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SYNTHESIS OF VARIOUS BIOPRECURSORS OF QUINOLONE DERIVATIVES AS ANTI-INFECTIVE AGENTS

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ABSTRACT:
A series of 1-ethyl-7-methyl-1,4-dihydro-4-oxo-*N*-substituted-1,8-naphthyridine-3-carboxamido derivatives (1-8) as prodrugs and 6-substituted quinolones were prepared. Representatives of the new compounds were subjected to microbiological screening.

INTRODUCTION

Since the discovery of nalidixic acid[1] (first quinolone antibiotic known) in 1963, this category of antibiotics has attained a prime and unique situation in the field of chemotherapy. These compounds have been shown to affect the bacterial growth by inhibiting the DNA gyrase, a key enzyme in bacterial DNA replication.

Nalidixic acid has a serious disadvantage of a high plasma protein binding, which led to its use in high and frequent dosages, causing high incidence rates of adverse reactions, such as, gastrointestinal intolerance and visual disturbances[2]. Like nalidixic acid, other agents of the first generation quinolones suffer from the same disadvantages. The introduction of an amino, cyano, chloro, or fluoro group at 6- position of the quinolone antibiotic molecule influences markedly the antibacterial activity[3-7]. On the other hand, sulphonamides possess a wide antimicrobial spectrum which includes most Gram-positive and Gram-negative bacteria[8]. Moreover, quinolones are structurally characterized by the presence of an ethyl, cyclopropyl, or fluorinated phenyl ring at N_1.

Meanwhile, nalidixic acid amides are typical prodrugs because masking the carboxylic acid group minimizes the ulcerogenecity and decreases plasma-protein binding of nalidixic acid, resulting in increased activity and lower doses[9,10].

In view of these observations and as a continuation of our work[11] on quinolone moiety, it was of interest to synthesize new series of nalidixic acid amides **1-8** as prodrugs and incorporate a sulphonamido moiety in the quinolone molecule at 6-position, with the hope to obtain compounds of better antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

The requisite 1-ethyl-7-methyl-1,4-dihydro-4-oxo-*N*-substituted-1,8-naphthyridine-3-carboxamide derivatives **(1-8)** (Scheme I) were prepared by refluxing a mixture of nalidixic acid, amine and phosphorus trichloride in chlorobenzene for 3 hours[12,13].

The preparation of 6-(*N*-substituted sulphamoyl)-quinolones are shown in scheme 2, following the usual method adopted in preparing quinolone antibiotics[14]. 4-Amino-*N*-substituted benzene sulphonamides were condensed with diethyl ethoxymethylenemalonate to give the corresponding malonates **9-14**, which were thermally cyclized to give the corresponding ethyl 4-oxoquinoline-3-carboxyl-ates, **15-20**.

Alkylation of the esters **15-20**, by heating with certain alkyl halides and anhydrous potassium carbonate for 24-48 hours gave ethyl 1-alkyl-6-(*N*-substituted sulphamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxylates **(21-32)**.

Several attempts were unsuccessful to hydrolyze the esters **21-32** using alkaline medium and different reaction times. These esters resisted hydrolysis apparently because of their insolubility[15,16].

However, the esters hydrolyzed in acidic medium using 6N HCl and the reaction time was extended to (56-90 hours) that the reaction succeeded to give the desired acids **33-38**.

Antibacterial Activity

Minimum inhibitory concentrations (MICs) of 7 compounds against different bacterial isolates were determined by the agar-dilution method according to the National Committee for Clinical Laboratory Standards (NCCLS)[17].

The in-vitro antibacterial activity of the tested compound was determined in a side by side comparison with pefloxacin by conventional agar-dilution procedures. The organisms were grown overnight in brain-heart infusion (BHI) broth (Oxoid, England) at 37°C. Two-fold serial dilutions of the stock solution (2000 µg/ml) of the tested compound were made in BHI agar to obtain a test concentration ranging from 0.09 – 400 µg/ml. The plate was inoculated with approximately 10^4 organisms. It was then incubated at 37 °C for 18 hours.

Table 6 summarizes the in-vitro antibacterial activity against Gram-positive bacteria (*staphylococcus aureus*, staphylococcus *saprophyticus*), laboratory cultures of Gram-positive bacteria (*Sarcina lutea* and *Bacillus subtilis*), acid-fast bacteria (*Mycobacterium phlei*) and Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *klebsiella oxytoca*, *Proteus mirabilis*, *Enterobacter cloacae*, and *pseudomonas aeruginosa*). The data for pefloxacin are included for comparison.

Results and Discussion

In the 1,8-naphthyridine carboxamide series (Scheme 1), it was interesting to find that compound **5** showed moderate activity in comparison with pefloxacin against Gram-positive, acid-fast bacteria except *staphylococcus aureus* and *Sarcina lutea* and Gram-negative bascteria except *pseudomonas aeruginosa* while 6-Sulphamoyl-

quinolone carboxylates (Scheme 2) showed no activity.(MICs > 200 µg/ml for compounds **23**, **27**, **29**, **32**) against all the tested organisms and higher concentrations of these compounds could not be tested due to their poor solubility.

EXPERIMENTAL

Melting points were determined on a Griffin apparatus and are uncorrected. Microanalyses were carried out at the Microanalytical Center, Cairo University. IR spectra were recorded on shimadzu 435 spectrometer, using KBr-discs. ^{1}H-NMR were performed on a Jeol NMR Fx-90 MHz spectrometer, using TMS as internal standard. Mass spectra were recorded on a GCMS-QP 1000 Ex, Mass spectrometer. Progress of the reactions was monitored by TLC using precoated sheets of silica gel Merck 60F 254 and were visualized by UV lamp. All the amines used were commercially available.

1-Ethyl-7-methyl-1,4-dihydro-4-oxo-*N*-substituted-1,8-naphthyridine-3-carboxamide derivatives (1-8).

A suspension of nalidixic acid (4.64g, 20 mmol) and the appropriate amine (30 mmol) in chlorobenzene (100ml) was heated under reflux with phosphorus trichloride (0.69g, 5 mmol) for 3 h and then filtered while hot. On cooling, the precipitated solid was collected by filtration, air dried and recrystallized from the suitable solvent to give **1-8**; **(Table 1)**.

^{1}H-NMR ($CDCl_3$, δ ppm) for 1

1.68 (t, J= 7 Hz, 3H, CH_2-$\underline{CH_3}$), 2.88 (s, 3H, CH_3), 4.80 (q, J= 7 Hz, 2H, $\underline{CH_2}CH_3$), 7.60-9.20 (m, 7H, Ar-H & C_2-H) and 12.88 (br s, 1H, NH, D_2O exchangeable)

^{1}H-NMR ($CDCl_3$, δ ppm) for 2

1.68 (t, J= 7 Hz, 3H, $CH_2\underline{CH_3}$), 2.88 (s, 3H, CH_3), 4.88 (q, J= 7 Hz, 2H, $\underline{CH_2}CH_3$), 7.60-9.28 (m, 9H, Ar-H & C_2-H) and 13.04 (br s, 1H, NH, D_2O exchangeable).

Mass spectrum for 1

m/z (relative abundance %); 308 (M^+) (4.67).

Diethyl 2-[(4-(*N*-Substituted sulphamoyl)phenyl-amino) methylene] malonates (9-14).

A mixture of the appropriate sulphonamide (70 mmol) and diethyl ethoxymethylenemalonate (15.12 g, 70 mmol) was heated in an open flask at 150°C in an oil bath for 2h. On cooling the reaction mixture, the separated solid was filtered and crystallized from chloroform to give **9-14 (table 2)**.

^{1}H-NMR ($CDCl_3$, δ ppm) for 9

1.36-1.60 (m, 6H, $2CH_2\underline{CH_3}$), 4.40-4.64 (m, 4H, $2\underline{CH_2}CH_3$), 5.84 (hump, 2H, NH_2, D_2O exchangeable), 7.60 - 8.24 (m, 4H, Ar-H), 8.88 (d, J= 14 Hz,1H, C_2-H) and 11.60 (d, J= 14 Hz, 1H, NH, D_2O exchangeable).

^{1}H-NMR ($CDCl_3$, δ ppm) for 11

1.20-1.54 (m, 6H, $2CH_2\underline{CH_3}$), 4.24-4.64 (m, 4H, $2\underline{CH_2}CH_3$), 7.36 (m, 3H, pyrimidin-H 7.52 - 8.40 (m, 4H, Ar-H), 8.96 (d, J= 14 Hz, 1H, C_2-H), 11.60 (d, J= 14 Hz, 1H, NH, D_2O exchangeable) and 12.56 (s, 1H, $SO_2\underline{NH}$, D_2O exchangeable).

^{1}H-NMR (CDCl3, δ ppm) for 13

1.36-1.60 (m, 6H, $2CH_2\underline{CH_3}$), 2.56 (s, 6H, CH_3), 4.40-4.64 (m, 4H, $2\underline{CH_2}CH_3$), 6.96 (s, 1H, Pyrimidine –H), 7.60 - 8.36 (m., 4H, Ar-H), 8.76 (d, J= 14 Hz, 1H, C_2-H) and 11.60 (d, J=13.8 Hz, 1H, NH, D_2O exchangeable).

Mass spectrum for 11

m/z (relative abundance %), 420 (M+)(2.30).

Ethyl-4-oxo-6-(*N*-Substituted sulphamoyl)-1,4-dihydro-quinoline-3-carboxylates (15-20).

A solution of the proper compound **9-14** (17 mmol) in diphenyl ether (50 ml) was heated under reflux for an hour. On cooling, the solid obtained was filtered, washed with benzene, dried and crystallized from dimethylformamide to afford **15-20 (Table 3)**.

^{1}H-NMR (DMSO-d_6, δ ppm) for 17

1.44 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 4.40 (q, J=7 Hz, 2H, $\underline{CH_2}CH_3$) 7.36 (m, 3H, pyrimidine-H), 8.08-9.20 (broad m, 4H, Ar-H & C_2-H), 11.20 (d, J= 6.1 Hz, 1H, NH, D_2O exchangeable) and 12.56 (s, 1H, $SO_2\underline{NH}$, D_2O exchangeable).

^{1}H-NMR (DMSO-d_6, δ ppm) for 19

1.36 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 2.64 (s, 6H, $2CH_3$), 4.40 (q, J=7 Hz, 2H, $\underline{CH_2}CH_3$), 7.12 (s, 1H, pyrimidine-H), 7.92-9.36 (m, 4H, Ar-H & C_2-H), 11.20 (d, J= 6.1 Hz, 1H, NH, D_2O exchangeable) and 12.56 (s, 1H, $SO_2\underline{NH}$, D_2O exchangeable).

Ethyl-4-oxo-1-alkyl-6-(*N*-Substitutedsulphamoyl)-1,4-dihydroquinoline-3-carboxylates (21-32).

A mixture of the proper compound **15-20** (10 mmol), anhydrous potassium carbonate (3.45g, 25 mmol) and the appropriate alkyl halide (50 mmol) in dimethylformamide (20 ml) was stirred and heated at 80-90°C for 24-48 h. The reaction mixture was evaporated to dryness and extracted with methylene chloride (20 ml). The methylene chloride layer was washed with water, dried and crystallized from chloroform –petroleum ether (60-80°) to yield **21-32**; **(Table 4)**.

^{1}H-NMR ($CDCl_3$, δ ppm) for 23

1.30-1.39 (m, 6H, $2CH_2\underline{CH_3}$), 4.26-4.53 (m, 4H, $2\underline{CH_2}CH_3$), 7.07-8.53 (m, 5H, Ar-H), 8.88 (s, 1H, C_5-H) and 8.92 (s, 1H, C_2-H).

^{1}H-NMR ($CDCl_3$, δ ppm) for 25

1.30-1.41 (m, 6H, $2CH_2\underline{CH_3}$), 2.51 (s, 6H, $2CH_3$), 4.20-4.51 (m, 4H, $2\underline{CH_2}CH_3$), 6.86 (s, 1H, Pyrimidine-H), 8.03-8.40 (m, 2H, C_7-H & C_8-H), 8.88 (s, 1H, C_5-H) and 9.07 (s, 1H, C_2-H).

^{1}H-NMR ($CDCl_3$, δ ppm) for 29

1.52 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 4.56 (q, J=7 Hz, 2H, $\underline{CH_2}CH_3$), 5.04-5.64 (m, 4H, N-$\underline{CH_2}$-CH=$\underline{CH_2}$), 6.08-6.32 (m, 1H, =CH), 7.28-8.72 (m, 5H, Pyrimidine-H C_7-H & C_8-H), 8.88 (s, 1H, C_5-H) and 8.96 (s, 1H, C_2-H).

^{1}H-NMR ($CDCl_3$, δ ppm) for 31.

1.52 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 2.48((s, 6H, $2CH_3$), 4.56 (q, J=7 Hz, 2H, $\underline{CH_2}CH_3$), 4.96-5.68 (m, 4H, N-$\underline{CH_2}$-CH=$\underline{CH_2}$), 6.08-6.32 (m, 1H, =CH), C_7-H & C_8-H), 8.88 (s, 1H, C_5-H) and 9.10 (s, 1H, C_2-H).

Mass spectrum for 25

m/z (relative abundance %), 430 (M^+ (0.98)

Mass spectrum for 31

m/z (relative abundance %), 442 (M^+ (4.23)

1-Alkyl-4-oxo-6-(*N*-substituted sulphamoyl)-1,4-dihydro-quinoline-3-carboxylic acid (33-38).

A mixture of ester **21**, **23-26,28** and 6 N hydrochloric acid (25 ml, 150 mmol) was heated under reflux with stirring for (56-90 h). The mixture was neutralized with concentrated ammonium hydroxide and the pH adjusted to 4-5 with acetic acid. The resulting precipitate was filtered, washed with water, and dried. The solid was crystallized from dimethyl-formamide to yield **33-38**; **(Table 5).**

^{1}H-NMR (DMSO-d_6, δ ppm) for 35

1.46 (t, J= 7 Hz, 3H, $CH_2\underline{CH_3}$), 2.52 (s, 3H, CH_3), 4.30 (q, J= 7 Hz, 2H, $\underline{CH_2}CH_3$), 7.03-8.54 (m, 5H, Ar-H & pyrimidine-H), 9.09 (s, 1H, C_2-H) and 14.74 (s, 1H, $\underline{COOH}$, D_2O exchangeable).

^{1}H-NMR (DMSO-d_6, δ ppm) for 36

1.60 (t, J= 7 Hz, 3H, $CH_2\underline{CH_3}$), 2.64 (s, 6H, $2CH_3$), 4.48 (q, J= 7 Hz, 2H, $\underline{CH_2}CH_3$), 7.25 (s, 1H, pyrimidine-H), 8.48-8.96 (m, 3H, Ar-H), 9.52 (s, 1H, C_2-H) and 15.36 (s, 1H, $\underline{COOH}$, D_2O exchangeable).

Table 1: Physical and analytical data for compounds **1-8.**

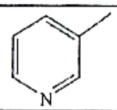
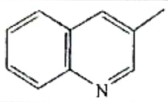
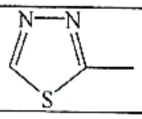
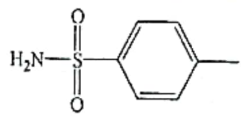
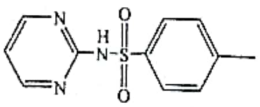
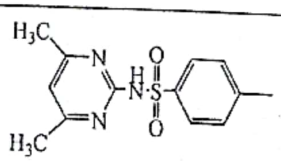
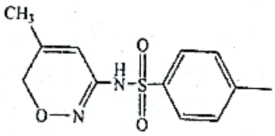
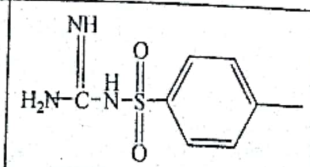
Compd no.	R	Solvent of Crystallization	mp °C	Yield %	Mol. Form. (Mol. weight)	Analysis %			IR (KBr, ν cm^{-1})
							Calcd	Found	
1		Isopropyl alc.	235-236	80	$C_{17}H_{16}N_4O_2$ (308)	C H N	66.26 5.19 18.18	65.90 4.90 17.80	3400 (NH), 1670 (CONH), 1620 (CO)
2		Acetonitrile	255-256	82	$C_{21}H_{18}N_4O_2$ (358)	C H N	70.39 5.03 15.64	70.00 4.70 16.00	3350 (NH), 1670 (CONH), 1620 (CO)
3		Acetone	216-217	63	$C_{14}H_{13}N_5O_2S$ (315)	C H N	53.33 4.13 22.22	53.50 4.40 22.00	3350 (NH), 1670 (CONH), 1610 (CO)
4		Acetonitrile	245-246	69	$C_{18}H_{18}N_4O_4S$ (386)	C H N	55.96 4.66 14.51	55.90 4.60 14.10	3400 (NH), 1670 (CONH), 1620 (CO)
5		Isopropyl alc.	255-256	70	$C_{22}H_{20}N_6O_4S$ (464)	C H N	56.90 4.31 18.10	56.80 4.50 18.20	3380 (NH), 1670 (CONH), 1620 (CO)
6		Acetone	280-281	72	$C_{24}H_{24}N_6O_4S$ (492)	C H N	58.54 4.88 17.07	58.80 4.80 16.80	3400 (NH), 1670 (CONH), 1620 (CO)
7		Isopropyl alc.	275-276	65	$C_{22}H_{21}N_5O_5S$ (467)	C H N	56.53 4.50 14.99	56.60 4.40 15.10	3400 (NH), 1670 (CONH), 1620 (CO)
8		Acetone	206-207	60	$C_{19}H_{20}N_6O_4S$ (428)	C H N	53.27 4.67 19.63	52.80 4.50 19.20	3350 (NH), 1670 (CONH), 1620 (CO)

Table 2: Physical and analytical data for compounds **9-14.**

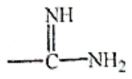
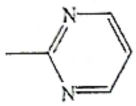
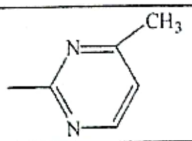
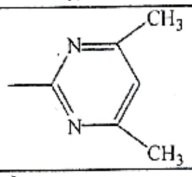
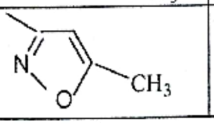
Compd no.	R	mp °C	Yield %	Mol. Form. (Mol. weight)	Analysis %			IR (KBr, ν cm^{-1})
						Calcd	Found	
9	H	121-122	77	$C_{14}H_{18}N_2O_6S$ (342)	C H N	49.12 5.26 8.19	49.00 5.00 8.00	3200 (NH), 1690 (CO, ester)
10		151-152	87	$C_{15}H_{20}N_4O_6S$ (384)	C H N	46.88 5.21 14.58	46.80 5.00 14.90	3200 (NH), 1695 (CO, ester)
11		150-152	90	$C_{18}H_{20}N_4O_6S$ (420)	C H N	51.43 4.76 13.33	51.70 5.15 13.00	3200 (NH), 1690 (CO, ester)
12		156-157	92	$C_{19}H_{22}N_4O_6S$ (434)	C H N	52.53 5.07 12.90	52.80 4.80 13.30	3200 (NH), 1690 (CO, ester)
13		129-130	98	$C_{20}H_{24}N_4O_6S$ (448)	C H N	53.57 5.36 12.50	53.30 5.40 12.30	3200 (NH), 1690 (CO, ester)
14		125-126	73	$C_{18}H_{21}N_3O_7S$ (423)	C H N	51.07 4.96 9.93	51.40 4.90 10.20	3200 (NH), 1695 (CO, ester)

Table 3: Physical and analytical data for compounds **15-20.**

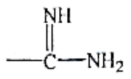
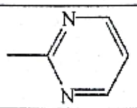
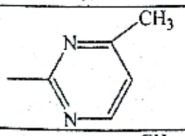
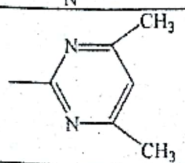
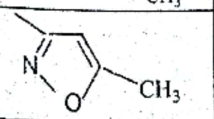
Compd no.	R	mp °C	Yield %	Mol. Form. (Mol. weight)	Analysis %			IR (KBr, ν cm^{-1})
						Calcd	Found	
15	H	201-202	50	$C_{12}H_{12}N_2O_5S$ (296)	C H N	48.65 4.05 9.46	49.00 4.00 9.20	3200 (NH), 1700 (CO, ester), 1635 (CO)
16		243-244	40	$C_{13}H_{14}N_4O_5S$ (339)	C H N	46.15 4.14 16.57	46.50 4.10 16.90	3200 (NH), 1695 (CO, ester), 1635 (CO)
17		278-280	60	$C_{16}H_{14}N_4O_5S$ (374)	C H N	51.34 3.74 14.97	51.50 4.30 15.10	3200 (NH), 1700 (CO, ester), 1635 (CO)
18		290-291	65	$C_{17}H_{16}N_4O_5S$ (388)	C H N	52.58 4.12 14.43	52.70 4.10 14.50	3200 (NH), 1700 (CO, ester), 1635 (CO)
19		299-300	69	$C_{18}H_{18}N_4O_5S$ (402)	C H N	53.73 4.48 13.93	53.90 4.70 14.10	3200 (NH), 1700 (CO, ester), 1635 (CO)
20		243-245	54	$C_{16}H_{15}N_3O_6S$ (377)	C H N	50.93 3.98 11.14	50.90 3.90 11.50	3200 (NH), 1695 (CO, ester), 1635 (CO)

Table 4: Physical and analytical data for compounds **21-32.**

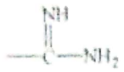
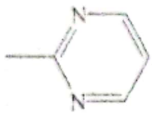
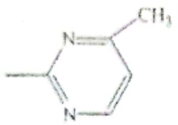
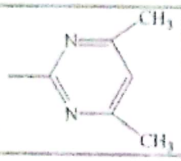
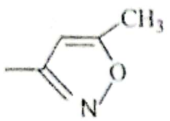
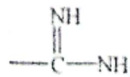
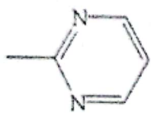
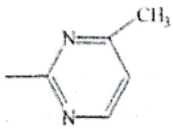
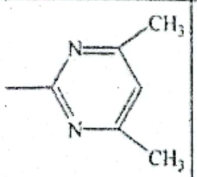
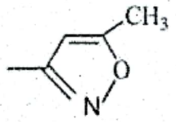
Compd no.	R^2	R^1	Reaction Time (hour)	mp °C	Yield %	Mol. Form. (Mol. weight)	Analysis %			IR (KBr, ν cm^{-1})
								Calcd	Found	
21	H	C_2H_5	40	100-101	24	$C_{14}H_{16}N_2O_6S$ (340)	C H N	51.85 4.94 8.64	51.60 5.10 8.60	3200 (NH), 1720 (CO, ester), 1635 (CO)
22		C_2H_5	47	120-121	20	$C_{15}H_{18}N_4O_5S$ (366)	C H N	49.18 4.92 15.30	49.00 4.90 15.10	3200 (NH), 1720 (CO, ester), 1635 (CO)
23		C_2H_5	30	110-111	30	$C_{18}H_{18}N_4O_5S$ (402)	C H N	53.73 4.48 13.93	54.00 4.60 4.60	3300 (NH), 1715 (CO, ester), 1635 (CO)
24		C_2H_5	34	120-121	26	$C_{19}H_{20}N_4O_5S$ (416)	C H N	54.81 4.81 13.46	54.80 5.00 13.40	3200 (NH), 1720 (CO, ester), 1630 (CO)
25		C_2H_5	38	148-150	32	$C_{20}H_{22}N_4O_5S$ (430)	C H N	55.81 5.12 13.02	56.00 5.20 13.00	3300 (NH), 1720 (CO, ester), 1635 (CO)
26		C_2H_5	42	133-134	22	$C_{18}H_{19}N_3O_6S$ (405)	C H N	53.33 4.69 10.37	53.70 4.80 10.00	3280 (NH), 1715 (CO, ester), 1630 (CO)
27	H	$-CH_2CH=CH_2$	30	80-81	28	$C_{15}H_{16}N_2O_5S$ (336)	C H N	53.57 4.76 8.33	54.00 5.20 8.30	3200 (NH), 1720 (CO, ester), 1635 (CO)
28		$-CH_2-CH=CH_2$	42	70-71	25	$C_{16}H_{18}N_4O_5S$ (378)	C H N	50.79 4.76 14.81	50.50 4.60 14.40	3200 (NH), 1720 (CO, ester), 1635 (CO)
29		$-CH_2-CH=CH_2$	24	78-79	40	$C_{19}H_{18}N_4O_5S$ (414)	C H N	55.07 4.35 13.53	55.40 4.20 13.10	3300 (NH), 1715 (CO, ester), 1630 (CO)
30		$-CH_2-CH=CH_2$	30	90-91	32	$C_{20}H_{20}N_4O_5S$ (428)	C H N	56.07 4.67 13.08	56.00 4.80 13.30	3300 (NH), 1715 (CO, ester), 1630 (CO)
31		$-CH_2-CH=CH_2$	35	96-98	40	$C_{21}H_{22}N_4O_5S$ (442)	C H N	57.01 4.98 12.67	57.30 5.20 12.60	3280 (NH), 1720 (CO, ester), 1635 (CO)
32		$-CH_2-CH=CH_2$	40	100-101	25	$C_{19}H_{19}N_3O_6S$ (417)	C H N	54.68 4.56 10.07	54.80 4.90 9.70	3200 (NH), 1720 (CO, ester), 1635 (CO)

Table 5: Physical and analytical data for compounds **33-38.**

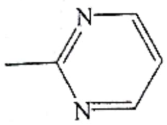
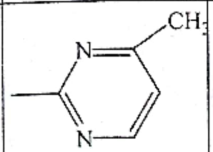
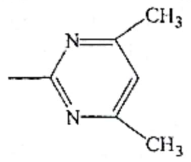
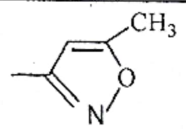
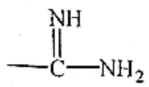
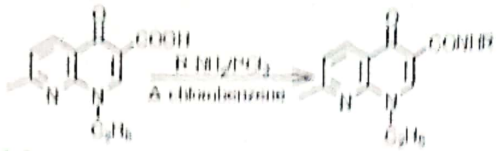
Compd no.	R^2	R^1	Reaction Time (hour)	mp °C	Yield %	Mol. Form. (Mol. weight)	Analysis %			IR (KBr, ν cm^{-1})
								Calcd	Found	
33	H	C_2H_5	72	235-236	48	$C_{12}H_{12}N_2O_5S$ (296)	C H N	43.90 3.66 8.54	44.20 4.00 8.70	3500-3100 (NH /or OH, br), 1715 (COOH), 1630 (CO)
34		C_2H_5	70	240-241	50	$C_{16}H_{14}N_4O_5S$ (374)	C H N	51.34 3.74 14.97	51.60 3.60 15.10	3500-3100 (NH /or OH, br), 1715 (COOH), 1630 (CO)
35		C_2H_5	76	269-270	53	$C_{17}H_{16}N_4O_5S$ (388)	C H N	52.58 4.12 14.43	53.00 4.30 14.20	3500-3100 (NH /or OH, br), 1715 (COOH), 1630 (CO)
36		C_2H_5	56	290-291	57	$C_{18}H_{18}N_4O_5S$ (402)	C H N	53.73 4.48 13.93	53.90 4.70 13.70	3500-3100 (NH /or OH, br), 1715 (COOH), 1625 (CO)
37		C_2H_5	65	> 300	40	$C_{16}H_{15}N_3O_6S$ (377)	C H N	50.93 3.98 11.14	50.60 3.80 11.00	3500-3100 (NH /or OH, br), 1715 (COOH), 1630 (CO)
38		$-CH_2-CH=CH_2$	80	250-251	38	$C_{14}H_{14}N_4O_5S$ (350)	C H N	48.00 4.00 16.00	48.40 4.20 16.30	3500-3100 (NH /or OH, br), 1715 (COOH), 1625 (CO)

Table 6: *In-vitro* antibacterial activity, MIC, µg/ml

Compound / Organisms	3	5	7	23	27	29	30	Pefloxacin
Staph. aureus	> 200	200	400	> 200	> 400	> 200	> 200	0.78
S. saprophyticus	> 200	12.5	400	> 200	> 400	> 200	> 200	0.19
Sarcina lutea	> 200	200	400	> 200	> 400	> 200	> 200	1.56
B. subtilis	> 200	50	400	> 200	> 400	> 200	> 200	0.39
M.phlei	> 200	25	200	> 200	> 400	> 200	> 200	0.19
E. coli	> 200	25	400	> 200	> 400	> 200	> 200	1.56
K. penumoniae	> 200	25	400	> 200	> 400	> 200	> 200	3.12
K. oxytoca	> 200	25	400	> 200	> 400	> 200	> 200	3.12
Proteus mirabilis	> 200	25	400	> 200	> 400	> 200	> 200	0.09
Enterobacter cloacae	> 200	12.5	400	> 200	> 400	> 200	> 200	0.39
Pseudomonas aeruginosa	> 200	> 400	> 400	> 200	> 400	> 200	> 200	1.56

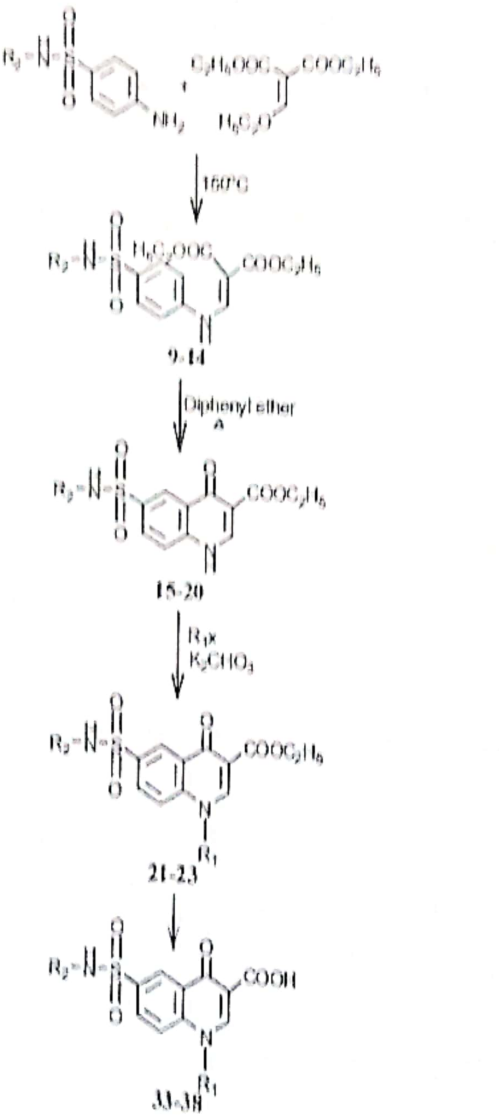
Scheme 1



1-8

R = 3-pyridyl; 3-quinolyl; 1,3,4-thiadiazolyl-2-yl; 4-aminosulphonylphenyl; 4-(pyrimid-2-ylaminosulphonyl)phenyl; 4-(4,6-dimethylpyrimid-2-ylaminosulphonyl)phenyl; 4-(5-methylisoxazol-3-ylaminosulphonyl)-phenyl and 4-(amidinoaminosulphonyl)phenyl.

Scheme 2



9-14

15-20

21-23

33-38

R^1 = Ethyl and allyl; R^2 = H; amidinyl; 2-pyrimidyl; 4-methyl-2-pyrimidyl; 4,6-dimethyl-2-pyrimidyl and 5-methyl-3-isoxazolyl.

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تشييد مماثلات لحمض الناليدكسيك والمضادات الحيوية الكينولونية

منصور خليفة حسنين - محمد عبدالرحمن شعبان- سميحة محمد رشدى - أمنية محمود خليل

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تضمن البحث عرضا مختصرا لكيفية عمل الكينولونات ، وقد اشتملت الدراسة الحالية على خطتين أنجز خلالها تشييد العديد من المركبات الجديدة. وتم التعرف على المركبات الجديدة بواسطة التحليل العنصرى الدقيق والتحاليل الطيفية. وقد تم اختبار بعض المركبات الجديدة لمعرفة تأثيرها كمواد فعالة ضد بعض البكتريا

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