by using different techniques such as Thin Layer Chromatography, Infrared Spectroscopy, 1H-Nuclear Magnetic Resonance Spectroscopy, 13C-Spectroscopy, Mass Spectroscopy. All the melting points measured in open-glass capillary tubes on a liquid paraffin bath using Optical Melting Point (Nutronics) apparatus. The Reaction progresses and the purity of the product was tested by Thin Layer Chromatography using silica Gel-G coated glass that was visualized as a visualizing agent by exposure to iodine vapors. Proton NMR spectroscopy was performed using Bruker Advance II (300MHz) NMR spectrometer for solution using tetramethylsilane (TMS) as internal reference in CDCl3/ DMSO-d6. Parts per million were used to report all chemical shifts (ppm). Chemical shifts were reported in ppm (§) and coupling constant (J) values in Hertz.

General procedure for the synthesis of amino acid substituted sulfonamides (7a-c)

Sodium carbonate ($NaCO_3$, 1.59 g, 15 mmol) was added to a solution of various amino acids (alanine, leucine and glycine) (2, 12.5 mmol) in water (15 mL) with continuous stirring until all the solutes dissolved. The solution was cooled to −5°C and the appropriate benzene sulphonyl chloride (1, 15 mmol) was added in four portions over a period of 1 h. The slurry was further stirred at room temperature for 4 h. The progress of the reaction was monitored using TLC (MeOH/DCM) 1:9). Upon completion, the mixture was acidified using 20% aqueous hydrochloric acid to pH 2. The products were obtained in their analytical grade after washing with tartaric acid solution of pH 2.2. The products were dried over self-indicating fused silica gel in a

desiccator. A simple method in aqueous media under dynamic pH control is adopted for synthesis of sulfonamides. Filtration after acidification is involved for isolation of products. All the amines were weighed accurately and dissolved completely by addition of distilled water by constant stirring using magnetic stirrer. The pH of the reaction contents was strictly monitored and maintained at 8–10 at regular intervals during the experimental reaction using Na_2CO_3 solution (1 M). Then benzene sulfonyl chloride was accurately weighed and added carefully into the above solution. The reaction was carried in round bottom flask equipped with magnetic stirrer. During stirring sulphonyl chloride initially floats on the surface and the completion of reaction was examined by the change in pH value due to formation of HCl by the consumption of sulphonyl chlorides during the reaction. On completion of the reaction pH was adjusted at 2-3 using HCl solution (2 M). The precipitates formed were filtered, washed several times with distilled water, and recrystallized using methanol and dried using rotary evaporator.



(7a-c)

R = Alanine, Leucine, Glycine

A. (Phenylsulfonyl)-*D*-alanine (7a)

The whole Procedure was carried according to the procedure prescribed above, 77%yield, M.P. 150-160°C, $C_{11}H_{15}NO_4S$, molecular weight 257.07g, Solubility DMSO.

B. (Phenylsulfonyl)-*D*-leucine (7b)

The whole Procedure was carried according to the procedure prescribed above, 74%yield, M.P. 150-160°C, $C_{12}H_{17}NO_4S$, molecular weight 271.33g, Solubility DMSO.

C. (Phenylsulfonyl)glycine (7c)

The whole Procedure was carried according to the procedure prescribed above, 79%yield, M.P. 150-160°C, $C_8H_9NO_4S$, molecular weight 360.34g, Solubility DMSO.

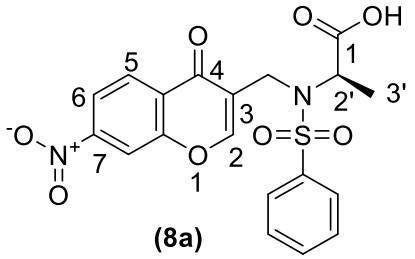
1. General procedure for the synthesis of chromone based sulfonamides (8a-f)

The compounds 3-Formylchromones **(4a-b)** and substituted sulphonamides **(7a-c)** were

refluxed with continuous stirring in dry ethanol at 80^{O}C. After 10 minutes, 1mL glacial acetic acid was added and the stirring was continued for 1hour at refluxing temperature. Then, stirring was kept continued, at room temperature, for another 12 hours leading to formation of a solid product **(8a-f).** The solid **(8a-f)** and recrystallized over alcohol, filtered and dried**.** The reaction completion was monitored by TLC (hexane-ethyl acetate, 9:1).

A. *N*-((7-nitro-4-oxo-4*H*-chromen-3-yl)methyl)-*N*-(phenylsulfonyl)-*D*-alanine (8a)

The whole Procedure was carried according to the procedure prescribed above, 77%yield, M.P. 150-160°C, $C_{19}H_{16}N_2O_8S$, molecular weight 432.40g, Solubility DMSO.

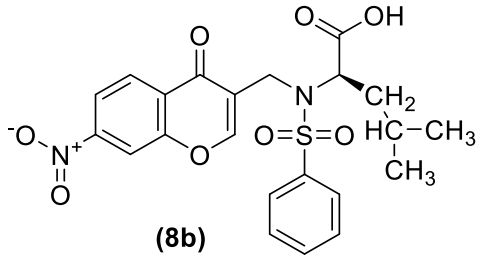


(8a)

^{1}H-NMR: §$_{ppm}$ (DMSO-d$_6$; 400MHz): 7.95-7.72(m, chromone), 3.83(s, -CH_2 at C-3), 1.22 (s, -CH_3, C-3'), 3.60 (s, -CH, C-2'), 12.39(s, -OH, C-1'), 7.70-7.51(m, N-SO_2-Ph)

B. *N*-((7-nitro-4-oxo-4*H*-chromen-3-yl)methyl)-*N*-(phenylsulfonyl)-*D*-leucine (8b)

The whole Procedure was carried according to the procedure prescribed above, 73%yield, M.P. 150-160°C, $C_{22}H_{22}N_2O_8S$, molecular weight 474.48g, Solubility DMSO.

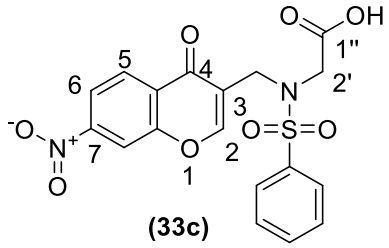


(8b)

^{1}H-NMR: §$_{ppm}$ (DMSO-d$_6$; 400MHz): 7.95-7.72(m, chromone), 3.83(s, -CH_2 at C-3), 3.40 (s, -CH_2, C-2'), 12.35(s, -OH, C-1'), 1.61 (s, -CH_2, C-3'), 1.40 (s, -CH, C-2'), 0.90 (s, 2-CH_3 C-4'), 7.70-7.51(m, N-SO_2-Ph)

C. *N*-((7-nitro-4-oxo-4*H*-chromen-3-yl)methyl)-*N*-(phenylsulfonyl)glycine (8c)

The whole Procedure was carried according to the procedure prescribed above, 75%yield, M.P. 150-160°C, $C_{18}H_{14}N_2O_8S$, molecular weight 418.38g, Solubility DMSO.

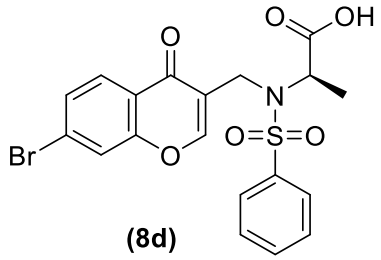


(33c)

^{1}H-NMR: §$_{ppm}$ (DMSO-d$_6$; 400MHz): 7.95-7.72(m, chromone), 3.83(s, -CH_2 at C-3), 4.10 (s, -CH_2, C-2'), 13.09(s, -OH, C-1'), 7.70-7.51(m, N-SO_2-Ph)

D. *N*-((7-bromo-4-oxo-4*H*-chromen-3-yl)methyl)-*N*-(phenylsulfonyl)-*D*-alanine (8d)

The whole Procedure was carried according to the procedure prescribed above, 72%yield, M.P. 150-160°C, $C_{19}H_{16}BrNO_6S$, molecular weight 466.30g, Solubility DMSO.

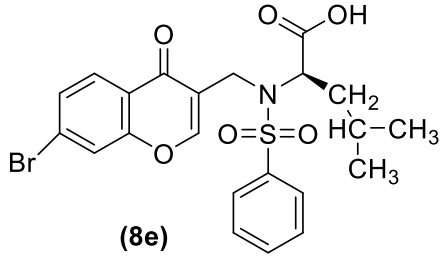


(8d)

^{1}H-NMR: §$_{ppm}$ (DMSO-d$_6$; 400MHz): 7.57-7.34(m, chromone), 3.83(s, -CH_2 at C-3), 1.22 (s, -CH_3, C-3'), 3.60 (s, -CH, C-2'), 12.39(s, -OH, C-1'), 7.88-7.60(m, N-SO_2-Ph)

E. *N*-((7-bromo-4-oxo-4*H*-chromen-3-yl)methyl)-*N*-(phenylsulfonyl)-*D*-leucine (8e)

The whole Procedure was carried according to the procedure prescribed above, 69%yield, M.P. 150-160°C, $C_{22}H_{22}BrNO_6S$, molecular weight 508.38g, Solubility DMSO.

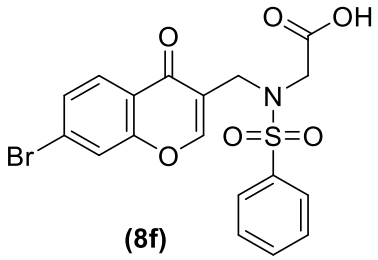


(8e)

^{1}H-NMR: §$_{ppm}$ (DMSO-d$_6$; 400MHz): 7.7-7.32(m, chromone), 3.83(s, -CH_2 at C-3), 3.40 (s, -CH_2, C-2'), 12.35(s, -OH, C-1'), 1.61 (s, -CH_2, C-3'), 1.40 (s, -CH, C-2'), 0.90 (s, 2-CH_3 C-4'), 7.90-7.62(m, N-SO_2-Ph)

F. *N*-((7-bromo-4-oxo-4*H*-chromen-3-yl)methyl)-*N*-(phenylsulfonyl)glycine (8f)

The whole Procedure was carried according to the procedure prescribed above,73% yield, M.P. 150-160°C, $C_{18}H_{14}BrNO_6S$, molecular weight 452.28g, Solubility DMSO.



(8f)

^{1}H-NMR: $\S_{ppm}$ (DMSO-d_6; 400MHz): 7.59-7.33(m, chromone), 3.83(s, -CH_2 at C-3), 4.10 (s, -CH_2, C-2'), 13.07(s, -OH, C-1'), 7.89-7.63(m, N-SO_2-Ph)

RESULTS

ANTIMICROBIAL ACTIVITY

The antibacterial activity was performed by calculating Zone of inhibition of the synthesized compounds (**8a-f**) against *S.aureus B.subtilis, P.aeroginosa* and *E.coli* at (10, 20 and 30) µg/mL by Kirby Bauer disc diffusion method using ciprofloxacin as standard drug. From the results of inhibition zone values, it was observed that most of the titled compounds have shown dose dependent activity. Their antimicrobial activity was found to increase, when concentration was increased from 10µg/mL to 20µg/mL and then, to 30µg/mL.

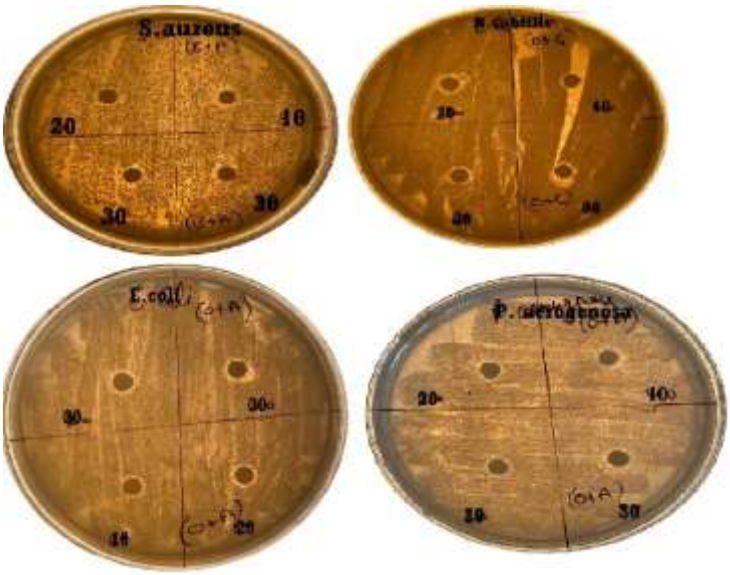


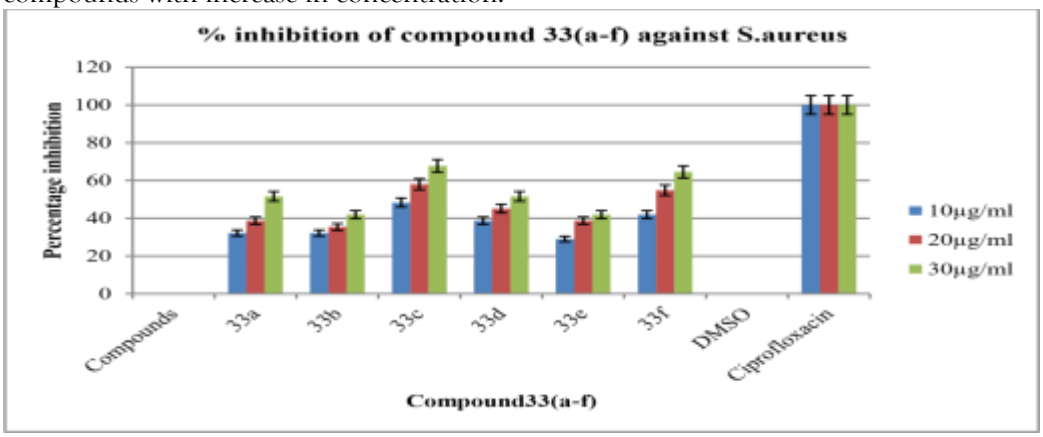
Figure 1: Zone of inhibition of the synthesized compounds (8a-f) against *S.aureus B.subtilis, P.aeroginosa* and *E.coli* at (10, 20 and 30) µg/mL by Kirby-Bauer disc diffusion method respectively.

Table 4: Percent inhibition results of the synthesized compounds (8a-f) against bacterial strains compared with standard drug Ciprofloxacin for antibacterial activity.

Compound	Con. (µg/ml)	S.aureus		B.subtilus		P.aeroginosa		E.coli	
		% Inhibition	ZOI	% Inhibition	ZOI	% Inhibition	ZOI	% Inhibition	ZOI
	10	10	32.2	9	29	9	29	-	-

8a	20	12	38.7	10	32.2	10	32.2	9	29
	30	16	**51.6**	11	35.4	12	38.7	11	35.4
8b	10	10	32.2	9	29	-	-	-	-
	20	11	35.4	9	29	-	-	-	-
	30	13	**41.9**	11	35.4	-	-	-	-
8c	10	15	48.3	11	35.4	10	32.2	9	29
	20	18	58	14	45.1	12	38.7	11	35.4
	30	21	**67.7**	16	**51.6**	13	**41.9**	13	**41.9**
8d	10	12	38.7	11	35.4	-	-	-	-
	20	14	45.1	13	41.9	-	-	-	-
	30	16	**51.6**	15	**48.3**	-	-	-	-
8e	10	9	29	10	32.2	-	-	-	-
	20	12	38.7	11	35.4	-	-	-	-
	30	13	**41.9**	12	38.7	-	-	-	-
8f	10	13	41.9	14	45.1	10	32.2	7	22.5
	20	17	54.8	17	54.8	13	41.9	10	32.2
	30	20	**64.5**	20	**64.5**	16	**51.6**	12	38.7
DMSO	-	-	-	-	-	-	-	-	-
Standard (Ciprofloxacin)	10	31	100	30	100	30	100	31	100

The results shown in table 4 concluded that the titled compounds were active against various bacterial strains at all the three concentrations i.e. 10µg/mL, 20µg/mL and 30µg/mL. However, results obtained at 30µg/mL concentration have been highlighted because most of the compounds were found active at this concentration and have given very good % inhibition. Further, an increase in %inhibition has been observed for all the compounds with increase in concentration.



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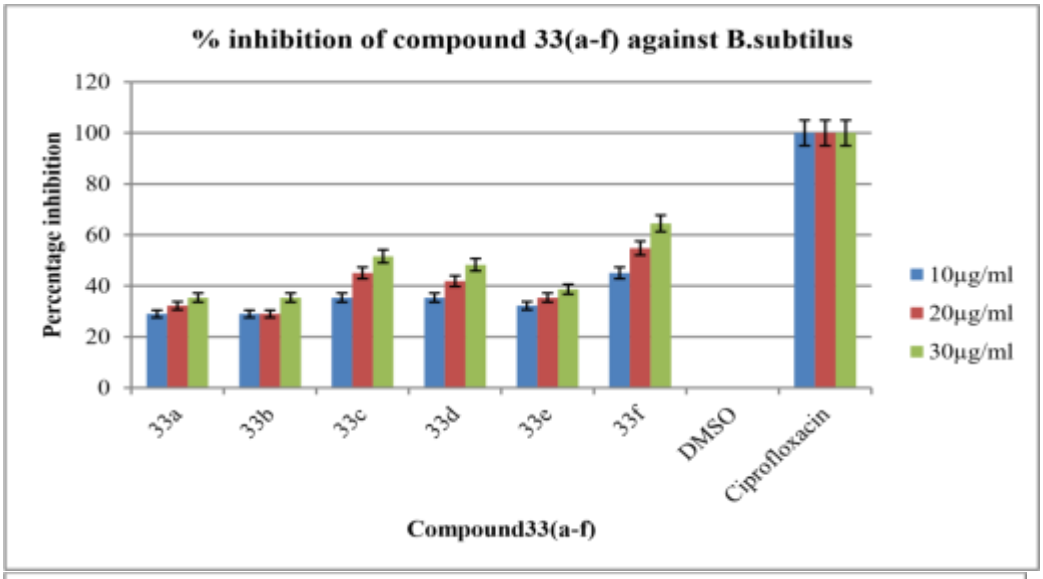
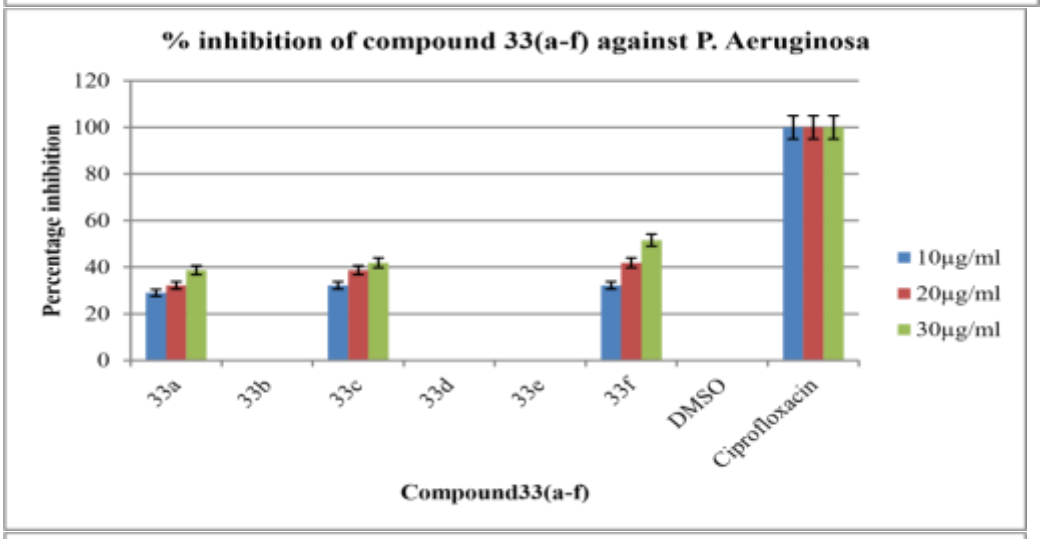
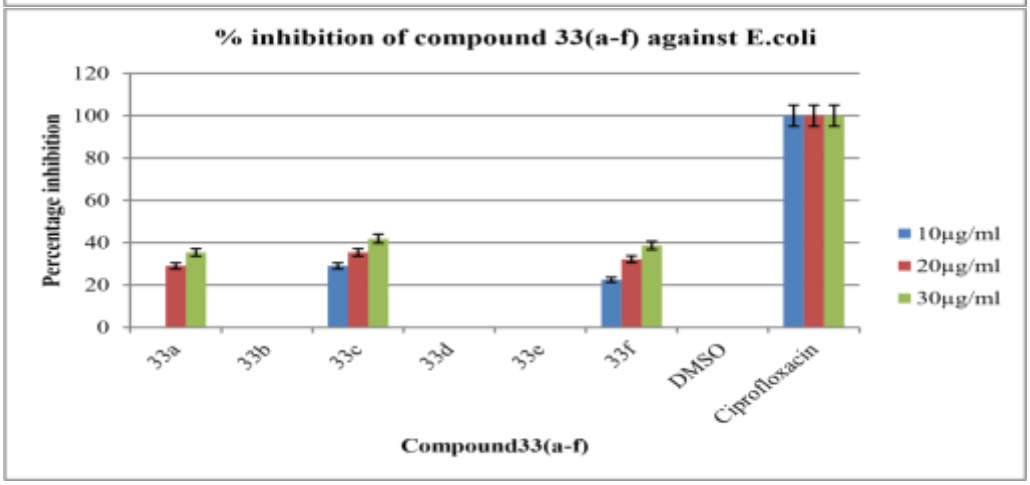






GRAPH (1-4): % Inhibition of compounds (33a-f) against ***S.aureus, B.subtilis, P.aeruginosa and E.coli*** **respectively.**

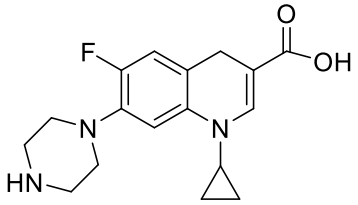
DISCUSSION

Bacterial infections may be treated with antibiotics which are classified as bactericidal and bacteriostatic. Micro-organisms resistant to multiple anti-infective agents have increased around the world and due to this resistance, several health and economic problems arises. The resistance towards wide spectrum antibacterial

has initiated the discovery and modification of new antibacterial. Among the various methods of prevention and cure of infectious diseases, inhibition of dihydrofolate reductase or DNA*gyrase* and RNA synthetase inhibition are proven success to cause selective inhibition of the growth and death of micro-organisms like bacteria. In relation to inhibition and death of micro-organisms, chromones are considered to be the effective molecules and have found to be the emerged as a main category of naturally occurring/synthetic flavonoids. The chromone moieties have their major utilization to either inhibit DNA*gyrase* or RNA synthetase or inhibit dihydrofolate reductase to show antimicrobial activities.

Similarly, Sulphonamides are synthetic bacteriostatic antibiotics that inhibit conversion of *p*-aminobenzoic acid to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis.

Keeping in view the above observations, it was decided to synthesize chromone based some novel heterocyclic hybrid derivatives i.e Chromeno-sulphonamides by a reaction of substituted 3-Formylchromone derivatives with various chemical reagents and evaluated for antibacterial activity. The pharmacological study was performed in comparison to standard drug Ciprofloxacin because from literature review it was observed that the target compounds will have structural similarities with Ciprofloxacin and Ciprofloxacin is also a DNA*gyrase* inhibitor. So, a close resemblance of the synthetic derivatives with ciprofloxacin was realized.



Ciprofloxacin

CONCLUSION

- The compounds were synthesized through reported synthetic methods and all were obtained in good yields.
- In vitro antibacterial evaluation was performed on all the titled compounds and compounds 8a, 8c and 8f were found to display promising antibacterial activity against various gram-positive and gram-negative bacterial strains at mainly 30µg/mL. While compounds 8b, 8d and 8e were found to be active against only on gram-positive bacterial strains.
- The results of in vitro antimicrobial activity evaluation have marked that the 6 & 7-positions of the 3-Formylchromone ring one as major influencing factor towards antimicrobial activity of these compounds.
- Though compounds have displayed very good antimicrobial activity (most of them are very active at 30 µg/mL concentration) but they have been found much less active than the standard drug ciprofloxacin (active at 10 µg/mL conc.).
- The reason behind low activity of these compounds as compared to the ciprofloxacin needs further probation into their binding patterns and their physicochemical properties.
- Compounds 8a, 8c and 8f have been found active against all the microbial strains used and can act as lead compounds for further investigations and improvement.
- Further investigations on these compounds will be kept going on in near future. In future, we will surely work on to develop some new derivatives having chiral side chains and also will extend our investigations to in vivo antimicrobial studies on rat or mouse models.

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