Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2013, Vol. 29, No. (2):
Pg. 507-511

Synthesis of substituted-4-oxo-1, 4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline Derivatives and their Biological Activity Against Bacterial Infections

N. SRIVATAVA* and A. KUMAR

Department of Applied Chemistry, Faculty of Engineering and Technology,
M.J.P. Rohilkhand University, Bareilly - 243 006, India.
*Corresponding author E-mail: drnimjpru@rediffmail.com, niveditacdri2000@yahoo.com

(Received: September 12, 2012; Accepted: November 04, 2012)

ABSTRACT

We have synthesized a series of quinolone and fluoroquinolones derivatives substituted with p-tosyl group. All these compounds were screened as antibacterial and datas were compared with reference marketed drug viz.; Ciprofloxacin & Norfloxacin.

Key words: Fluoroquinolones, hydrazine, p-tosyl and antibacterial.

INTRODUCTION

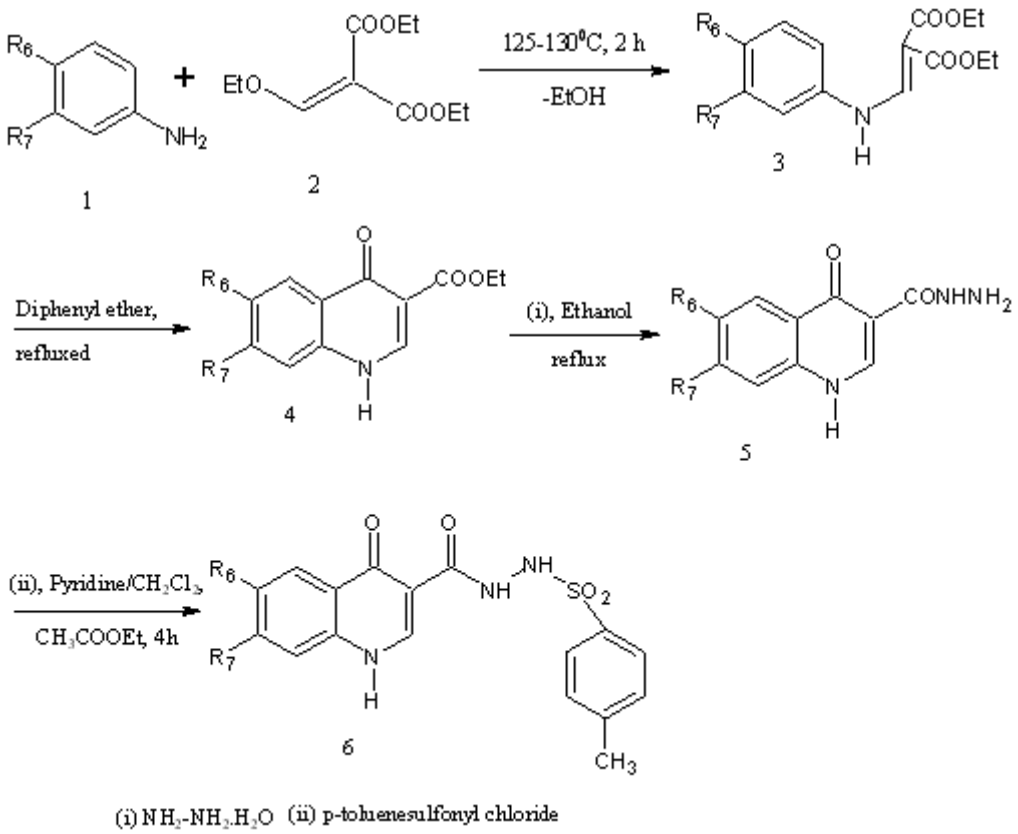
The antibiotic drugs such as Penicillin and cephalosporin used to treat bacterial infections by inhibit cell wall biosynthesis[1], thereby causing bacterial cell death. In recent study quinolones are one of the largest classes of antibacterial agents used worldwide in the emergency room. They are chemotherapeutic gyrase or topoisomerases-II inhibitors eradicating bacteria by interfering with DNA replication[2]. Sulfonamide are also use as antibacterial agents. They inhibit cell metabolism of bacteria i.e. act as anti metabolites and check the growth of bacteria. Sulfonamide act as inhibitors as it mimick p-amino benzoic acid (PABA), one of the normal constitutes of folic acid. The enzyme is fooled by accepting sulfonamide into its active site as the structure of sulfonamide is similar to PABA. Once it is bound, the sulfonamide prevents PABA from binding. As a result, folic acid is no longer synthesized. Since folic acid is essential for cell growth, the cell will stop dividing. Thereby the growth of bacteria will inhibit.

In our study we have synthesized quinolone - sulfonamide drugs, by substituting quinolone with p-tosyl group and want to see the results of these molecules as antibacterials. This combination therapy of sulfonamide and fluoroquinolone is new approach for the treatment of bacterial infections.

Chemistry

Here series of hydrazine and p-tosyl substituted compounds 6a-6f were synthesized and screened against bacterial infections. Substituted aniline 1 condensed with diethyl ethoxy methylene malonate 2 to give ethyl anilinomethylenemalonate

3[3] derivatives. Cyclization of the latter in diphenylether gave the substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester 4.[4,5] The 1,4-dihydro-4-oxo-quinoline-3-carbohydrazide derivatives 5 is obtained by the refluxing ester 4 with hydrazine monohydrate in absolute ethanol. The carbohydrazide derivatives 5 were treated with p-toluenesulfonyl chloride in the presence of pyridine as base and CH_2Cl_2, ethyl acetate as solvent. All these reaction steps involved are represented in scheme 1.



Scheme 1.

RESULTS AND DISCUSSION

Biological results of newly synthesized compounds 6a-6f by the above described method are as follows. The results of antibacterial activity of compounds 6a-6f against *E.coli (ETEC) and Salmonella typhi* are given in the table 2.

Minimum inhibitory concentrations of the compound 6a and 6b were not found. The compound 6c, 6d, 6e and 6f have considerable MIC. All these compounds 6a-6f was less potent to reference marketed Norfloxacin and Ciprofloxacin against bacteria *E.coli* and *Salmonella typhi*. Efforts are in progress to get more better results in this pipe line.

Table 1.

Comp.	R_6	R_7	%Yield	mp °C
6a	H	H	90.13	225-230
6b	F	H	84.59	242
6c	Cl	H	87.79	266
6d	H	Cl	85.97	240
6e	Br	H	83.21	265-270
6f	F	Cl	82.78	250

Table 2.

S. No.	Compound No.	Minimum Inhibitory Concentration (MIC) µg/mL Bacterial activity	
		E.coli (ETEC)	*Salmonella typhi*
1	6a	NF	NF
2	6b	NF	NF
3	6c	2	2
4	6d	2	2
5	6e	NR	2
6	6f	2	2
7	Norfloxacin	0.0625	0.25
8	Ciprofloxacin	0.0625	0.0625

NF= MICs were not found. NR= Compound was nonreactive towards screened bacteria.

EXPERIMENTAL

Spectral data were recorded as follows: IR Spectra was run on a Perkin Elmer and Schimadzu 8201 PC, FT Infrared spectrophotometer (ν_{max} in cm^{-1}). ESI-HRMS were recorded by Agilent 6520 Q-TOF mass spectrometer. Micro analysis determined by Elementar Vario EL III, Carlo Erba 1108. ^{1}H NMR, (300MHz) and ^{13}C NMR, (75MHz) spectra have been recorded on Bruker Avance 400. Melting points were determined in open capillary method and are uncorrected. All reagents were commercial grade and were used as received without further purification unless otherwise specified. Dry DMF and anhydrous potassium carbonate was used wherever required. Reagent grade solvents were used in all other cases unless otherwise specified. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a Buchi rotary evaporator at low pressure. Yield of purified products were not optimized.

General methods for the synthesis of substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester 4

Substituted aniline 1 (0.01 mol) and diethyl ethoxy methylene malonate 2 (0.01 mol) were mixed and heated at 125-130 ^{0}C for 2 h. Ethanol was evaporated off from the resulting mixture of ethyl anilinomethylene malonate 3. The crude solid was filtered on sintered funnel, dried and recrystallized from n-hexane. The malonate 3 (0.01 mol) was refluxed with diphenylether (50 mL) for 1 h to give 1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester 4. After 1 h the solution was cooled and the resulting precipitate was filtered off, washed with n-hexane, and dried. The solid was recrystallized from DMF to give substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester 4.

Preparation of substituted-1, 4-dihydro-4-oxoquinoline-3-carbohydrazide derivatives 5

Substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester 4 (0.01 mol) was refluxed for 12 h with hydrazine monohydrate (0.01 mol) in absolute ethanol (9 mL) to give substituted-4-oxo-1,4-dihydroquinoline-3-carbohydrazide 5. The excess solvent was evaporated off and the resulting mixture was poured into crushed ice. The solid separated was filter on sintered funnel, washed with water and dried. The crude solid was purified by recrystallized from Dioxane: ethanol to give **5** as white solid. Purity of the compound was checked on silica gel TLC plates. TLC was run in chloroform-methanol (9:1) as eluent.

Preparation of substituted-4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline derivatives 6

A mixture of substituted-1, 4-dihydro-4-oxoquinoline-3-carbohydrazide derivatives **5** (0.05 mol), pyridine (0.01 mol), dichloromethane (6 mL)

and ethyl acetate (6 mL) was placed in ice bath. The p-toluenesulfonyl chloride (0.05 mol) was added into the reaction mixture under ice condition and stirred for 4 h. The reaction mixture was allowed to stand in ice for further 30 min. The excess solvent was removed by filtration and washed with water and dried. The solid compound was recrystallized with dichloromethane. Purity of the compound was checked on silica gel TLC plates. TLC was run in chloroform-methanol (9.5:0.5) as eluent.

Spectral data

1, 4-dihydro-4-oxoquinoline-3-carbohydrazide 5a

IR (KBr): 3651-3021 (bs), 1654.3(>CO hydrazide), 1615.4(>CO ketone), 1494.2(w), 1218.1(s), 764.2(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 12.68(bs, 1H, H-1), 10.70(s, 1H, -CONH-), 8.73(s, 1H, H-2), 8.27-7.45(m, 4H, ArH), 4.57(s, 2H, -N**H**$_2$); ^{13}C NMR ($CDCl_3$-d, 75MHz) δ (ppm): 175.29, 165.01, 143.19, 139.19, 135.30, 129.21, 128.18, 127.12, 126.41, 110.26; HRMS calcd. for m/z ($C_{10}H_9N_3O_2$): 203.1973, found 203.1968, Anal. Calcd for ($C_{10}H_9N_3O_2$): C, 59.16; H, 4.46; N, 20.70. Found: C, 59.09; H, 4.43; N, 20.67.

6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbohydrazide 5b

IR (KBr): 3645.8-3018.6 (bs), 1656.1(>CO hydrazide Str.) 1604.9(>CO), 1492.7(w), 1216.5(s), 762.4(s) cm^{-1}; ^1H NMR ($CDCl_3$-d, 400MHz) δ (ppm): 12.67(bs, 1H, H-1), 10.62(s, 1H, -CONH-), 8.76(s, 1H, H-2), 7.81-7.62 (m, 3H, ArH), 4.71(s, 2H, -NH_2); ^{13}C NMR ($CDCl_3$-d, 75MHz) δ (ppm): 175.26, 165.32, 146.52, 135.25, 129.62, 129.60, 121.14, 121.09, 118.08, 110.62; HRMS calcd. for m/z ($C_{10}H_8FN_3O_2$): 221.1878, found 221.1869, Anal. Calcd for ($C_{10}H_8FN_3O_2$): C, 54.10; H, 3.63; N, 18.92. Found: C, 54.08; H, 3.60; N, 18.90.

6-Chloro-1,4-dihydro-4-oxoquinoline-3-carbohydrazide 5c

IR (KBr): 3603.7-3008.4 (bs), 1655.4(>CO hydrazide Str.) 1607.4(>CO), 1483.7(w), 1216.5(s), 764.7(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 12.80(bs, 1H, H-1),10.61(s, 1H, -CONH-), 8.77(s, 1H, H-2), 8.58-7.73 (m, 3H, ArH), 4.62 (s, 2H, -NH_2); ^{13}C NMR ($CDCl_3$-d, 75MHz) δ (ppm): 174.76, 165.09, 147.02, 137.04, 133.13, 131.51, 129.81, 127.19, 117.88, 111.76; HRMS calcd. for m/z ($C_{10}H_8ClN_3O_2$): 237.6424, found 237.6419, Anal. Calcd for ($C_{10}H_8ClN_3O_2$): C, 50.46; H, 3.38; N, 17.65. Found: C, 50.43; H, 3.36; N, 17.60.

7-Chloro-1,4-dihydro-4-oxoquinoline-3-carbohydrazide 5d

IR (KBr): 3578.1-3014.4 (bs), 1657.5(>CO hydrazide) 1597.6(>CO), 1465.9(w), 1217.0(s), 762.6(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 12.43(bs, 1H, H-1), 10.58(s, 1H, -CONH-), 8.77(s, 1H, H-2), 8.67-7.42(m, 3H, ArH), 4.60(s, 2H, -NH_2); ^{13}C NMR ($CDCl_3$-d, 75MHz) δ (ppm): 175.12, 165.19, 147.21, 139.23, 139.12, 129.02, 126.13, 125.69, 115.48, 111.64; HRMS calcd. for m/z ($C_{10}H_8ClN_3O_2$): 237.6424, found 237.6417, Anal. Calcd for ($C_{10}H_8ClN_3O_2$): C, 50.46; H, 3.38; N, 17.65. Found: C, 50.42; H, 3.37; N, 17.64.

7-Chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbohydrazide 5e

IR (KBr): 3651.5-3016.0 (bs), 1640.0(>CO hydrazide) 1616.7(>CO), 1498.6(w), 1217.7(s), 769.4(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 12.79(bs, 1H, H-1), 10.53(s, 1H, -CONH-), 8.80(s, 1H, H-2), 8.61(d, 1H, H-5), 8.08(d, 1H, H-8), 4.64(s, 2H, -N**H**$_2$); ^{13}C NMR ($CDCl_3$-d, 75MHz) δ (ppm): 174.89, 165.12, 155.68, 147.29, 135.89, 128.13, 126.11, 119.06, 115.01, 113.98; HRMS calcd. for m/z ($C_{10}H_7ClFN_3O_2$): 255.6328, found 255.6316, Anal. Calcd for ($C_{10}H_7ClFN_3O_2$): C, 46.91; H, 2.75; N, 16.41. Found: C, 46.89; H, 2.74; N, 16.38.

4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 6a

IR (KBr): 3474.6-2947.6 (bs), 1653.5(>CO hydrazide), 1623(>CO), 1479.5(w), 1328.3(-$NHSO_2$-), 1217.1(s), 762.4(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 12.87(d, 1H, H-1), 11.46(s, 1H, -CONH-), 9.99(s, 1H, -$NHSO_2$-), 8.65(d, 1H, H-2), 8.24-7.37(m, 8H, ArH), 2.39(s, 3H, -CH_3); ^{13}C NMR (DMSO-d_6, 75MHz) δ (ppm): 175.79, 163.88, 144.19, 143.54, 139.02, 135.80, 133.08, 129.61, 127.61, 125.84, 125.54 125.37, 119.19, 109.45, 21.12; HRMS calcd. for m/z ($C_{17}H_{15}N_3O_4S$): 357.3837, found 357.3825, Anal. Calcd for ($C_{17}H_{15}N_3O_4S$): C, 57.03; H, 4.22; N, 11.73. Found: C, 57.00; H, 4.19; N, 11.70.

6-fluoro-4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 6b

IR (KBr): 3474.8-3022.0 (bs), 1666.5(>CO hydrazide), 1611.7(>CO), 1487.9(w), 1344.1(-

$NHSO_2$-), 1217.6(s), 762.7(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 13.01(d, 1H, H-1), 11.37(s, 1H, -CONH-), 10.03(s, 1H, -$NHSO_2$-), 8.68(d, 1H, H-2), 7.88-7.36(m, 7H, ArH), 2.38(s, 3H, -C**H**$_3$); ^{13}C NMR ($CDCl_3$-d, 75MHz) δ (ppm): 174.91, 163.66, 144.99, 144.24, 143.54, 135.85, 135.75, 129.60, 127.33, 122.10, 121.76, 109.98, 109.68, 108.89, 21.11; HRMS calcd. for m/z ($C_{17}H_{14}FN_3O_4S$): 375.3741, found 375.3736, Anal. Calcd for ($C_{17}H_{14}FN_3O_4S$): C, 54.30; H, 3.75; N, 11.17. Found: C, 54.27; H, 3.71; N, 11.12.

6-Chloro-4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 6c

IR (KBr): 3458.8-3018.1 (bs), 1679.4(>CO hydrazide), 1618.2(>CO), 1481.1(s), 1337.7(-$NHSO_2$-), 1218.6(s), 759.2(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 13.03(bs, 1H, H-1),11.30(s, 1H, -CONH-), 10.01(s, 1H, -$NHSO_2$-), 8.69(s, 1H, H-2), 8.39(d, 1H, H-5), 7.99(d, 1H, H-7), 7.97(d,1H, H-8), 7.73(dd, 2H, ArH), 7.38(dd, 2H, ArH), 2.39(s, 3H, -C**H**$_3$);^{13}C NMR (DMSO-d_6, 75MHz) δ (ppm): 173.68, 162.99, 148.39, 143.69, 136.89, 135.63, 133.16, 130.20, 129.60, 128.43, 127.55, 125.29, 120.26, 109.96, 21.32; HRMS calcd. for m/z ($C_{17}H_{14}ClN_3O_4S$): 391.8287, found 391.8274, Anal. Calcd for ($C_{17}H_{14}ClN_3O_4S$): C, 52.08; H, 3.60; N, 10.71. Found: C, 52.01; H, 3.57; N, 10.67.

7-Chloro-4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 6d

IR (KBr): 3407.7-3015.2 (bs), 1669.6(>CO hydrazide), 1619.3(>CO), 1471.2(w), 1338.6(-$NHSO_2$-), 1217.5(s), 763.4(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 12.95(d, 1H, H-1), 11.32(s, 1H, -CONH-), 10.00(s, 1H, -$NHSO_2$-), 8.69(s, 1H, H-2), 8.57(d,1H, H-5), 8.29(d, 1H, H-8), 7.78(dd, 2H, ArH), 7.74(d, 1H, H-6), 7.13(dd, 2H, ArH), 2.38(s, 3H, -C**H**$_3$);^{13}C NMR (DMSO-d_6, 75MHz) δ (ppm): 175.80, 163.47, 145.53, 144.99, 143.51, 137.57, 135.74, 133.33, 130.65, 129.56, 127.80, 125.65, 119.17, 110.01, 21.07; HRMS calcd. for m/z ($C_{17}H_{14}ClN_3O_4S$): 391.8287, found 391.8276, Anal. Calcd for ($C_{17}H_{14}ClN_3O_4S$): C, 52.08; H, 3.60; N, 10.71. Found: C, 52.03; H, 3.58; N, 10.69.

7-Chloro-6-fluoro-4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 6e

IR (KBr): 3469.9-3021.6 (bs), 1669.7(>CO hydrazide), 1615.8(>CO), 1485.7(s), 1339.8(-$NHSO_2$-), 1218.3(s), 764.9(s) cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz) δ (ppm): 13.09(d, 1H, H-1), 10.41(s, 1H, -CONH-), 8.89(s, 1H, -$NHSO_2$-), 8.62(s, 1H, H-2), 8.51(d, 1H, H-5), 8.46(d, 1H, H-8), 7.98(dd, 2H, ArH), 7.12(dd, 2H, ArH), 2.38(s, 3H, -C**H**$_3$);^{13}C NMR (DMSO-d_6, 75MHz) δ (ppm): 174.45, 163.27, 156.14, 152.67, 148.61, 143.47, 135.45, 129.51, 127.47, 126.44, 126.19, 120.33, 112.16, 109.56, 21.12; HRMS calcd. for m/z ($C_{17}H_{13}FClN_3O_4S$): 409.8192, found 409.8186, Anal. Calcd for ($C_{17}H_{13}FClN_3O_4S$): C, 49.92; H, 3.20; N, 10.27. Found: C, 49.90; H, 3.18; N, 10.24.

ACKNOWLEDGEMENTS

This work was financially supported by the University Grant Commission (UGC), Grant no 31-128/2005 SR. We are gratefully acknowledged the UGC, New Delhi for financial support and Sophisticated Analytical Instrument Facility (SAIF), Central Drug Research Institute, Lucknow-226001(India) for providing spectral data on payment basis. We are also thankful to BioGenics, Research and Training Centre in Biotechnology, Hubli -580 031, Karnataka for providing antibacterial assays to generate MIC data on payment basis.

REFERENCES

1. Murry R. K.; Granner D. K.; Mayer P. A. and Rodwell V. W. ,Protein Synthesis and the Genetic Code. Harper's Illustrated Biochemistry (27ed.) Mc Graw-Hill Medical., 378, (2006).
2. Elsea S. H.; Osheroff N. and Nitiss J. L., *J. Biol. Chem.*, 19, 267: 13150-3 (1992).
3. Claisen L.*, An.*, **77**: 297 (1897).
4. Camps R., *Ber.*, **34**: 2714 (1901).
5. Koga H.; Itoh A.; Murayama S.; Suzue S. and Irikura T., *J. Med. Chem.,* **23**: 1358-1363 (1980)