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Synthesis, Characterization and Biological evaluation of some newer 5-[6-chloro/fluoro/nitro-2-(p-chloro/ fluoro/ methyl phenyl)-quinolin-4-yl]-1,3,4-oxadiazole-2-thiols

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ABSTRACT

Recent study shows that quinolines represent one of the most active classes of compounds possesses wide spectrum biodynamic activities and use as potent therapeutic agents. In present research work, 5-[6-chloro/fluoro/nitro-2-(p-chloro/fluoro/methyl phenyl)-quinolin-4-yl]-1,3,4-oxadiazole-2-thiols have been synthesized by condensation of substituted quinoline-4-carbohydrazides and mixture of carbon disulphide and potassium hydroxide. All of these compounds were screened for their *in vitro*anti microbial assay against gram (+ve), gram (-ve) bacteria and fungi activity compared with standard drugs viz., Ampicilin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Griseofulvin and Nystatin at different concentrations.

***Keywords*:** Quinolines; 1,3,4-oxadiazole-2-thiols; therapeutic agents; anti-microbial assay

1. INTRODUCTION

Tuberculosis (TB) is a global epidemic caused by various strains of mycobacterium, usually *Mycobacterium tuberculosis (H$_{37}$RV)*. Tuberculosis has been considered to be a disease of poverty for many years with quite rare occurrence in the developed countries. Unfortunately recently more people in the developed world are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs, substance abuse or AIDS. Several decades ago effective anti-TB drugs have been launched and one could hardly find a TB case to be demonstrated at the medicinal universities. But TB stroke back[1]. The return of tuberculosis was declared by World Health Organization (WHO) as a global emergency compared to a hypothetic third world war with 9 million new TB cases and two million deaths reported each year[2,3]; about one-third of the world's population is already infected with *M. tuberculosis.*[4]

The quinoline was reported to exhibit various biological activity such as antiamoebic[5,] antimalarial[6,7], antiviral[8,9], as well as anti-inflammatory activity[10,11]. In addition, the

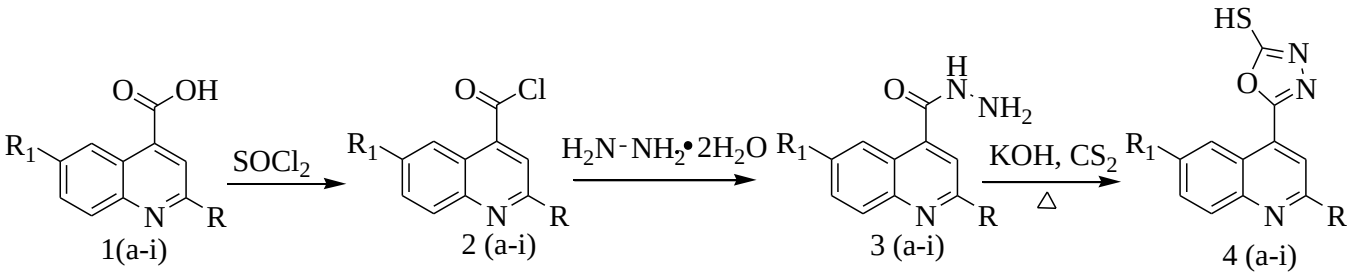
discovery of nalidixic acid, a urinary tract antimicrobial drug[12], prompted the synthesis of many quinoline derivatives and evaluation for their antimicrobial activity[13-15]and antibacterial activity.

Norfloxacin, ofloxacin and ciprofloxacin (nalidixic acid analogs) were marketed as antibacterial agent[16]. Besides, oxadiazole rings are important examples of the heteroazoles that by themselves or in combination with other ring systems possess antimicrobial[17-19,21] as well as antibacterial activity. In view of this fact and as a continuation of a research program carried out in our laboratory series of substituted oxadiazolyquinoline have been synthesized to investigate their antimicrobial activity and antitubercular activity.

2. RESULT AND DISCUSSION

2. 1. Chemistry

Preparation of 5-(2-(4-chloro/flouro/methylphenyl)-6-fluoro/chloro/nitroquinoline-4-yl)-1,3,4-oxadiazole-2-thiol (4a-i) is summarized in Scheme 1. Various 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carbohydrazide (3a-i) were treated with potassium hydroxide and carbon disulphide in ethanol was heated under reflux until the evolution of H_2S ceases. The reaction mixture was concentrated and dissolved in water and acidified with HCl. The resulting product was recrystallised from methanol. The yields of the products were obtained in the range of 65-80 %. Designed series of molecules scheme-1 were characterized by ^1H NMR, IR and Mass spectrometry techniques before evaluating for antimicrobacterial and antitubercular activity.



R= 4-Cl-C_6H_4, 4-F-C_6H_4, 4-CH_3-C_6H_4
R_1=4-F, 4-Cl, 4-NO_2

Scheme 1. Comparative antimicrobial activity of 5-[6-chloro/fluoro/nitro-2-(p-chloro/ fluoro/ methyl phenyl)-quinolin-4-yl]-1,3,4-oxadiazole-2-thiols (4a-i). (Different Inhibition Concentration in μg/ml).

2. 2. Antimicrobial and antitubercular activity

The products (4a-i) were assayed for their in vitro biological assay like antibacterial activity towards S. pyogens MTCC-442, S. aureus MTCC-96 (Gram positive) and E. coli MTCC- 443, P. aeruginosa MTCC-424 (Gram negative) bacterial strain and antifungal activity towards A. niger MTCC-282 and A. clavatus MTCC-1323 at different concentrations: i.e. 0 (control), 5, 25, 50, 100, 250 (μg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds (Xa-i) were compared with standard drugs viz., Ampicilline, Chloramphenicol, Ciprofloxacin, Norfloxacin, Griseofulvin and Nystatin. The result of antimicrobial activity is

presented Table in given below bold value presented that, these compounds are biological active near or above than the standard drugs.

Table 1

Entry	R	R_1	Antibacterial activity (Zone of inhibition in m.m.)									
			S.Pyogens MTCC-442					S.aureus MTCC-96				
			5	25	50	100	250	5	25	50	100	250
4a	4-Cl-C_6H_4	4-F	-	09	14	17	**19**	-	**13**	**14**	15	**19**
4b	4-Cl-C_6H_4	4-Cl	-	10	13	15	17	-	10	12	**16**	**18**
4c	4-Cl-C_6H_4	4-NO_2	-	10	12	14	16	-	11	13	14	17
4d	4-F-C_6H_4	4-F	-	11	13	14	17	-	11	13	**16**	17
4e	4-F-C_6H_4	4-Cl	-	09	11	14	**19**	-	10	13	15	16
4f	4-F-C_6H_4	4-NO_2	-	10	13	14	18	-	12	13	**16**	17
4g	4-CH_3-C_6H_4	4-F	-	11	13	15	18	-	09	11	14	**19**
4h	4-CH_3-C_6H_4	4-Cl	-	10	14	17	**20**	-	10	13	14	**18**
4i	4-CH_3-C_6H_4	4-NO_2	-	11	14	**18**	**20**	-	09	**14**	**17**	**20**
Comparative activity of 4(a-i) with known chosen standard drugs												
Standard drug			Antibacterial activity									
Ampicilline			11	14	19	18	19	10	13	14	16	18
Chloramphenicol			10	13	19	20	20	12	14	19	20	21
Ciprofloxacin			16	19	21	21	22	17	19	21	22	21
Norfloxacin			18	19	20	21	21	19	22	25	26	28

Table 2

Entry	R	R_1	Antibacterial activity (Zone of inhibition in m.m.)									
			E.coli MTCC-443					P.aeruginose MTCC-424				
			5	25	50	100	250	5	25	50	100	250
4a	4-Cl-C_6H_4	4-F	-	**15**	**17**	**20**	**21**	-	12	13	14	15
4b	4-Cl-C_6H_4	4-Cl	-	12	13	17	19	-	13	**15**	**18**	19
4c	4-Cl-C_6H_4	4-NO_2	-	14	**16**	17	**21**	-	10	12	13	15
4d	4-F-C_6H_4	4-F	-	11	12	15	**21**	-	10	13	15	17
4e	4-F-C_6H_4	4-Cl	-	12	15	**19**	**21**	-	12	14	16	19
4f	4-F-C_6H_4	4-NO_2	-	14	**16**	17	18	-	11	**15**	16	18
4g	4-CH_3-C_6H_4	4-F	-	12	13	15	17	-	12	14	16	18
4h	4-CH_3-C_6H_4	4-Cl	-	**15**	**17**	18	**20**	-	11	14	16	19
4i	4-CH_3-C_6H_4	4-NO_2	-	**15**	**17**	**19**	**22**	-	10	12	16	17
Comparative activity of 4(a-i) with known chosen standard drugs												
Standard drug			Antibacterial activity									
Ampicilline			14	15	16	19	20	14	15	15	18	20
Chloramphenicol			14	17	23	23	23	14	17	18	19	21
Ciprofloxacin			20	23	28	28	28	20	23	24	26	27
Norfloxacin			22	25	26	27	29	18	19	21	23	23

Table 3

Entry	R	R_1	Antifungal activity (Zone of inhibition in m.m.)									
			A.nigar MTCC-282					A.clavatus MTCC-1323				
			5	25	50	100	250	5	25	50	100	250
4a	4-Cl-C_6H_4	4-F	-	**19**	21	24	25	-	19	21	**22**	**24**
4b	4-Cl-C_6H_4	4-Cl	-	18	20	23	24	-	18	20	**22**	23
4c	4-Cl-C_6H_4	4-NO_2	-	**20**	22	23	25	-	18	19	**22**	**24**
4d	4-F-C_6H_4	4-F	-	16	17	20	23	-	10	20	21	**24**
4e	4-F-C_6H_4	4-Cl	-	18	19	22	25	-	18	20	**22**	**24**
4f	4-F-C_6H_4	4-NO_2	-	17	19	22	24	-	**21**	**22**	**23**	**25**
4g	4-CH_3-C_6H_4	4-F	-	**19**	22	23	24	-	**21**	**22**	**23**	**25**
4h	4-CH_3-C_6H_4	4-Cl	-	18	21	22	24	-	19	20	**22**	**24**
4i	4-CH_3-C_6H_4	4-NO_2	-	**19**	20	21	23	-	18	18	21	22
Comparative activity of 4(a-i) with known chosen standard drugs												
Standard drug			Antifungal activity									
Griseofulvin			19	23	25	25	28	18	21	22	22	24
Nystain			18	19	24	29	29	18	21	24	25	26

All compounds were initially screened for their antitubercular activity at 6.25 μg/mL concentration against MTB H37Rv strain by the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) in BACTEC 12B medium using the Microplate Alamar Blue Assay[20]. Unfortunately In the preliminary screening all compounds (4a-i) were inactive against MABA assay and all compounds possess both$IC_{50} > 100$ and $IC_{90} > 100$.

3. EXPERIMENTAL SECTION

All research chemicals were purchased from Sigma–Aldrich and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates from E-Merck Co and compounds visualized either by exposure to UV light or staining with reagents. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on SHIMADZU- FTIR-8400 spectrophotometer using KBr pellet method. ^{1}H NMR spectra were recorded on Bruker 300-MHz NMR spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectrum was recorded on JOEL SX 102/DA-600-Mass spectrometer and elemental analysis was carried out using Heraus C, H, and N rapid analyzer

General procedure for the synthesis of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carboxylic acid (1a-i)

A mixture of 4-chloro/fluro/methylbenzaldehyde (0.01 mole), freshly distilled pyruvic acid (0.01 mole; 0.88 g) and absolute ethyl alcohol (25 ml) was refluxed to the boiling point on a water bath and a solution of 4-fluro/chloro/nitroaniline (0.01 mole) in absolute ethyl alcohol (25 ml) was added slowly with frequent shaking. The content was refluxed for 3 hours and allowed to stand overnight. The product was filtered and recrystallised from ethanol. Yield: 70-80 %.

General procedure for the synthesis of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carbohydrazide (3a-i)

A mixture of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carboxylic acid (1a-i)(0.001 mole; 2.84 g) in dioxan (40 ml) and thionyl chloride (10 ml) was refluxed at 60-70 °C for 3 hours. Excess of thionyl chloride was removed by distillation and product obtained was kept at 0 °C and 2-3 drops of pyridine and further refluxed with hydrazine hydrate 99 % (0.1 mole; 4 ml) for 6 hours. The contents were poured in to ice-cold water. The resulting product was filtered, dried and crystallized from DMF.Yield: 68-75 %.

General procedure for the synthesis of 5-(2-(4-chloro/flouro/methylphenyl)-6-fluoro/chloro/nitroquinoline-4-yl)-1,3,4-oxadiazole-2-thiol (4a-i)

A mixture of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carbohydrazide (3a-i)(0.01 mole; 2.67 g), potassium hydroxide (0.01 mole; 0.4 g), carbon disulphide (4 ml) and ethanol (15 ml) was heated under reflux until the evolution of H_2S ceases. The reaction mixture was concentrated, dissolved in water and acidified with HCl. The resulting product was recrystallized from methanol. Yield: 65-80 %.

5-(2-(4-chlorophenyl)-6-fluoroquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4a)

Yield: 72 %; mp 156 °C; ^{1}H NMR (DMSO-d_6) δ ppm:3.11 (s, 1H, -SH), 6.82-6.84 (d, 2H, Ar-H), 7.30-7.33 (m, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.72-7.74 (d, 1H, Ar-H), 7.86-7.88 (d, 2H, Ar-H), 7.96-7.98 (m, 1H, Ar-H) ; IR (KBr, cm^{-}1): 3054, 2935, 2900, 1530, 1458, 1340, 1300, 1110, 1027, 807, 644.;Anal. Calcd for $C_{17}H_9ClFN_3OS$: C, 57.07; H, 2.54; N, 11.74; O, 4.47; S, 8.96. Found: C, 57.10; H, 2.50; N, 11.70; O, 4.50; S, 8.92.; MS: m/z 357.

5-(6-chloro-2-(4-chlorophenyl)quinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4b)

Yield: 65 %; mp 186 °C; ^{1}H NMR (DMSO-d_6) δ ppm:3.04 (s, 1H, -SH), 6.80-6.82 (d, 2H, Ar-H), 7.30-7.34 (m, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.68-7.70 (d, 1H, Ar-H), 7.88-7.90 (d, 2H, Ar-H), 7.97-7.99 (m, 1H, Ar-H) ; IR (KBr, cm^{-}1): 3300, 3050, 2940, 2904, 1534, 1456, 1340, 1310, 1050, 807, 640.;Anal. Calcd for $C_{17}H_9Cl_2N_3OS$: C, 54.56; H, 2.42; N, 11.23; O, 4.28; S, 8.57. Found: C, 54.50; H, 2.50; N, 11.20; O, 4.32; S, 8.60.; MS: m/z 374.

5-(2-(4-chlorophenyl)-6-nitroquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4c)

Yield: 62 %; mp 142 °C; ^{1}H NMR (DMSO-d_6) δ ppm:3.10 (s, 1H, -SH), 6.92-6.94 (d, 2H, Ar-H), 7.50-7.53 (m, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 8.10-8.12 (d, 1H, Ar-H), 8.30-8.32 (d, 2H, Ar-H), 8.60-8.67 (m, 1H, Ar-H) ; IR (KBr, cm^{-}1): 3310, 2954, 2900, 1530, 1458, 1344, 1300, 1110, 1026, 807, 630, 540.;Anal. Calcd for $C_{17}H_9ClN_4O_3S$: C, 53.06; H, 2.30; N, 14.56; O, 12.47; S, 8.33. Found: C, 53.20; H, 2.35; N, 14.60; O, 12.50; S, 8.40.; MS: m/z 384.

5-(6-fluoro-2-(4-fluorophenyl)quinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4d)

Yield: 72 %; mp 150 °C; ^{1}H NMR (DMSO-d_6) δ ppm:3.06 (s, 1H, -SH), 6.72-6.74 (d, 2H, Ar-H), 7.30-7.34 (m, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.70-7.72 (d, 1H, Ar-H), 7.92-7.94 (d, 2H, Ar-H), 8.01-8.03 (m, 1H, Ar-H) ; IR (KBr, cm^{-}1): 3300, 2954, 3010, 2850, 2700, 1530, 1440, 1050, 834, 750, 640. ;Anal. Calcd for $C_{17}H_9F_2N_3OS$: C, 59.82; H, 2.60; N, 12.30; O, 4.69; S, 9.39. Found: C, 59.80; H, 2.55; N, 12.20; O, 4.72; S, 9.50.; MS: m/z 341.

5-(6-chloro-2-(4-fluorophenyl)quinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4e)

Yield: 75 %; mp 168 °C; ^{1}H NMR (DMSO-d_6) δ ppm:3.04 (s, 1H, -SH), 6.70-6.72 (d, 2H, Ar-H), 7.28-7.32 (m, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 7.65-7.67 (d, 1H, Ar-H), 7.98-8.00

(d, 2H, Ar-H), 8.03-8.05 (m, 1H, Ar-H) ; IR (KBr, cm-1): 3010, 2936, 2902, 1674, 1458, 1344, 1305, 1117, 1027, 807, 644. ;Anal. Calcd for $C_{17}H_9ClFN_3OS$: C, 57.05; H, 2.52; N, 11.70; O, 4.47; S, 8.96. Found: C, 57.15; H, 2.57; N, 11.20; O, 4.76; S, 8.52.; MS: m/z 357.

5-(2-(4-fluorophenyl)-6-nitroquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4f)

Yield: 68 %; mp 126 °C; ^{1}H NMR (DMSO-d_6) δ ppm:3.10 (s, 1H, -SH), 6.80-6.82 (d, 2H, Ar-H), 7.40-7.42 (m, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.90-7.92 (d, 1H, Ar-H), 8.18-8.20 (d, 2H, Ar-H), 8.60-8.62 (m, 1H, Ar-H) ; IR (KBr, cm-1): 3300, 3010, 2856, 1734, 1300, 1110, 1022, 860. ;Anal. Calcd for $C_{17}H_9FN_4O_3S$: C, 55.43; H, 2.46; N, 15.21; O, 13.03; S, 8.71. Found: C, 55.40; H, 2.50; N, 15.30; O, 13.10; S, 8.80.; MS: m/z 368.

5-(6-fluoro-2-p-tolylquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4g)

Yield: 77 %; mp 138 °C; ^{1}H NMR (DMSO-d_6) δ ppm:1.10 (s, 3H, -CH_3), 3.10 (s, 1H, -SH), 6.80-6.82 (d, 2H, Ar-H), 7.40-7.42 (m, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.90-7.92 (d, 1H, Ar-H), 8.18-8.20 (d, 2H, Ar-H), 8.60-8.62 (m, 1H, Ar-H) ; IR (KBr, cm-1): 3300, 3010, 2856, 1734, 1300, 1110, 1022, 860. ;Anal. Calcd for $C_{18}H_{12}FN_3OS$: C, 55.43; H, 2.46; N, 15.21; O, 13.03; S, 8.71. Found: C, 55.40; H, 2.50; N, 15.30; O, 13.10; S, 8.80.; MS: m/z 337.

5-(6-chloro-2-p-tolylquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4h)

Yield: 69 %; mp 149 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.12 (s, 3H, -CH_3), 3.04 (s, 1H, -SH), 6.98-7.00 (d, 2H, Ar-H), 7.10-7.12 (m, 1H, Ar-H), 7.39-7.42 (m, 1H, Ar-H), 7.80-7.82 (d, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 8.04-8.06 (m, 1H, Ar-H) ; IR (KBr, cm-1): 3330, 3240, 2900, 2535, 1850, 1670, 1110, 980, 830, 650. ;Anal. Calcd for $C_{18}H_{12}ClN_3OS$: C, 61.10; H, 3.40; N, 11.86; O, 4.63; S, 9.00. Found: C, 61.05; H, 3.42; N, 11.80; O, 4.50; S, 9.05.; MS: m/z 354.

5-(6-nitro-2-p-tolylquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4i)

Yield: 77 %; mp 152 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.11 (s, 3H, -CH_3), 3.10 (s, 1H, -SH), 7.10-7.13 (d, 2H, Ar-H), 7.60-7.62 (d, 2H, Ar-H), 8.10-8.13 (s, 1H, Ar-H), 8.40-8.44 (m, 1H, Ar-H), 8.50-8.52 (m, 1H, Ar-H), 8.80-8.83 (m, 1H, Ar-H) ; IR (KBr, cm-1): 3325, 3240, 2939, 2900, 1850, 1670, 1116, 970, 820. ;Anal. Calcd for $C_{18}H_{12}N_4O_3S$: C, 59.33; H, 3.30; N, 15.40; O, 13.17; S, 8.88. Found: C, 59.20; H, 3.15; N,15.45; O, 13.20. S, 8.80.; MS: m/z 364.

4. CONCLUSIONS

In the present paper, we report the synthesis, spectral studies and its Antimicrobial and antimycobacterial activity of various quinoline derivatives. The high bioactivity of these compounds makes them suitable hits for additional *in vitro* and *in vivo* evaluations, in order to develop new class of Antimicrobial and antimycobacterial drugs or prodrugs with potential use in the antibacterial, antifungal and tuberculosis treatment. Further studies in this area are in progress in our laboratory.

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