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Synthesis of Various Sulphonamide-Linked Fluoroquinolones as Antibacterial Agents

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In the present study various derivatives of sulphonamide linked moxifloxacin were synthesized and their chemical structures were confirmed by means of elemental analysis and spectral data (IR, NMR and mass). These compounds were screened for antibacterial activity against *Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Bacillus cereus* ATCC 11778, *Pseudomonas aeruginosa* ATCC 2853, *Klebsiella pneumoniae* ATCC 11298 and *Escherichia coli* ATCC 25922 by paper disc diffusion techniques. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method using the standard drug ciprofloxacin. All the compounds exhibited moderate to good antibacterial activity. The acute oral toxicity of the compounds were determined and found to be non-toxic at the dose of 2000 mg/kg. Selected compounds were screened for *in vivo* antibacterial activity by Mouse protection test.

Key Words: Sulphonamide, Antibacterial, Moxifloxacin.

INTRODUCTION

Despite a numerous to develop new structural prototype in the search for more effective antimicrobials, the sulphonamides[1,2] and fluoroquinolones[3] still remain as one of the ubiquitous class of compounds against microbes and therefore are useful substructures for further molecular exploration. The fluoroquinolone antibacterial[4] agents have been found to be one of the fastest growing group drugs in recent years. To date, more than 20,000 different analogues have been synthesized. Most of these agents are substituted at the 7th position by a nitrogen heterocycle[5-8]. Antibiotics are among the most prescribed drugs in the world today, where sulphonamides are used for the treatment of bacterial infections[9]. Bioreversible form of the drug will increase the lipophilicity of the drugs. In view of the facts mentioned above and as a part of our initial efforts to discover potentially active new bioreversible agents; we have synthesized ten derivatives (**K1-K10**) of sulphonamide-linked moxifloxacin and evaluated for their antibacterial activity.

EXPERIMENTAL

Melting points of the synthesized compounds were determined in open capillary tubes. IR spectra were recorded on ABB Bomem FTIR spectrometer using potassium bromide pellets. ^{1}H NMR spectra of the compounds in dimethyl sulphoxide was recorded on Jeol GSX 400 spectrometer (with TMS as internal standard). Mass spectra were recorded on GCMS QP 5000 Shimadzu. The purity of the compounds was checked by TLC on pre-coated silica gel.

General method of synthesis: 0.005 mol of respective fluoroquinolone was suspended in 200 mL pyridine or triethylamine. To this suspension slowly added 0.02 mol of corresponding chloro derivative of various sulphonamides in 20 mL of DMF with stirring at 120-130 ºC until the reaction is complete. After completion of the reaction, the reaction mass was concentrated under reduced pressure. To the residue added 1 N sodium hydroxide solution to dissolve. The pH of the solution is then adjusted to 4 with acetic acid, precipitating crystals are collected by filtration, washed with water and recrystallized with DMF-ethanol. The synthetic scheme is shown in Fig. 1. The physical data of the synthesized compounds are given in Table-1.

TABLE-1
PHYSICAL DATA OF COMPOUNDS **K1-K10**

R	m.f.	m.p. (ºC) (± 2 ºC)	Yield (%)	Elemental analysis (%): Found		
				C	H	N
4,6-Dimethyl	$C_{33}H_{35}N_6O_6SF$	189	52	59.81	5.32	12.68
6-Methyl	$C_{32}H_{33}N_6O_6SF$	168	58	59.25	5.13	12.96
2-Pyrimidinyl	$C_{31}H_{31}N_6O_6SF$	152	49	58.66	4.92	13.24
2-Pyridinyl	$C_{32}H_{32}N_5O_6SF$	197	51	60.65	5.09	11.05
Benzenesulphonamide	$C_{27}H_{29}N_4O_6SF$	204	38	58.26	5.25	10.07
Acetamido	$C_{29}H_{31}N_4O_7SF$	186	60	58.18	5.22	9.36
Methyl isoxazolyl	$C_{31}H_{32}N_5O_7SF$	208	48	58.39	5.06	10.98
Thiazolyl	$C_{30}H_{30}N_5O_6S_2F$	178	58	56.33	4.73	10.95
Methyl	$C_{28}H_{30}N_3O_6SF$	220	38	61.15	5.66	7.38
5-Methyl	$C_{32}H_{33}N_6O_6SF$	148	51	59.25	5.13	12.96

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(4,6-dimethyl-2-pyrimidinyl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K1): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3471 (N-H), 3040 (C-H), 1707 (C=O), 1605 (COOH) and 1372 (S=O); ^{1}H NMR (DMSO-d_6) δ: 0.4-0.6 (q, 2H, -CH_2- of cyclopropyl), 1.5 (s, 4H, N-CH of cyclopropyl), 10.8 (s, H, OH), 4.1 (s, H, NH-SO_2), 2.4 (s, 6H, -CH_3), 3.8 (s, 3H, -OCH_3), 6.3-7.9 (m, 6H, ArCH), 1.6-1.8 (m, 6H, -CH_2- of piperidine), 2.7-2.9 (m, 6H, -CH-of piperidine), Mass: m/z value: 662.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(6-methyl-2-pyrimidinyl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K2): The sample was recrystallized using DMF and ethanol.

IR (KBr, ν_{max}, cm^{-1}): 3497 (N-H), 3077 (C-H), 1707 (C=O), 1641 (COOH) and 1371 (S=O); ^{1}H NMR (DMSO-d_6) δ: 0.4-0.7 (q, 4H, -CH_2- of cyclopropyl), 1.35 (s, H, N-CH of cyclopropyl), 11.2 (s, H, OH), 3.9 (s, H, NH-SO_2), 2.3 (s, 3H, CH_3), 3.6 (s, 3H, -OCH_3), 6.8-7.8 (m, 8H, Ar-CH), 1.7-1.9 (m, 6H, -CH_2- of piperidine), 2.5-2.7 (m, 6H, -CH-of piperidine), Mass : m/z value: 648.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(2-pyrimidinyl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K3): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3394 (N-H), 3068 (C-H), 1701 (C=O), 1652 (COOH) and 1371 (S=O) and 2954 (CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.5-0.7 (q, 4H, -CH_2- of cyclopropyl), 1.2 (s, H, N-CH of cyclopropyl), 11.4 (s, H, OH), 4.2 (s, H, NH-SO_2), 3.9 (s, 3H, OCH_3), 7.5-8.5 (m, 9H, Ar-CH), 1.3-1.5 (m, 6H, -CH_2-of piperidine), 2.7-2.8 (m, 6H, -CH- of piperidine), Mass: m/z value: 634.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(2-pyridinyl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K4): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3453 (N-H), 3075 (C-H), 1717 (C=O), 1652 (COOH), 1407 (S=O) and 2938 (CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.5-0.6 (q, 4H, -CH_2- of cyclopropyl), 1.4 (s, H, N-CH of cyclopropyl), 11.3 (s, H, OH), 4.3 (s, H, NH-SO_2), 3.7 (s, 3H OCH_3), 6.6-7.9 (m, 10H, Ar-CH), 1.6-1.8 (m, 6H, -CH_2- of piperidine), 2.5-2.7 (m, 6H, -CH- of piperidine), Mass: m/z value: 633.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K5): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3478 (N-H), 3071 (C-H), 1704 (C=O), 1574 (COOH), 1407 (S=O) and 2938 (CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.5-0.6 (q, 4H, -CH_2- of cyclopropyl), 1.4 (s, H, N-CH of cyclopropyl), 11.3 (s, H, OH), 4.3 (s, H, NH-SO_2), 3.7 (s, 3H, OCH_3), 6.6-7.9 (m, 10H, Ar-CH), 1.6-1.8 (m, 6H, -CH_2- of piperidine), 2.5-2.7 (m, 6H, -CH-of piperidine), Mass: m/z value: 556.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(acetamidobenzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K6): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3374 (N-H), 3039 (C-H), 1709 (C=O), 1658 (COOH), 1364 (S=O), 2876 (CH_3) and 2673 (C-O-CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.3-0.5 (q, 4H, -CH_2- of cyclopropyl), 1.5 (s, H, N-CH of cyclopropyl), 11.3 (s, H, OH), 8.2 (s, H, NH-SO_2), 2.3 (s, H, -CH_3), 3.7 (s, 3H -OCH_3), 6.8-7.9 (m, 6H, Ar-CH), 1.8-2 (m, 6H, -CH_2- of piperidine), 2.4-2.6 (m, 6H, -CH- of piperidine), Mass: m/z value: 598.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(5-methyl-3-isoxazolyl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K7): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3478 (N-H), 3009 (C-H), 1753 (C=O), 1685 (COOH), 1345 (S=O), 2935 (CH_3) and 2780 (C-O-CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.3-0.6 (q, 4H, -CH_2- of

cyclopropyl), 1.5 (s, H, N-CH- of cyclopropyl), 11.2 (s, H, OH), 4.4 (s, H, NH-SO_2), 2.4 (s, 3H,-CH_3), 3.8 (s, 3H, -OCH_3), 6.6-8.0 (m, 7H, Ar-CH), 1.7-1.9 (m, 6H, -CH_2- of piperidine), 2.7-2.9 (m, 6H, -CH- of piperidine), Mass: m/z value: 637.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(1,3-thiazol-2-yl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K8): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3378 (N-H), 3067 (C-H), 1735 (C=O), 1624 (COOH), 1366 (S=O), 1596 (C=N), 2931 (CH_3) and 2811 (C-O-CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.4-0.6 (q, 4H, -CH_2- of cyclopropyl), 1 (s, 1H, N-CH of cyclopropyl), 10.9 (s, H, OH), 4.1 (s, H, NH-SO_2), 3.9 (s, 3H, -OCH_3), 6.4-7.8 (m, 8H, Ar-CH), 1.6-1.8 (m, 6H, -CH_2- of piperidine), 2.6-2.8 (m, 6H, -CH- of piperidine), Mass: m/z value: 638.

1-cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(4-methyl)benzenesulphonyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K9): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3467 (N-H), 3020 (C-H), 1705 (C=O), 1626 (COOH), 1372 (S=O); 2968 (CH_3), 2899 (C-O-CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.3-0.5 (q, 4H, -CH_2- of cyclopropyl), 1.3 (s, H, N-CH- of cyclopropyl), 11.0 (s, H, OH), 3.5 (s, 3H, -OCH_3), 6.6-8.2 (m, 6H, Ar-CH), 1.5-1.8 (m, 6H, -CH_2- of piperidine), 2.4-2.6 (m, 6H, -CH- of piperidine), Mass: m/z value: 555.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2,8-diazabicyclo(4,3,0)non-8-yl-4-N(5-methyl-2-pyrimidinyl)benzenesulphonamido)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (K10): The sample was recrystallized using DMF and ethanol. IR (KBr, ν_{max}, cm^{-1}): 3075 (C-H), 1731 (C=O), 1684 (COOH), 1371 (S=O), 2937 (CH_3) and 2876 (C-O-CH_3); ^{1}H NMR (DMSO-d_6) δ: 0.4-0.6 (q, 4H, -CH_2- of cyclopropyl), 1.4 (s, H, N-CH of cyclopropyl), 11.0 (s, H, OH), 4.2 (s, H, NH-SO_2), 2.1 (s, 3H, -CH_3), 3.8 (s, 3H, -OCH_3), 6.4-7.9 (m, 8H, Ar-CH), 1.6-1.8 (m, 6H, -CH_2 of piperidine), 2.5-2.8 (m, 6H, -CH- of piperidine), Mass: m/z value: 648.

Biological evaluation

***In vitro* antibacterial activity:** All the synthesized compounds were screened for antibacterial activities by paper disc diffusion technique. The antibacterial activity of the compounds were evaluated against three Gram-positive bacteria *Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155 and *Bacillus cereus* ATCC 11778 and three Gram-negative bacteria *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853 and *Klebsiella pneumoniae* ATCC 11298. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method. The *in vivo* antibacterial activity of the compounds against *Staphylococcus aureus* and *Escherichia coli* was also evaluated by mouse protection test. Acute oral toxicity test was performed for all the synthesized compound as per Organization of Economic Co-operation and Development (OECD) guidelines.

Paper disc diffusion technique: The sterilized[10] (autoclaved at 120 °C for 0.5 h) medium (40-50 °C) was inoculated (1 mL/100 mL of medium) with the suspension (10^5 cfu mL^{-1}) of the micro-organism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (1000 μg mL^{-1} in dimethyl formamide) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37 °C for 24 h. Ciprofloxacin (50 μg/disc) is used as standard drug for comparison. The observed zone of inhibition is presented in Table-2.

TABLE-2
ANTIMICROBIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound	*In vitro* activity-zone of inhibition (MIC 100 μg/mL)						*In vivo* activity (ED_{50}) mg/kg	
	S. aureus	*S. epidermidis*	*B. cereus*	*E. coli*	*P. aeuriginosa*	*K. pneumoniae*	*S. aureus*	*E. coli*
K1	26 (0.8)	27 (2.0)	21 (1.2)	30 (1.4)	20 (2.6)	28 (1.3)	-	-
K2	30 (1.0)	24 (1.4)	24 (1.6)	32 (1.2)	15 (1.4)	24 (1.0)	-	-
K3	28 (0.7)	26 (1.2)	28 (1.8)	28 (0.9)	18 (0.9)	32 (0.8)	5	7.5
K4	28 (1.2)	23 (2.2)	20 (2.0)	26 (1.0)	20 (1.4)	26 (1.2)	-	-
K5	23 (1.2)	22 (1.6)	25 (1.8)	26 (1.2)	17 (1.8)	23 (1.4)	-	-
K6	28 (1.4)	26 (1.1)	24 (1.4)	22 (0.8)	15 (1.6)	21 (1.0)	7.5	17.5
K7	24 (0.6)	28 (1.2)	28 (0.8)	28 (0.9)	19 (1.2)	25 (1.6)	10	25
K8	19 (0.9)	25 (1.6)	21 (2.2)	20 (0.7)	22 (2.2)	15 (0.9)	10	10
K9	28 (0.9)	20 (1.4)	22 (1.6)	24 (1.4)	28 (1.4)	26 (1.0)	-	-
K10	26 (0.8)	22 (2.2)	20 (1.4)	28 (0.9)	20 (2.4)	23 (1.0)	-	-
Ciprofloxacin (100 μg/disc)	26(0.51)	30 (0.225)	25 (0.5)	28 (0.9)	24 (1.5)	26 (0.2)	5	7.5

Minimum inhibitory concentration (MIC): Minimum inhibitory concentration[11] of the compound was determined by agar streak dilution method. A stock solution of the synthesized compound (100 μg mL^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar). A specified quantity of the medium (40-50 °C) containing the compound was poured into a petri dish to give a depth of 3-4 mm and allowed to solidify. Suspension of the microorganism were prepared to contain approximately 10^5 cfu mL^{-1} and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37 °C for 24 h. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate. The observed MIC is presented in Table-2.

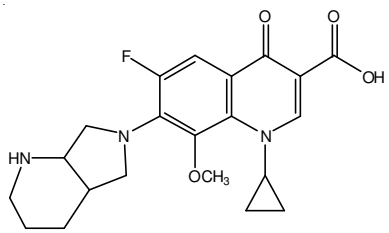
***In vivo* antibacterial activity:** The *in vivo* antibacterial activity[12] of synthesized compounds against systemic infections in mice was determined. Four-week old male Swiss albino mice weighing 18 to 22 g (in bred) were used for systemic infection model. They were maintained in animal rooms kept at 23 ± 2 ºC with 55 ± 20 % relative humidity. Test organisms for infection were cultured in Hinton nutrient agar medium at 37 °C for 18 h. For use as inocula, *Staphylococcus aureus* and *Escherichia coli* was suspended in 0.9 % saline solution containing 5 % gastrin mucin.

Acute oral toxicity: In the present study the acute oral toxicity[13] of the synthesized compounds were performed as per OECD 423 guidelines (acute toxic class method). In this method the toxicity of the synthesized compounds were tested using a stepwise procedure, each step using three mice of a single sex. The mice were fasted prior to dosing (food but not water should be with held) for 3 to 4 h. Following the period of fasting the animal should be weighed and the synthesized compounds were administered orally at a dose of 2000 mg/kg body weight. Animals were observed individually after dosing at least once during the first 0.5 h; periodically during the first 24 h with special attention given during the first 4 h and daily thereafter for a total of 14 days. As no mortality was observed with the above dose, the compound was declared as non-toxic class-1 and a series doses of 5, 10, 25, 50 for mg/kg body weight were selected for the *in vivo* antibacterial study.

Mouse protection test: Mice were used in groups of six for each inoculum and were given intraperitoneally with a single 0.5 mL portion of the bacterial suspension, (which contain 108 CFU) corresponding to an inoculum range of 10 to 100 times the minimal lethal dose of bacteria. Four dose levels were used for each synthesized drugs, depending on the *in vitro* antibacterial activity of the compound *i.e.* 5, 10, 25, 50 mg/kg. Synthesized compounds at various dose regimens were orally administered to mice twice, at 1st and 4th hour of post infection. Synthesized compounds were suspended in 1 % CMC. Mortality was recorded for 7 days and the median effective dose needed to protect 50 % of the mice (ED_{50}) was calculated by interpolation among survival mice (% protection) in each group after a week. They express the total dose of compound (mg/kg) required to protect 50 % of the mice from an experimentally induced systemic infection of the indicated organism. The challenge inoculum was sufficient to kill 100 % of the untreated control mice, which died within 48 h post infection. The ED_{50} values were tabulated in Table-2.

RESULTS AND DISCUSSION

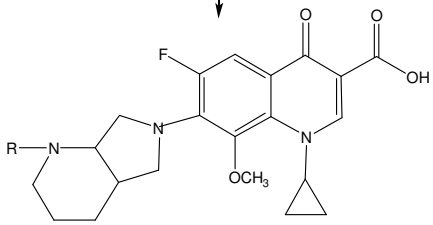
In the present study certain sulphonamide linked moxifloxacin were synthesized (Fig. 1) and the synthesized compounds were characterized by IR, ^{1}H NMR and mass spectra. All the synthesized compounds showed characteristic absorption peaks for C=O, C–F, COOH and S=O in IR. In ^{1}H NMR spectra characteristic absorption peaks are formed for aromatic C-H, COOH and N-CH. Expected Base peak and molecular ion (M^+) fragments were observed for all the compounds in the mass spectra. The synthesized compounds were subjected to *in vitro* antimicrobial evaluation. The zone of inhibition of various concentrations of synthesized compounds against Gram-positive, Gram-negative bacteria were measured. The minimum inhibitory concentration of the synthesized compounds against various bacteria were determined by agar streak dilution method. From the antimicrobial evaluation it was revealed that all the compounds possess activity against gram-positive bacteria. Among the compounds evaluated for *in vitro* antibacterial activity, compounds **K3**, **K6**, **K7**, **K8**, **K9**, showed good activity against *Escherichia coli* and compounds **K1**, **K3**, **K6**, **K7** displayed



1-Cyclopropyl-7-(2,8-diazabicyclo(4,3,0)non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid.

120-130°C for 5hrs

i) pyridine
ii) DMF



1-cyclopropyl-8-Methoxy7-(2,8-diazabicyclo(4,3,0) non-8-yl)-4-N-substituted benzene sulphonamido) -6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

R =

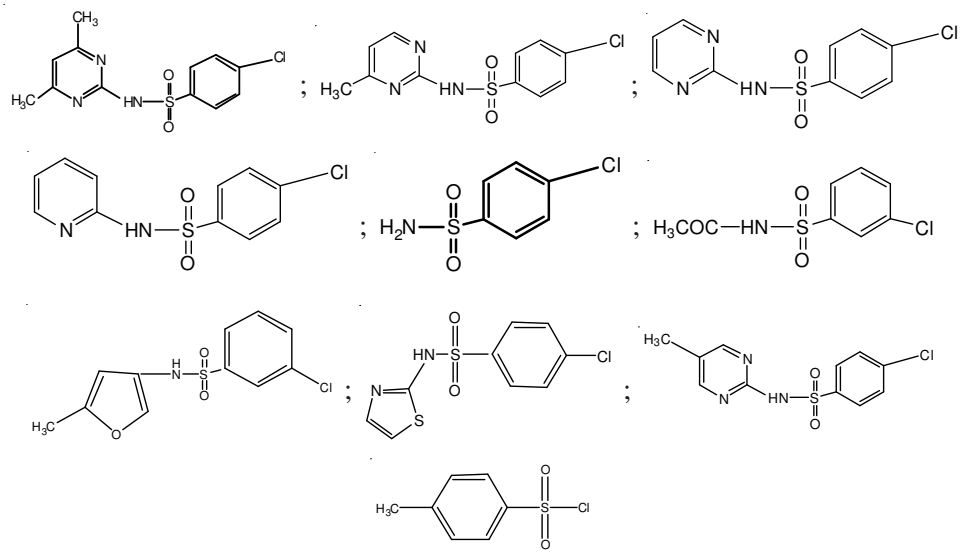


Fig. 1.

good activity against *Staphylococcus aureus* compared with the standard ciprofloxacin. The acute oral toxicities of the compounds were determined. All the compounds found to be non-toxic at the dose of 2000 mg/kg. Among the synthesized compounds four compounds were subjected to *in vivo* antibacterial activity against experimentally induced systemic infection of *Escherchia coli* and *Staphylococcus aureus* selected on the basis of their *in vitro* results of the compounds and their ED_{50} values were determined. Among the compounds synthesized **K3**, **K6**, **K7**, **K8** were evaluated for *in vivo* antibacterial evaluation **K3** showed good activity, **K6** showed moderate activity **K7** and **K8** showed mild activity against experimentally induced systemic infection of *Staphylococcus aureus* and **K3** showed good activity **K8** showed moderate activity **K6** and **K7** showed mild activity against experimentally induced systemic infection of *Escherichia coli* compared with the standard ciprofloxacin. Finally it was concluded that substitution of sulphonamides at 7th position of moxifloxacin increases both *in vitro* and *in vivo* efficiency of the synthesized compounds against various Gram-positive strains, which are the challenging microbes against various leading antibiotics.

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