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SYNTHESIS, CHARACTERIZATION & BIOLOGICAL STUDIES OF NEWER CLASS OF QUNINOLONE DERIVATIVES

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Keywords:

Quinolones, Gould-Jacob reaction, characterization, anti-microbial activity

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ABSTRACT: Background: Antimicrobials are used for bacterial infections & has a great benefits in health related problems of human life. The main objectives of medicinal chemistry is synthesising and producing newer molecules having a valuable significant therapeutic action. Quinolones has a considerable scientific and clinical interest since their discovery. **Objective:** Quinolones class of drugs are useful in the treatment of serious bacterial infections thus keeping in view a potential approach is made for synthesising & characterizing of newer quinolone derivatives for their biological activity. **Method:** Quinolone ester was synthesised from Gould-Jacob reaction by using substituted aniline & diethylethoxymethelene malonate (EMME) **Results:** Solubility of all synthesised compounds were checked in various solvents & were characterized by FT-IR, ^{1}H-NMR. **Conclusion:** The result of the present study thus demonstrates the anti-microbial activity against gram positive (*Bacillus subtilis*) & gram negative (*Escherichia coli*) strains.

INTRODUCTION: Infectious diseases [1] caused by bacteria affects millions of people and is a leading causes of death worldwide. Three of the top ten causes of death, or sixteen percent of all deaths each year, are from infectious diseases, for which the treatment is still remains an important and challenging problem because of multidrug resistant microbial pathogens. As one of the biggest challenges in 21st century is facing the modern medicine system. Discovery of newer drug substances with a potential pharmacological effectiveness against several pathogenic microorganisms becomes highly desirable.

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Antimicrobials [2] are one of the most significant use for bacterial infections (Penicillin the first anti-microbial agent) [3] has a great benefits in health related problems of human life. The main objectives of medicinal chemistry is synthesising and producing newer molecules having a value of significant therapeutic agents. Development of new antibiotics [4] has been achieved from derivatives of known antimicrobial agents or by identification of novel agents active against previously unexploited targets.

Quinolones has a considerable scientific and clinical interest since their discovery. The term quinolones is commonly used for the quinolone carboxylic acids or 4-quinolones; a group of synthetic antibacterial agents containing 4-oxo-1,4-dihydroquinoline skeleton [5]. They are relatively new class of synthetic antibiotics with potent bactericidal against many clinically important pathogens which are responsible for variety of

infections including urinary tract infections (UTI) [6], gastrointestinal infections, respiratory tract infections (RTI) [7] & some other infections. Different structural modifications in the quinolone nucleus have been made to increase antimicrobial activity and improve its performance. During 1980, s, it was discovered that a fluorine atom at position 6 greatly enhance the spectrum of activity [8].

Quinolones & Fluoroquinolones [9] are active against the DNA-gyrase enzyme, a type II topoisomerase [10]. It is believed that DNA-gyrase introduces negative supercoils in DNA by wrapping the DNA around the enzyme. The enzyme then catalyses the breakage of a segment of the wrapped DNA, the passage of a segment of the same DNA through the break and finally the relegation of the break. In this way, DNA "knots" are resolved and the DNA is exposed for replication process. DNA-gyrase is essential for all bacteria and is therefore an excellent target for antibiotics. Quinolones nucleus turn the action of gyrase against the bacteria by blocking the strand passage and thereby hindering proper replication of DNA. This eventually leads to cell death[11].

Since the introduction, following **Fig: 1** depicts quinolones class of drugs are useful in the treatment of serious bacterial infections. They potentially offer a high potency, oral and intravenous formulations, high serum levels, good bioavailability and large volume of distribution indicating concentration in tissues with a potentially low incidence of side-effects. Nalidixic acid [12] was the first quinolone to be developed, but Norfloxacin [13] became the first available for clinical use. On the other hand, it is emphasized that further developments are required in order to combat with the infectious conditions. Thus, keeping in view a potential approach is made in our research of synthesising, characterization & *in-vitro* anti-microbial studies of newer quinolone using disc-plate agar diffusion method.

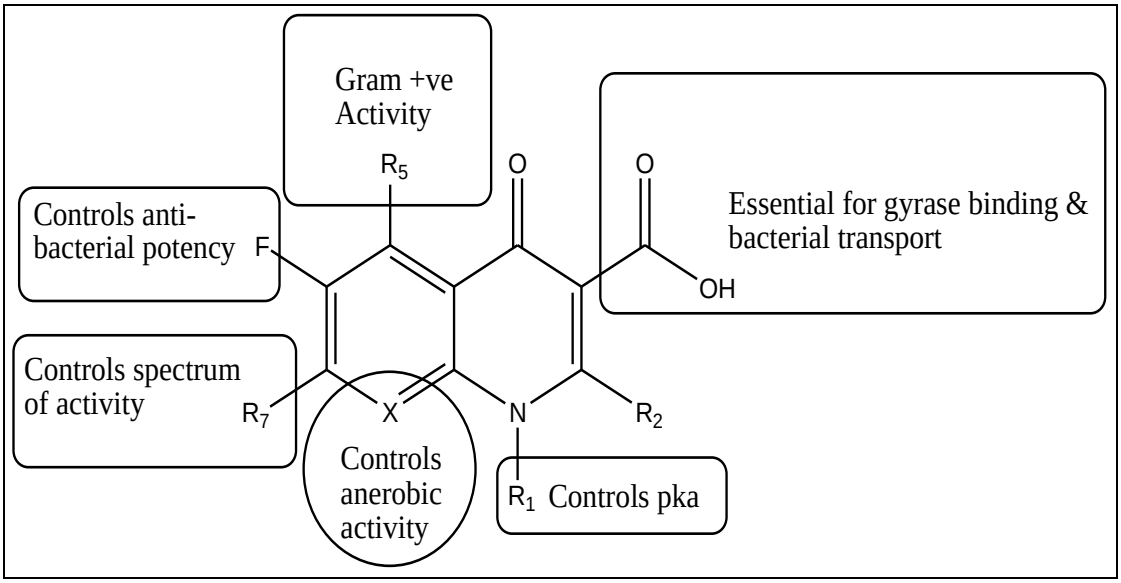

FIG.1: IMPORTANT PROPERTIES OF QUINOLONE NUCLEUS

MATERIAL AND METHODS: All the chemicals & reagents collected were of LR grade from Pallav Chemicals & Loba Chemie. The reactions were monitored by thin layer chromatography on TLC silica gel 60 F254 plates for completion of the reaction; mobile phase solvents were selected as n-hexane: ethyl acetate (3:2) for step-1 reaction; chloroform: methanol (9:1) with a drop of ammonia liquid for step-2, 3 & 4. Melting points of all the synthesized compounds were checked in capillary tubes by using a melting point apparatus (VEEGO melting point apparatus). All the compounds were characterized by FT-IR spectrometer (IR-Affinity, Shimadzu) using ATR correction method; ^{1}HNMR spectra were obtained from 500MHz instrument and chemical shifts were measured as parts per million downfield from Dimethyl sulfoxide (DMSO) as internal standard.

Experimental Section: [14, 15, 16, 17, 18]

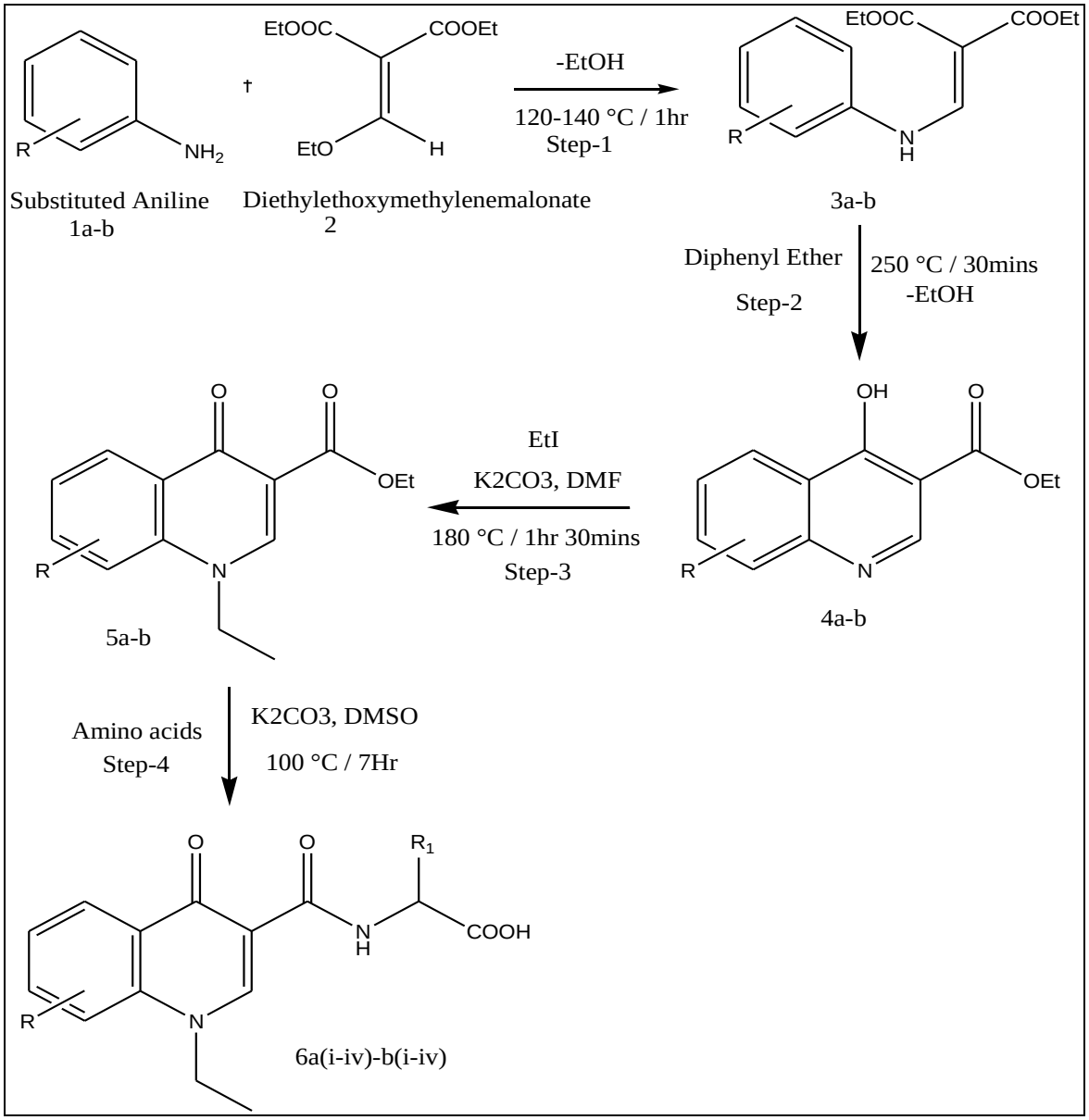

TABLE 1: SUBSTITUENTS FOR ANILINE AND AMINO ACID USED

Sr. No	Substituents	Compound code
1	R= 3-chloro	a
2	R= 3-chloro-4-fluoro	b
3	R1= -H	i
4	R1= -CH3	ii
5	R1= -CH2-CH(CH3)2	iii
6	R1= -CH2-OH	iv

Scheme of Synthesis:

Step-1: Preparation of 3-chloro-ethyl aniline methylene malonate 3a: A mixture of 3-chloro-aniline a (1.45gm, 0.01mol) and diethyl ethoxy methylene malonate (2.16gm, 0.01mol) was taken in RBF and refluxed for 1hrs. Ethanol was removed under vacuum. The crude solid was dried and recrystallized from n-hexane.

Preparation of 3-chloro-4-fluoro-ethyl aniline methylene malonate 3b: A mixture of 3-chloro-4-fluoro-aniline a (1.27gm, 0.01mol) and diethyl ethoxymethylene malonate (2.16gm, 0.01mol) was taken in RBF and refluxed for 1hrs. Ethanol was removed under vacuum. The crude solid was dried and recrystallized from n-hexane.

Step-2: Preparation of 7-Chloro-4-hydroxy-3-carboxylic Acid Ethyl Ester quinolone 4a: The 3-chloro-ethyl anilinomethylene malonate (3.15gm, 0.01mol) was added to diphenyl ether (3.17mol, 10 mL) and refluxed for 30mins at 250˚C with stirring. The mixture was cooled, filtered, washed with n-hexane and dried. The crude solid obtained was purified by recrystallization from DMF; excess of DMF was removed under vacuum.

Preparation of 7-Chloro-6-fluoro-4-hydroxy-3-carboxylic Acid Ethyl Ester quinolone 4b: The 3- chloro-4-fluoro-ethyl anilinomethylene malonate (2.97gm, 0.01mol) was added to diphenyl ether (3.17mol, 10 mL) and refluxed for 30mins at 250˚C with stirring. The mixture was cooled, filtered, washed with n-hexane and dried. The crude solid obtained was purified by recrystallization from DMF; excess of DMF was removed under vacuum.

Step-3: Procedure for Synthesis of 7-Chloro-1-ethyl-1,4-dihydro-4-oxoquinoline - 3 - carboxylic Acid Ethyl Ester) 5a: The mixture of 7-chloro-1,4-dihydro- 4-oxoquinoline-3-carboxylic acid ethyl ester (2.69gm, 0.01mol), ethyl iodide (1.56g, 0.01mol), potassium carbonate (2.76gm, 0.02mol), and charged with dimethyl formamide (20 mL) in 50mL round bottom flask and heated at 180˚C for 1hr30mins. Ice cold water was added to the reaction mixture. The crude solid obtained was purified by extracting in dichloromethane: methanol in ratio of 3: 1.

Procedure for Synthesis of 7-Chloro-6-fluoro-1-ethyl-1,4-dihydro-4-oxoquinoline – 3 -carboxylic Acid Ethyl Ester) 5b: The mixture of 7-chloro-6-fluoro-1,4-dihydro- 4-oxoquinoline-3-carboxylic acid ethyl ester (2.51gm,0.01mol), ethyl iodide (1.56gm, 0.01mol), potassium carbonate (2.76g, 0.02mol), and charged with dimethyl formamide (20 mL) in 50mL round bottom flask and heated at 180˚C for 1hr30mins. Ice cold water was added to the reaction mixture. The crude solid obtained was purified by extracting in dichloromethane: methanol in ratio of 3: 1.

Step-4: Preparation of amino acid linked quinolone derivative Procedure for synthesis of L-Amino acid linked 7-chloro-1-ethyl-functionalized quinolone 6a (i-vi): General reaction: the mixture of 7-Chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Ester (0.22gm, 7.46mmol), L-amino acid (14.8mmol), potassium carbonate(3.07g, 22.38 mmol) & DMSO (10ml) was refluxed for 7hrs with stirring. The reaction mixture was neutralized with 1N HCl until pH reaches to 4 followed by addition of 25ml cold water to precipitate out crude solid compound was extracted in dichloromethane & was evaporated to dryness to obtain pure compound.

Procedure for synthesis of L-Amino acid linked 7-chloro - 6 - fluoro - 1- ethyl-functionalized quinolone 6b (i-vi): General reaction: the mixture of 7 – Chloro - 6-fluoro-1-ethyl-1,4-dihydro-4-oxo quinoline-3-carboxylic Acid Ethyl Ester (0.20gm, 7.46mmol), L-amino acid (14.8mmol), potassium carbonate(3.07gm, 22.38mmol) & DMSO (10ml) was refluxed for 7hrs with stirring. The reaction mixture was neutralized with 1N HCl until pH reaches to 4 followed by addition of 25ml cold water to precipitate out crude solid compound was extracted in dichloromethane & was evaporated to dryness to obtain pure compound.

TABLE 2: COMPOUND CODE WITH IUPAC NAMES FOR SYNTHESISED COMPOUNDS.

Sr.No	Compound codes	IUPAC name
1	6a(i)	2-(7-chloro-1-ethyl-4-oxoquinoline-3-carboxamido)ethanoic acid
2	6a(ii)	2-(7-chloro-1-ethyl-4-oxoquinoline-3-carboxamido)propanoic acid
3	6a(iii)	2-(7-chloro-1-ethyl-4-oxoquinoline-3-carboxamido)-4-methyl pentanoic acid
4	6a(iv)	2-(7-chloro-1-ethyl-4-oxoquinoline-3-carboxamido)-3-hydroxy-propanoic acid
5	6b(i)	2-(7-chloro-1-ethyl-6-fluoro-4-oxoquinoline-3-carboxamido)ethanoic acid
6	6b(ii)	2-(7-chloro-1-ethyl-6-fluoro-4-oxoquinoline-3-carboxamido)propanoic acid
7	6b(iii)	2-(7-chloro-1-ethyl-6-fluoro-4-oxoquinoline-3-carboxamido)-4-methyl pentanoic acid
8	6b(iv)	2-(7-chloro-1-ethyl-6-fluoro-4-oxoquinoline-3-carboxamido)-3-hydroxy-propanoic acid

Procedure for *In-vitro* Anti-bacterial studies [19, 20, 21]**:** The amino acid linked synthesized compounds were studied for their antibacterial activity against isolated Gram-positive strain *(B. subtilis)* and Gram-negative strain *(E. coli)* using disc diffusion method. All the cultures were

prepared by Mueller-Hinton agar and the turbidity of all the bacterial cultures was adjusted to 0.5McFarland standard which is approximately 1 to 2×10^{-8} CFU/ml. The synthesized compounds and standard drug (10mg) were dissolved in DMSO (10 mL) and which was further diluted to achieve 25µg/ml; 50 µg/ml & 100 µg/ml. Agar plates were inoculated by streaking swab over the entire sterile agar surface, the procedure was repeated for 2 more times rotating the plates at 60˚ each time to ensure even distribution, the rim of the plates were also swabbed. After allowing inoculum to dry for 10mins at room temperature (RT) paper disc were placed which were previously soaked in the different concentration solution of synthesised compounds. The plates were allowed to stand at RT for 30mins & then incubated at 37˚C for 24hrs. Then plates were examined for the bacterial growth inhibition which were calculated in zone of inhibition (mm).

RESULT AND DISCUSSIONS:

1. **Table 3**, shows physical characteristic parameter of intermediate & final synthesised compounds were the synthesised compounds are produce in good yields.
2. The FT-IR spectra of final compounds shows various functional groups which are illustrated in **Table 4**, the band in a range 1690-1720cm^{-1} for –COOH group which is shifted to lower frequency due to presences of carbonyl (-C=O) group neighbouring to it at a range of 1600cm^{-1} value, –NH group present at 3400-3500cm^{-1} value, aromatic band in a range of 700-850cm^{-1}, -C-Cl ranges in 600-650cm^{-1}, were as –C-F in 1150-1180cm^{-1}.
3. ^{1}H-NMR of the final compounds are illustrated in **Table 5** were the in ppm with no of ‘H’ & splitting patterns are represented for protons present in the compounds.
4. Elemental analysis of final compounds are calculated in terms of percent & given in **Table 6**.
5. **Anti-bacterial studies:** The disc diffusion method was employed in antibacterial studies of synthesised compounds. The antibacterial activity was tested against the gram positive (B. *subtilis*) & gram negative (*E. coli*) strains. The Zone of inhibition diameter values were determined and tabulated in **Table 7**.

Physical Characteristic Data:

TABLE 3: PHYSICAL CHARACTERISTIC

Sr. No	Compound No.	Melting Point (˚C)	Rf Value	Solubility	Percent Yield (%)
1	3a	57	0.63	Soluble in MeOH, EtOH	90
2	3b	55	0.61		91
3	4a	>295	0.68	Soluble in MDC, DMSO	95
4	4b	>295	0.71		93
5	5a	140	0.79	Soluble in MDC, CHCl3, DMSO	86
6	5b	146	0.81		89
7	6a(i)	258	0.87	Soluble in: MDC; DMSO & DMF Insoluble in: EtOH; MeOH; Hexane	78
8	6a(ii)	262	0.88		76
9	6a(iii)	272	0.91		72
10	6(iv)	248	0.89		78
11	6b(i)	264	0.91		75
12	6b(ii)	268	0.89		79
13	6b(iii)	270	0.90		76
14	6b(iv)	254	0.91		79

[*Mobile Phase Solvents: Step-1 & Step-2: n-hexane: ethyl acetate (3: 2)
Step-3 & Step-4: Chloroform: methanol (0.9: 1) + drop of liquid ammonia]

FT-IR Spectral Data:

TABLE 4: FT-IR SPECTRAL DATA (FREQUENCY VALUES IN CM^{-1}) FOR FINAL COMPOUNDS

Compound No.	ν(-COOH)	ν (-NH-)	ν (-C=CH-N-)	ν (-C=O)	ν (-C-Cl)	ν (-C-F)	ν (Aromatic)	ν (-OH)
6a(i)	1717	3462	1546, 1374	1687	607	-	750, 802	-
6a(ii)	1718	3414	1545, 1378	1628	643	-	742, 796	-
6a(iii)	1720	3481	1539, 1386	1656	665	-	741, 811	-
6a(iv)	1716	3427	1544, 1377	1676	666	-	742, 810	3231
6b(i)	1717	3383	1545, 1374	1688	607	1169	750, 809	-
6b(ii)	1719	3421	1541, 1384	1655	604	1180	750, 803	-
6b(iii)	1716	3439	1546, 1377	1671	644	1159	746, 827	-
6b(iv)	1697	3390	1529, 1379	1612	623	1172	738, 796	3254

^{1}H-NMR Data:

TABLE 5: ^{1}H- NMR SPECTRA FOR FINAL COMPOUNDS

Compound No.	^{1}H- NMR (δppm; No. of H; splitting pattern)
6a(i)	δ=1.3(3H,t,-N-CH2-CH3); δ=3.6(2H,q,-N-CH2-CH3); δ=3.8(2H,d,-NH-CH2-COOH); δ=7.6(1H,d,ArH); δ=8.0(1H,d,ArH); δ=8.2(1H,d,ArH); δ=8.5(1H,s, =C-H); δ=8.8(1H,t,-CO-NH-CH);δ=11.8(1H,s,-COOH).
6a(ii)	δ=1.0(3H,t,-N-CH2-CH3); δ=1.3(3H,d,-NH-CH-CH3); δ=3.8(2H,q,-N-CH2-CH3); δ=4.4(1H,m,-NH-CH-COOH); δ=7.4(1H,d,ArH); δ=7.9(1H,d,ArH); δ=8.2(1H,d,ArH); δ=8.7(1H,s, =C-H); δ=9.0(1H,d,-CO-NH-CH); δ=12.3(1H,s,-COOH).
6a(iii)	δ=1.0(9H,m,-CH-CH2(CH3)2); δ=1.4(3H,t,-N-CH2-CH3); δ=4.2(2H,q,-N-CH2-CH3); δ=4.6(1H,m,-NH-CH-COOH); δ=7.4(1H,d,ArH); δ=7.7(1H,d,ArH); δ=8.7(1H,d,ArH); δ=8.9(1H,s, =C-H); δ=10.2(1H,d,-CO-NH-CH); δ=12.2(1H,s,-COOH).
6a(iv)	δ=1.4(3H,t,-N-CH2-CH3); δ=2.5(1H,d,-CH2-OH); δ=4.2(2H,q,-N-CH2-CH3); δ=4.4(1H,m,-NH-CH-COOH); δ=4.6(2H,t,-CH2-OH); δ=7.4(1H,d,ArH); δ=7.8(1H,d,ArH); δ=8.4(1H,d,ArH); δ=8.7(1H,s, =C-H); δ=10.2(1H,d,-CO-NH-CH); δ=12.4(1H,s,-COOH).
6b(i)	δ=1.4(3H,t,-N-CH2-CH3); δ=2.2(2H,q,-N-CH2-CH3); δ=4.6(2H,d,-NH-CH2-COOH); δ=7.6(1H,d,ArH); δ=8.0(1H,d,ArH); δ=8.4(1H,s, =C-H); δ=9.9(1H,t,-CO-NH-CH); δ=12.5(1H,s,-COOH).
6b(ii)	δ=1.3(3H,t,-N-CH2-CH3); δ=1.5(3H,d,-NH-CH-CH3); δ=2.5(2H,q,-N-CH2-CH3); δ=4.2(1H,m,-NH-CH-COOH); δ=8.0(1H,d,ArH); δ=8.2(1H,d,ArH); δ=8.7(1H,s, =C-H); δ=10.2(1H,d,-CO-NH-CH); δ=12.6(1H,s,-COOH).
6b(iii)	δ=0.90(6H,d,-CH-(CH3)2); δ=1.1(1H,m,-CH2-CH-(CH3)2); δ=1.2(2H,t,-CH-CH2-CH); δ=1.6(3H,t,-N-CH2-CH3); δ=2.2(2H,q,-N-CH2-CH3); δ=4.1(1H,m,-NH-CH-COOH); δ=8.2(1H,d,ArH); δ=8.3(1H,d,ArH); δ=8.9 (1H,s, =C-H); δ=10.6(1H,d,-CO-NH-CH); δ=12.8(1H,s,-COOH).
6b(iv)	δ=1.0(3H,t,-N-CH2-CH3); δ=2.4(2H,q,-N-CH2-CH3); δ=3.2(1H,d,-CH2-OH); δ=4.1(1H,m,-NH-CH-COOH); δ=4.5(2H,d,-CH-CH2-OH); δ=7.8(1H,d,ArH); δ=8.1(1H,d,ArH); δ=8.9(1H,s, =C-H); δ=9.8(1H,d,-CO-NH-CH); δ=12.0(1H,s,-COOH).

[*δ values in ppm; s=singlet; m=multiplte; d=doublet; t=triplet; q=quartet; Ar=Aromatic]

Elemental Analysis:

TABLE 6:- ELEMENTAL ANALYSIS DATA FOR FINAL COMPOUNDS

Compound No.	Elemental Analysis		
	C% Obs. (Cal)	H% Obs. (Cal)	N% Obs. (Cal)
6a(i)	54.47 (54.46)	4.24 (4.24)	9.07 (9.07)
6a(ii)	55.83 (55.82)	4.68 (4.68)	8.67 (8.67)
6a(iii)	59.73 (59.42)	5.54 (5.54)	7.69 (7.69)
6a(iv)	53.19 (53.18)	4.46 (4.46)	8.26 (8.26)
6b(i)	51.47 (51.46)	3.70 (3.70)	8.57 (8.57)
6b(ii)	52.88 (52.85)	4.14 (4.14)	8.22 (8.22)
6b(iii)	56.63 (56.62)	5.01 (5.01)	7.33 (7.33)
6b(vi)	50.51 (50.50)	3.95 (3.95)	7.85 (7.85)

Anti-bacterial Activity:

TABLE 7: ACTIVITY OF THE COMPOUNDS AT 25 µg/ml; 50µg/ml & 100µg/ml

Sr. No	Compound code	Gram Positive *(B. subtilis)*			Gram Negative *(E. coli)*		
		25 µg/ml	50 µg/ml	100 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml
1	6a(i)	-	10	12	-	9	13
2	6a(ii)	-	-	-	7	10	12
3	6a(iii)	8	11	10	9	12	15
4	6a(iv)	-	9	12	11	15	18
5	6b(i)	9	10	12	-	10	14
6	6b(ii)	-	11	12	-	13	16
7	6b(iii)	7	10	12	10	12	17
8	6b(iv)	-	7	9	10	13	15
9	Norfloxacin	9	13	16	12	15	20
10	DMSO (control)				-		

[*values in mm for Zone of inhibition]

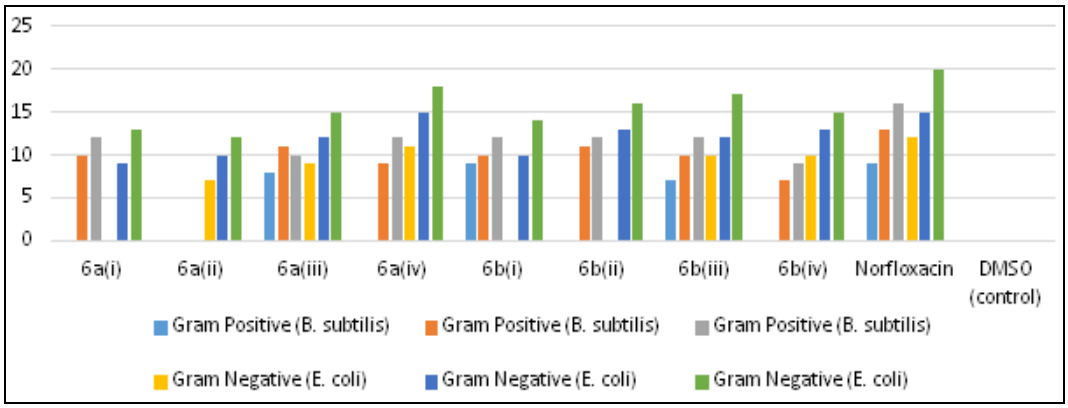

FIG: 2- GRAPHICAL REPRESENTATION FOR COMPARISON ANTI-BACTERIAL ACTIVITY

CONCLUSION: The Amino acid linked quinolone derivatives have been synthesized successfully as per the designed scheme of synthesis. Physical characteristic like melting point, solubility have being determined for intermediate as well as for final compounds. Compounds were structurally characterized by spectral techniques (FT-IR, ^{1}H-NMR) & elemental analysis is calculate in terms of percent for C, H & N. Anti-bacterial was carried out to determine the potency of the synthesised compounds.

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CONFLICT OF INTEREST: No conflict of interest.

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