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Original Article

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF SOME N-SUBSTITUTED DERIVATIVES OF 6-FLUORO-1-METHYL-4-OXO-7-(PIPERAZIN-1-YL)-4*H*-[1,3]THIAZETO[3,2-*A*]QUINOLINE-3-CARBOXYLIC ACID

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ABSTRACT

Objective: N-substituted derivatives of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid: Synthesis and antibacterial activity.

Methods: In the present study N-substituted derivatives of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid were prepared by using Triethylamine and DMF. This procedure was modified by adding tetra butyl ammonium bromide (TBAB) to facilitate completion in few reactions. Other reactions which did not proceed in both the aforementioned ways were facilitated by the use of Morwet-D425. All the new title compounds were characterized by their spectral data and were screened for antibacterial activity.

Results: Some of the reported compounds were synthesized using the process disclosed by us in U.S.Pat.No.8, 410,268B2. In our present work, we have achieved good yields and purity. Many compounds exhibited substantial antibacterial activity.

Conclusion: It can be inferred that the title compounds with substituted phenyl and quinoline rings exhibited comparable antibacterial activity with respect to the standard.

Keywords: Synthesis, Quinoline, Piperazine, Phenyl, Biphenyl, Pyridine, Pyrazole, Characterization, Antibacterial activity.

INTRODUCTION

Quinolones are unusual among antibacterial agents in the fact that they are not isolated from living organisms, but rather synthesized by chemists. The first quinolone, Nalidixic acid, was derived from the anti malarial drug Chloroquine[1]. Subsequent agents were derived through side chain and nuclear manipulation [2]. The development of the fluoroquinolone class may be described in generational terms, with each generation sharing similar features or antibacterial spectra. First-generation agents possess activity against aerobic gram-negative bacteria, but little activity against aerobic gram-positive bacteria or anaerobes. Second-generation agents are the original fluoroquinolones, named for the addition of a fluorine atom at position C-6 .These agents offer improved coverage against gram-negative bacteria and moderately improved gram-positive coverage. Third-generation agents achieve greater potency against gram-positive bacteria, particularly pneumococci, in combination with good activity against anaerobes. Fourth-generation fluoroquinolones have superior coverage against pneumococci and anaerobes. This article focuses on the fluoroquinolone agents.

Regarding antibacterial activity, fluoroquinolones interfere with bacterial cell replication, transcription, and DNA repair by disabling two bacterial enzymes crucial to these processes, DNA gyrase (formerly topoisomerase II) and topoisomerase IV. These enzymes are necessary for bacteria to manage the topological challenge of containing their genetic material. Using *Escherichia coli* as an example, a bacterial cell that is 1 to 3 mm long must accommodate a chromosome that is a double-stranded DNA circle longer than 1000 mm. Chromosomal volume is reduced via tertiary folding and compaction. These processes must be reversed in order for bacterial replication to occur; DNA topoisomerases facilitate this [4].

Piperazines are a broad class of chemical compounds with many important pharmacological properties. Piperazine and substituted piperazine nuclei have constituted an attractive pharmacological scaffold present in various potent marketed drugs. The incorporation of piperazine is an important synthetic strategy in drug discovery due to its easy modifiability, proper alkalinity, water solubility, the capacity for the formation of hydrogen bonds and adjustment of molecular physicochemical parameters. This di - nitrogen moiety has been an inseparable component of plethora of drugs. A number of substituted piperazines posses significant pharmacological action such as antihistamic [5-6], antibacterial [7], acetylcholinesterae inhibitors [8], antimalarial [9], dopamine transporter [10-11], D2/D4 antagonist [12], MC4Receptor [13], and HIV-protease inhibitor [14-15].

Our present work forays into the field of research which has not been studied extensively i.e. substitution of the piperazine nucleus of 6-fluoro-4-oxo-7-(piperazin-1-yl)-1, 4-dihydroquinoline-3-carboxylic acid.

From the N-substituted 4-fluoro phenyl ring at fluoroquinolone nucleus in Sarafloxacin(16) and similar 2, 4-difluoro phenyl substitutions in Trovafloxacin(17), Tosufloxacin(18) and Temafloxacin(19),it can be inferred that substituted phenyl ring pertains to enhance the antibacterial activity of fluoroquinolones. Quinoline substitutions at the fluoroquinolone nucleus in case of Rosoxacin(20) also demonstrates good antibacterial activity. Pyridines (21) and pyrazoles (22) have been reported to exhibit prominent antibacterial activity.

We have tried to explore the effect of the substituted phenyl, biphenyl, quinoline and pyrazole substitutions at the piperizine ring of the fluoroquinolone nucleus in 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid . The synthesized molecules were characterized and checked for antibacterial activity.

MATERIALS AND METHODS

Chemicals and Instrument

6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 2-(bromomethyl)-1,3-difluorobenzene, 5-[4'-(bromomethyl) biphenyl-2-yl]-1-trityl- l-1*H*-tetrazole, 6-chloro-5-(2-chloroethyl)-1,3-dihydro-2*H*-indol-2-one, 4' (bromomethyl)

biphenyl-2-carbonitrile, benzyl 2-(benzyloxy)-4-(bromocarbonyl) benzoate, 2-(4-chlorobutoxy)-1,2,3,4-tetrahydroquinolin-7-ol, 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine, 1-[3-(trifluoromethyl) benzyl]-1*H*-pyrazole-4-carbonyl chloride were synthesized and characterized in our lab. Morwet®D425 was provided by Alkem laboratories limited. Analytical TLC was performed on Silica plates- GF254 (Merck) with visualization by UV or in iodine. Melting points were determined by MP50 (Mettler Toledo). The IR spectra (KBr, λ Max, cm^{-1}) were run on Perkin Elmer FTIR Spectrophotometer. 1H-NMR (in $CDCl_3$ / DMSO-*d6*) spectra were recorded using Bruker - 400 with TMS as internal standard. MS spectra were recorded on Brucker DPX 200. Elemental analyses were performed on Carlo Erba 1108 elemental analyzer and were within ± 0.4% of theoretical values. All the chemicals used were of Laboratory grade.

Synthesis of 7-(4-(2, 6-diflurobenzyl) piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1 *H*, 4H-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I-a):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 2-(bromomethyl)-1,3-difluorobenzene, 0.0143 mol of Triethylamine, dimethylformamide (DMF) 5 times based on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight,were charged in to a round bottom flask and heated to 85-90°C under nitrogen, under stirring for 4-6 hrs. A chilled water circulation was maintained in the condenser to prevent the escape of triethylamine during the course of the reaction. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was poured onto ice cold water (0-5°C). It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were slurried again in diisopropyl ether to obtain pure compounds.

Synthesis of 6-fluro-1-methyl-4-oxo-7-(4-((2'-(1-trityl-1*H*-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) piperazin-1-yl)-1*H*, 4H-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I-b):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 5-[4'-(bromomethyl)biphenyl-2-yl]-1-trityl- l-1*H*-tetrazole, 0.0143 mol of Triethylamine, 5% Tetra butyl ammonium bromide with respect to the weight of **I**, dimethylformamide (DMF) 5 times based on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight,were charged in to a round bottom flask and heated to 85-90°C under nitrogen, under stirring for 4-6 hrs. A chilled water circulation was maintained in the condenser to prevent the escape of triethylamine during the course of the reaction. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was poured onto ice cold water (0-5°C). It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were slurried again in diisopropyl ether to obtain pure compounds.

Synthesis of 7-(4-(5-(2-chloroethyl)-1, 3-dihydro-2*H*-indol-2-one) piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1 *H*, 4H-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I-c):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 6-chloro-5-(2-chloroethyl)-1,3-dihydro-2*H*-indol-2-one, 0.024 mole of Sodium carbonate, water 5.2 times based on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight and 1% of dispersing agent MORWET® D-425 were charged in to a round bottom flask and refluxed under nitrogen, under stirring for 7-8 hrs. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was filtered. It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were recrystalized from tetrahydrofuran (THF) to obtain pure compounds.

Synthesis of 7-(4-((2'-cyano- [1,1'-biphenyl]-4-yl)methyl)piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1 *H*,4*H*-[1,3] thiazeto[3,2-a] quinoline-3-carboxylic acid (I-d):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 4' (bromomethyl)biphenyl-2-carbonitrile, 0.0143 mol of triethylamine, dimethylformamide (DMF) 5 times based on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight,were charged in to a round bottom flask and heated to 85-90°C under nitrogen, under stirring for 4-6 hrs. A chilled water circulation was maintained in the condenser to prevent the escape of triethylamine during the course of the reaction. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was poured onto ice cold water (0-5°C). It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were slurried again in diisopropyl ether to obtain pure compounds.

Synthesis of 7-(4-(1-(4-(benzyloxy)-2-((benzyloxy) carbonyl) phenyl) vinyl) piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I-e):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of benzyl 2-(benzyloxy)-4-(bromocarbonyl) benzoate, 0.0143 mol of Triethylamine, dimethylformamide (DMF) 5 times based on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight,were charged in to a round bottom flask and heated to 85-90°C under nitrogen, under stirring for 4-6 hrs. A chilled water circulation was maintained in the condenser to prevent the escape of triethylamine during the course of the reaction. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was poured onto ice cold water (0-5°C). It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were slurried again in diisopropyl ether to obtain pure compounds.

Synthesis of 6-fluro-7-(4-(5-(7-hydroxy-1, 2, 3, 4-tetrahydroquinolin-2-yl) pentyl) piperazin-1-yl)-1-methyl-4-oxo-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I-f):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 2-(4-chlorobutoxy)-1,2,3,4-tetrahydroquinolin-7-ol, 0.024 mol of sodium carbonate, water 5 .2 times based on of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight and 1% of dispersing agent MORWET® D-425 were charged in to a round bottom flask and refluxed under nitrogen, under stirring for 7-9 hrs. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was filtered. It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were recrystalized from tetrahydrofuran(THF) to obtain pure compounds.

Synthesis of 6-fluro-7-(4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methyl) piperazin-1-yl)-1-methyl-4-oxo-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I-g):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine, 0.0143 mol of triethylamine, 5% tetra butyl ammonium bromide with respect to the weight of **I**, dimethylformamide (DMF) 5 times based

on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight,were charged in to a round bottom flask and heated to 85-90°C under nitrogen, under stirring for 4-5 hrs. A chilled water circulation was maintained in the condenser to prevent the escape of triethylamine during the course of the reaction. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was poured onto ice cold water (0-5°C). It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were slurried again in diisopropyl ether to obtain pure compounds.

Synthesis of 6-fluro-1-methyl-4-oxo-7-(4-(1-(3-(trifluromethyl)benzyl)-1*H*, 4*H*-[1,3] thiazeto[3,2-*a*] quinoline-3-carboxylic acid(I-h):

0.0072 mol of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, 0.0086 mol of 1-[3-(trifluoromethyl)benzyl]-1*H*-pyrazole-4-carbonyl chloride, 0.0143 mol of triethylamine, 5% tetra butyl ammonium bromide with respect to the weight of **I**, dimethylformamide (DMF) 5 times based on 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid weight,were charged in to a round bottom flask and heated to 85-90°C under nitrogen, under stirring for 4-5 hrs. A chilled water circulation was maintained in the condenser to prevent the escape of triethylamine during the course of the reaction. The progress of the reaction was checked by thin layer chromatography (Eluent: ethyl acetate: hexane=50:50). After the completion of the reaction, the reaction mass was cooled to room temperature and the resulting mass was poured onto ice cold water (0-5°C). It was slurried in water and then in isopropyl alcohol (IPA) and isolated by filtration. The solid was dried at 95-100°C. The isolated solids were slurried again in diisopropyl ether to obtain pure compounds.

7-(4-(2, 6-diflurobenzyl) piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1 *H*, 4H-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [I (a)]:

M.P:228°C; Yield: 78%; MS: 475.12(100%) 476.12(26.0%); IR max cm^{-1}: 3275-2800 (O-H stretch); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ= 11.8(-OH,s,1H), 7.8 (Aromatic CH,S,1H),7.5 (Aromatic CH,m,1H),7.3(Aromatic CH,d,2H)6.5(Aromatic CH,s,1h),4.0(CH,m,1H),3.7(CH,s,2H),3.4(-CH_2,t,4H),2.7(-CH_2,t,4H),2.2(-CH_3,6H)

^{13}CNMR: 23.6(1C,-CH_3);38.5(1C,-CH_2);50.2(2C, piperazine -CH_2); 53.2(2C, piperazine -CH_2); 91.4(1C, Aromatic C=C);110.8-118.2 (6C,Aromatic CH); 130.5-144.6 (4C,Aromatic CH); 163.0(2C,Aromatic C-F); 166.1(1C,carboxylic acid); 175.1(1C,Aromatic S-C-N); 177.5 (1C,Aromatic C=O);Elemental analysis: C-58.10 %, H-4.24 %,F-11.99 %, N-8.84 %,O-10.09%;S-6.74%

6-fluro-1-methyl-4-oxo-7-(4-((2'-(1-trityl-1*H*-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) piperazin-1-yl)-1*H*, 4H-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [I (b)]:

M.P:231°; Yield: 71%, MS: 825.29(100%), 826.29(56.5%), 827.30(14.1%); IR max $cm^{-1:}$ 3275-2800 (O-H stretch); 1630.22(C=N); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ= 11.0(-OH,s,1H), 7.0-7.30 (Aromatic CH, 17 H, Phenyl rings),7.3-7.6 (Aromatic CH,4H,Phenyl rings), 7.12(Aromatic CH,s,1H of fluoroquinolone ring),7.3(Aromatic CH,d,2H), 6.5(Aromatic CH,s,1h),5.93(1H,s,Aromatic CH, fluoroquinolone ring)3.84 (CH,m,1H),3.7(CH,s,2H),3.62(CH_2, s,2H) 3.45(-CH_2,t,4H),2.59 (-CH_2,t,4H),2.0 (-CH_3,6H)

^{13}CNMR: 22.9(1C,-CH_3); 50.0(2C, piperazine -CH_2); 53.2(2C, piperazine -CH_2); 60.1(1C,-CH_2); 67.2 (1C,-CH_2); 91.4(1C, Aromatic C=C, fluoroquinolone ring);100-118.2 (3C,Aromatic CH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 128.3-129.3 (23C,Aromatic C, phenyl rings); 134.5-141.9 (8C,Aromatic C, phenyl rings) 154.1 (1C,triazole ring)166.3(1C,carboxylic acid); 175.5(1C,Aromatic S-C-N); 177.5 (1C,Aromatic C=O);Elemental analysis:C-71.25%,H-4.88%,F-2.30%,N-11.87%,O-5.81%,S-3.88%

7-(4-(5-(2-chloroethyl)-1, 3-dihydro-2*H*-indol-2-one) piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1 *H*, 4H-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [I(c)]

M.P:233°; Yield: 71%, MS: 542.12(100%), 544.12(33.45%), 543.12(30.6%); IR max cm^{-1}: 3275-2800 (O-H stretch); 1712.30(NH bend) 1648.25(Carbonyl of oxindole); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ= 11.0(-OH,s,1H), 8.0 (NH, s,1 H, Oxindole ring),7.48 (Aromatic CH,s,1H,Oxindole), 7.12(Aromatic CH,s,1H of fluoroquinolone ring),6.84(Aromatic CH,s,1H of Oxindole ring),5.93(1H,s,Aromatic CH, fluoroquinolone ring)3.84 (CH,m,1H),3.7(CH,s,2H),3.62(CH_2, s,2H) 3.41(-CH_2,t,4H,piperazine ring),2.59 (-CH_2,t,4H,piperazine ring),2.6-2.7 (-CH_2,4H),1.58(-CH_3,3H)

^{13}CNMR: 23.6 (1C,-CH_3); 25.6 (1C,-CH_2);36.6(-CH_2, 1C,oxindole ring);50.0(2C, piperazine -CH_2); 53.2(2C, piperazine -CH_2); 60.1(1C,-CH_2); 67.2 (1C,-CH); 91.4(1C, Aromatic C=C, fluoroquinolone ring);100-118.2 (3C,Aromatic CH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 122.3-132.2 (4C,Aromatic C, oxindole ring); 139.8-143.0 (2C,Aromatic C, oxindole rings),165.8(1C,carboxylic acid); 175.1(1C,Aromatic S-C-N); 176.6 and 177.5 (2C, C=O)Elemental analysis:C-57.51 %,H-4.45%,Cl-6.53%,F=3.50%,N=10.32 %, O=11.79%S-5.91%

7-(4-((2'-cyano- [1,1'-biphenyl]-4-yl)methyl)piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1 *H*,4*H*-[1,3] thiazeto[3,2-a] quinoline-3-carboxylic acid [I(d)]:

M.P: 211° C, Yield: 78%; MS: 540.16(100%), 541.17(32.80%), 542.17(6.1%); IR max cm^{-1}: 3275-2800 (O-H stretch); 2310.32(Nitrile group); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ= 11.0(-OH,s,1H), 7.8 (Aromatic CH, d,1 H, biphenyl ring),7.6-7.7 (Aromatic CH,2H,Biphenyl ring), 7.2 (Aromatic CH,d,2H,Biphenyl ring), 7.4 (Aromatic CH,3H,Biphenyl ring),7.12(Aromatic CH,s,1H of fluoroquinolone ring), 5.93(1H,s,Aromatic CH, fluoroquinolone ring)3.91 (CH,m,1H),3.75 (CH,s,2H),3.62(CH_2, s,2H) 3.45(-CH_2,t,4H,piperazine ring),2.61 (-CH_2,t,4H,piperazine ring),1.85 (-CH_3,3H)

^{13}CNMR: 23.6 (1C,-CH_3) ; 50.0(2C, piperazine -CH_2); 53.2(2C, piperazine -CH_2); 60.7(1C,-CH); 67.2 (1C,-CH_2); 91.4(1C, Aromatic C=C, fluoroquinolone ring);100-118.2 (3C,Aromatic CH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 104.5 (1C,-C-CN); 115.4(1C,CN),127.6-129.4 (6C, biphenyl rings),132.7-135.0(4H,biphenyl ring),166.3 (1C,carboxylic acid); 175.1(1C,Aromatic S-C-N);177.5 (2C, C=O) Elemental analysis:C-66.65 %,H-4.66%,Cl-6.53%,F=3.50%,N=10.36 %, O=8.88 %S-5.93%

7-(4-(1-(4-(benzyloxy)-2-((benzyloxy) carbonyl) phenyl) vinyl) piperazin-1-yl)-6-fluro-1-methyl-4-oxo-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [1(e)]:

M.P: 220° C, Yield: 58%; MS: 693.19 (100%), 694.20 (41.7 %), 695.20(10.3 %); IR max cm^{-1}: 3275-2800 (O-H stretch); 1648.25(Carbonyl of oxindole); 1215.12(C-O); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ= 11.0(-OH,s,1H), 8.04 (Aromatic CH, d,1 H, phenyl ring),7.62 (Aromatic CH,d,1H,phenyl ring), 7. 57 (Aromatic CH,s,1H, phenyl ring), 7.2-7.3 (Aromatic CH,10 H, phenyl ring),7.12(Aromatic CH,s,1H of fluoroquinolone ring), 5.93(1H,s,Aromatic CH, fluoroquinolone ring),5.3-5.4(-CH_2, 4H),3.81 (CH,m,1H),3.65(CH_2, t,4H,piperazine ring) 3.42(-CH_2,t,4H,piperazine ring),1.85 (-CH_3,3H)

^{13}CNMR: 23.6 (1C,-CH_3) ; 47.5(2C, piperazine -CH_2); 49.5(2C, piperazine -CH_2); 60.7(1C,-CH); 68.1 (1C,-CH_2); 70.2 (1C,-CH_2); 101.0(1C, Aromatic C=C, fluoroquinolone ring); 100-118.2 (3C,Aromatic CH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 111.3-119.4 (3C,phenyl ring); 127.2-130.7(11C,phenyl ring),140.5-141.2 (3C, phenyl rings),161.0(1H,-C-

O),165.8(1C,-C=O);164.3 (1C,carboxylic acid); 167.3(1C,Aromatic S-C-N);183.5 (2C, C=O) Elemental analysis:C-65.79 %,H-4.66%,F=2.74%,N=6.06 %, O=16.14 % S-4.62 %

6-fluro-7-(4-(5-(7-hydroxy-1, 2, 3, 4-tetrahydroquinolin-2-yl) pentyl) piperazin-1-yl)-1-methyl-4-oxo-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [1(f)]:

M.P: 212° C, Yield: 6 8%; MS: 538.24 (100%), 539.29 (33.6 %), 540.25 (5.5 %); IR max cm^{-1}: 3275-2800 (O-H stretch); 1712.30(NH bend); 1215.12(C-O); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ= 10.0(CH_2-OH,s,1H),7.12(Aromatic CH,S,1H),6.85(Aromatic CH,m,2H),6.5 (Aromatic CH,t,1H) 6.4(Aromatic CH,d,2h),,4.45 (NH,d,1H),3.9 (-CH,m,2H),3.5 (-CH_2,m,4H),3.0(-CH_2,t,2H), 2.8 (-CH_2,t,4H), 2.4-2.5 (-CH_2,5H), 1.8-2.2(-CH_2,5H)

^{13}CNMR: 23.6 (1C,-CH_3) ;24.0(1C,-CH_2);24.7-27.8(2C,-CH_2);41.9(1C,-CH_2); 50.0(2C, piperazine -CH_2); 52.6(2C, piperazine -CH_2); 54.8(1C,-CH_2);60.7(1C,-CH); 68.1 (1C,-CH_2); 70.2 (1C,-CH_2);88.6(1C,-CH); 101.0(1C, Aromatic C=C, fluoroquinolone ring);100-118.2 (3C,Aromatic CH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 113.6-126.9 (5C,phenyl ring); 145.6(1C,phenyl ring);166.3 (1C,carboxylic acid); 167.3(1C,Aromatic S-C-N);183.5 (2C, C=O) Elemental analysis:C-64.66 %,H-6.55%,F=3.53%,N=10.40 %, O=8.91 % S-5.95 %

6-fluro-7-(4-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methyl) piperazin-1-yl)-1-methyl-4-oxo-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [1(g)]:

M.P: 233° C, Yield: 61%; MS: 528.22 (100%), 529.22 (31.6 %), 530.22 (6.0 %); IR max cm^{-1}: 3275-2800 (O-H stretch); 1215.12(C-O); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ=10.2(-OH,s,1H),8.3 (Aromatic CH,d,1H),7.85 (Aromatic CH,s,1H),6.8 (Aromatic CH,d,1H)6.4 (Aromatic CH,s,1h),4.0-4.2 (CH_2,4H), 3.8 (-CH_2,t,1H),3.6 (-CH and -CH_2,m,3H), 3.4-3.5(-CH_2, 3H),3.3(-CH_2,m,2H),(-CH_2,t,4H), 2.8 (-CH_2,t,4H), 2.4-2.5 (-CH_3,3H), 2.1-2.3(-CH_3,6H)

^{13}CNMR: 10.6(1C,-CH_3);23.6 (1C,-CH_3) ;29.0(1C,-CH_2); 50.0(2C, piperazine -CH_2); 52.6(2C, piperazine -CH_2); 54.8(1C,-CH_2);59.3(1C,-CH_3); 60.7(1C,-CH); 68.1 (1C,-CH_2); 70.2 (1C,-CH_2);88.6(1C,-CH); 101.0(1C, Aromatic C=C, fluoroquinolone ring);100-118.2 (3C,Aromatic CH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 103.6-111.9 (2C,phenyl ring); 147.6(1C,phenyl ring); 160.3 (1C,phenyl ring); 165.3 (1C,phenyl ring);166.3 (1C,carboxylic acid); 167.3(1C,Aromatic S-C-N);183.5 (2C, C=O)

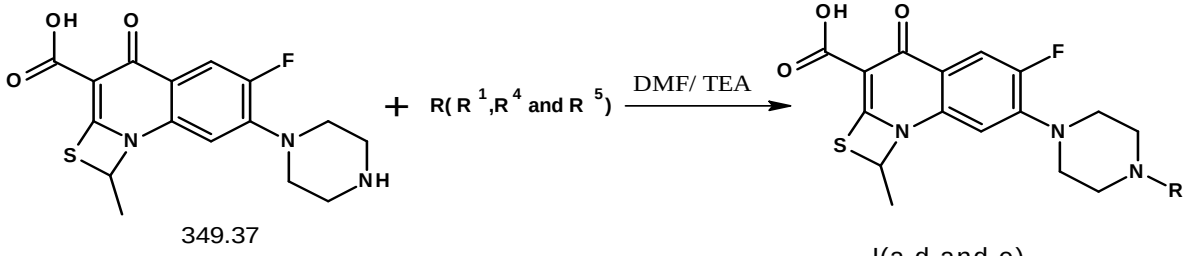
Elemental analysis:C-61.34 %,H-6.29%,F=3.59%,N=10.60 %, O= 12.11 % S-6.07 %

6-fluro-1-methyl-4-oxo-7-(4-(1-(3-(triflurомethyl) benzyl)-1*H*, 4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid [1(h)]

M.P: 223° C, Yield: 51%; MS: 587.16 (100%), 588.16 (32.9 %), 589.16 (5.4 %); IR max cm^{-1}: 3275-2800 (O-H stretch); 1215.12(C-O); 1490.56 (Ar C=C); 1220.15(C-F)

^{1}HNMR (DMSO D^{6}): δ=10.2(-OH,s,1H),7.5 (Aromatic CH of pyrazole ring,s,1H),7.4(Aromatic CH of pyrazole ring,s,1H),7.26(Aromatic CH,d,2H),7.10(Aromatic CH,m,2H),6.8(Aromatic CH,d,1H),6.4(Aromatic CH,s,1h),4.26 (CH_2,s,2H),3.73 (-CH,m,1H of thiazeto ring),3.34(-CH_2,m,4H of piperazine ring), 2.84 (-CH_2,m,4H of piperazine ring), 2.34 (-CH_3,s,3H)

^{13}CNMR: 22.8 (1C,-CH_3) ; 47.1(2C, piperazine -CH_2); 50.6(2C, piperazine -CH_2); 58.8(1C,-CH_2); 60.7(1C,-CH); 89.6(1C,-CH); 101.0(1C, Aromatic C=C, fluoroquinolone ring);100-118.2(3C,AromaticCH,fluoroquinolone ring); 140.6-144.6 (3C,Aromatic CH,fluoroquinolone ring); 103.6(1C,pyrazol); 122.2-129.2(3C,Phenyl ring);124.5(1C,CF_3);131.9-139.6(1C,pyrazol ring); 130.5-136.5 (3C,phenyl ring);166.3 (1C,carboxylic acid); 167.3(1C,Aromatic S-C-N);183.5 (1C, C=O) ; Elemental analysis:C-57.23 %,H-4.29%,F=12.93 %,N=11.92 %, O= 8.17 % S-5.46 %

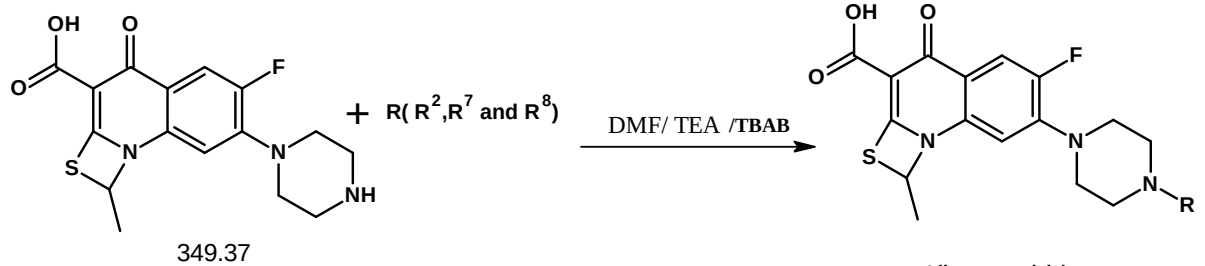


349.37

6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid

I(a,d and e)

I

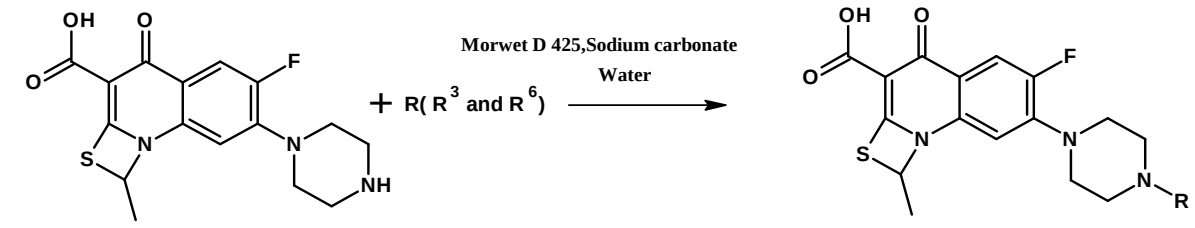


349.37

6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid

I(b,g and h)

I



349.37

6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1 ,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid

I

I(c and f)

R (R¹ to R⁸): 2-(bromomethyl)-1, 3-difluorobenzene, 5-[4'-(bromomethyl) biphenyl-2-yl]-1-trityl-l-1*H*-tetrazole,6-chloro-5-(2-chloroethyl)-1,3-dihydro-2*H*-indol-2-one,4' (bromomethyl) biphenyl-2- carbonitrile, benzyl 2-(benzyloxy)-4-(bromocarbonyl) benzoate, 2-(4-chlorobutoxy)-1,2,3,4-tetrahydroquinolin-7-ol, 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine, 1-[3-(trifluoromethyl) benzyl]-1*H*-pyrazole-4-carbonyl chloride

Scheme 1: Synthesis of N-substituted derivatives of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid I (a-h)

Table 1: Zone of inhibition and Minimum inhibitory concentration of test compounds against *Bacillus subtilis*

S. No.	Test Compound	Concentration (µg/mL)	Zone of Inhibition (in mm) *Test organism: Bacillus subtilis*	Minimum Inhibitory Concentration (µg/mL)
1	I(a)	1024	21.00	32
		512	17.00	
		128	14.00	
		32	11.00	
		8	-	
2	I(b)	1024	19.50	128
		512	16.00	
		128	7.00	
		32	-	
		8	-	
3	I(c)	1024	10.00	512
		512	8.0	
		128	-	
		32	-	
		8	-	
4	I(d)	1024	20.00	32
		512	14.00	
		128	12.00	
		32	10.0	
		8	-	
5	I(e)	1024	13.00	512
		512	9.00	
		128	-	
		32	-	
		8	-	
6	I(f)	1024	21.00	32
		512	26.00	
		128	18.00	
		32	11.00	
		8	-	
7	I(g)	1024	10.00	128
		512	7.00	
		128	7.00	
		32	-	
		8	-	
8	I(h)	1024	19.00	32
		512	17.00	
		128	14.00	
		32	8.00	
		8	-	
9	Ciprofloxacin Positive Control	1024	14.00	-
10	DMSO Negative Control	1%	0.00	-

Evaluation of antibacterial activity and determination of minimum inhibitory concentration by disk diffusion method

1. Test organisms: *Bacillus subtilis and Escherichia coli*

2. Test compounds*:* Eight synthesized molecules and Ciprofloxacin as positive control

3. Inoculum: Cell suspension was prepared from cultures grown on Trypticose soya broth adjusted to 1-2 x 10^8 cells/mL

4. Drug concentrations: drug concentration prepared: (a) Test compounds: 8 - 1024 µg/mL in 1% DMSO **(b)** Control: 1% DMSO in Sterile water

5. Procedure: (a) Determination of Antibacterial activity: (i)100 µl Inoculum of test cultures was inoculated on Muller Hinton Agar plates (90 mm).**(ii)**Test compounds (5µl, 1024 µg/mL) and ciprofloxacin (5 µl, 1 mg/mL) were impregnated on 6mm sterile Whatmann No. 1 Disks.**(iii)**Test compounds and standard disks were placed on Agar plates.**(iv)** The plates were Incubated @ 35°C for 24-48 hrs and observed for zone of inhibition around the disk.**(v)** The Compounds showing activity were further tested for determination of Minimum Inhibitory Concentration.

(b)Determination of minimum inhibitory Concentration: (i) 100 µl Inoculum of test cultures was inoculated on Muller Hinton Agar plates (90 mm).**(ii)**Test compounds (5ul, Different test concentrations, 8, 32, 128, 512 and 1024 ug/mL) and ciprofloxacin (5 ul, 1 mg/mL) were impregnated on 6mm sterile Whatmann No. 1 Disks.**(iii)**Test compounds and standard disks were placed on Agar plates.**(iv)**The plates were Incubated @ 35 0C for 24-48 hrs and observe for zone of inhibition around the disk.**(v)**Lowest concentration of test compound showing zone of inhibition was considered as MIC.

Determination of Minimum Inhibitory concentration: The zone of inhibition and MIC determined for each test compound is summarized in Table 1**.**

RESULTS

Eight derivatives were synthesized and their structure was confirmed by IR, NMR, mass spectrum and elemental analysis. All the eight derivatives were subjected to antibacterial activity. Among the tested compounds seven compounds showed antibacterial activity against *Bacillus subtilis* (Gram positive bacteria). None of the compounds showed zone of inhibition against *Escherichia coli* (Gram negative Bacteria). The zone of inhibition observed for different test compounds is tabulated in Table. 1. The five derivatives [1(f), 1(d), 1(a) and 1(h)] showed comparable antibacterial activity, in test conditions, with respect to ciprofloxacin.

DISCUSSION

The N-substituted 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid derivatives were prepared by three different methods. The general procedure, which involved the use of Triethylamine and DMF, was modified by the addition of tetra butyl ammonium bromide (TBAB) to facilitate completion in few reactions. Other reactions which did not proceed in both the aforementioned ways were facilitated by the use of Morwet-D425. The problem faced in these reactions was the incompletion of the reaction or the formation of sticky material and difficult stirrability of the reaction mass which in turn results in lesser purity and lower yields. In U.S.Pat.No.8, 410,268B2 [16] we have disclosed a process for the preparation of Ziprasidone, involved the same procedure. In our present work, we have achieved substantially good yields and purity. All the compounds were screened for antibacterial activity. The derivatives involving substituted phenyl and substituted quinoline ring showed substantial activity against *Bacillus subtilis* (Gram positive bacteria).

CONCLUSION

The preparation procedures followed in this work offers reduction in the reaction time, operation simplicity, cleaner reaction and easy work-up. Observation has showed the importance of electronic environment on antibacterial activity. The quinoline substitution along with the halogen and cyano substituted phenyl ring has increased the activity of the compounds compared to those with other substituent's. This may be due to the presence of the versatile pharmacophore which might increase the lipophilic character of the molecules and thus facilitate the crossing through the biological membrane of the microorganisms and thereby inhibit their growth .The title compounds [I(a-h)] were prepared from the starting material 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1, 3] thiazeto [3, 2-*a*] quinoline-3-carboxylic acid (I) and were screened for antibacterial activity. Among all compounds it was found that derivatives with 2-(4-chlorobutoxy)-1,2,3,4-tetrahydroquinolin-7-ol, 4' (bromomethyl)biphenyl-2-carbonitrile, 2-(bromomethyl)-1,3-difluorobenzene and 1-[3-(trifluoromethyl)benzyl]-1*H*-pyrazole-4-carbonyl chloride showed comparable antibacterial activity when compared to ciprofloxacin .

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