Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Synthesis, Characterization and Biological Evaluation of Novel Isoxazolo [5,4-b] Quinolines as Potent Antimicrobial Agents

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ARTICLE INFO

Article history:

Received: 18 August, 2022

Revised: 11 October, 2022

Accepted: 18 October, 2022

Published: 30 November, 2022

Keywords:

Antibacterial activity, Antifungal activity, Isoxazole, Quinoline

DOI:

10.25004/IJPSDR.2022.140609

ABSTRACT

In order to combat antimicrobial resistance, antimicrobial chemotherapy made advances in the development of new potent antibiotics and antifungal agents. This is because the microorganisms are becoming resistant to the drugs due to improvements in current antibiotic classes by changing their pore formation mechanism and membrane permeability as well as by adjusting to combat the efficacy of the drugs. In order to address the microbial resistance, a series of novel isoxazolo [5,4-b] quinolines are synthesized and evaluated for antibacterial and antifungal activities. The synthesized compounds 4c, 4f and 4g exhibited potent antibacterial activity, and 4c and 4e revealed moderate antifungal activity.

Introduction

Many naturally occurring physiologically active substances such as quinine, chloroquine, bulaquine, primaquine and tafenoquine include the quinoline core structure.[1-4] Typical drug design formulations aim to mimic naturally occurring heterocycles and exert potency by interfering with and interrupting the regular pathways required for the development of harmful organisms.[5] They have made major contributions to society by its use as therapeutic agents,[6-8] use in animals and in humans,[7] application in agriculture,[9,10] used as dyes,[11] polymers,[12] used in bioinformatics,[13] molecular engineering[14] and many other uses.

The numerous reported biological and pharmacological activities of functionalized quinoline moieties make them highly important pharmacophoric motifs with undeniable therapeutic propensity including anticancer,[15] anti-inflammatory,[16] antimicrobial,[17] antioxidant,[18] antimalarial,[19] antitubercular,[20] anti-leishmanial,[21] anti-HIV,[22] antiprotozoal[23] and DNA binding.[24]

Synthetic quinolines are widely accepted, useful and indispensible antibacterial agents. The structure activity relationship of antibacterial quinolines has been extensively investigated, the optimum functionalities are found to be chloro at C-7 , carbonyl at C-4 position, aryl and large alkyl at C-3, amines at C-2, hydroxyl at C-8 position. These includes ciprofloxacin, norfloxacin, ofloxacin, perfloxacin,[25] etc. Though quinolines captured the market as antibacterials antifungals, some are resistant to certain bacterial and fungal infections. To overcome this problem, heterocyclic fused quinoline compounds are synthesized as a new class of compounds for their bioevaluation and some of them are found to be as potent as ciprofloxacin. Among tricyclic compounds, imidazo,[26] pyrazolo,[27] pyrimido, pyrrolo,[28,29] triazole, pyrano,[29]

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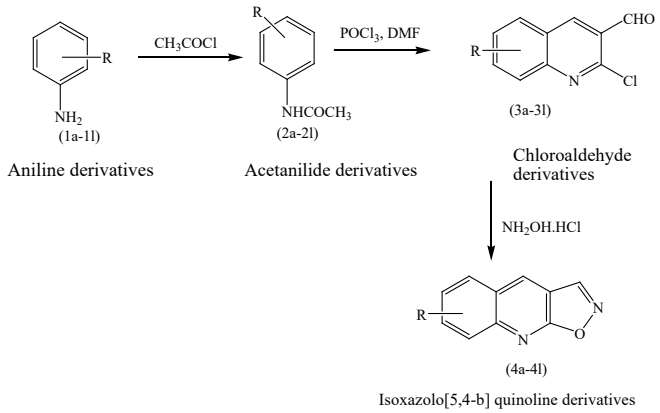
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



Scheme 1: Synthetic pathway to produce isoxazolo [5,4-b] quinoline derivatives

(1a) R= 2-chloro	(4a) R= 2- chloro
(1b) R= 3- chloro	(4b) R= 3- chloro
(1c) R= 4- chloro	(4c) R= 4- chloro
(1d) R= 2,3- dichloro	(4d) R= 2,3- dichloro
(1e) R= 2,4- dichloro	(4e) R= 2,4- dichloro
(1f) R= 3,4- dichloro	(4f) R= 3,4- dichloro
(1g) R= 3,5- dichloro	(4g) R= 3,5- dichloro
(1h) R= 2- ethyl	(4h) R= 2- ethyl
(1i) R= 3- ethyl	(4i) R= 3- ethyl
(1j) R= 2- nitro	(4j)R= 2- nitro
(1k) R= 3- nitro	(4k) R= 3- nitro
(1l) R= 4- nitro	(4l) R= 4- nitro

oxazino,[30] fused quinolines were reported by several researchers. We have synthesized 5,4-b isoxazole fused quinolines retaining acceptable functionalities in the system at appropriate positions.

The active compounds can be further extensively evaluated for their antibacterial and antifungal activity and acute toxicity studies of the potent compound can be performed which will be more advantageous looking at the bacterial resistance scenario.

Materials and Methods

Chemistry

All the chemicals were obtained from Sigma-Aldrich, Rankem, SD fine chemicals and CDH. The melting point was determined on a precision melting point apparatus with a digital thermometer. Fourier transform infrared spectra was recorded on FT-IR shimadzu 8300 spectrophotometer, ^{1}H-NMR spectra on a Bruker 400 MHz NMR spectrophotometer in $CDCl_3$, the chemical shifts were recorded in ppm and TMS was used as reference standard. Mass spectra were obtained on shimadzu 2010A LC-MS spectrometer. Thin-layer chromatography was performed on manually prepared silica gel-G plates to monitor the reactions and determine compounds' purity using benzene and ethyl acetate in different ratios as mobile phase.

The synthetic pathway that was designed to produce the compounds mentioned in the title illustrated in scheme.

The synthesized compound's uncorrected melting points were measured in open capillary tubes.

The compounds (2a-2l) were synthesized using previously reported literature.[31]

2, 8-Dichloroquinoline-3-carbaldehyde (3a)

$POCl_3$ (60 mmol) was added dropwise to a solution of 2-chloro acetanilide (2a) (5 mmol) in dry dimethylformamide (15 mmol) at 0–5°C with stirring and it was heated at 80–90°C for 4–6 hours. The mixture was poured into crushed ice and stirred for 5 minutes before being filtered, washed thoroughly with water, dried and recrystallized in order to purify the compound.

Using the corresponding acetanilide derivatives (2b-2l), a similar process was used to produce the quinoline derivatives (3b-3l).

Off white solid; Yield 70%, MP: 198.3-199.5°C; IR (υmax, cm^{-1}): 3067, 2737 (aromatic, C-H), 1694 (C=O), 1601, 1497 (Ar. C=C), 1092 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.384 (t,1H, H-6), 7.682 (d,1H, H-5), 7.716 (d,1H, H-7), 8.752 (s,1H, H-4), 10.437 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 224.975 (M^+); Calculated for $C_{10}H_5Cl_2NO$: C, 53.13; H, 2.23; Cl, 31.37; N, 6.20 ; Found: $C_{10}H_5Cl_2NO$: C, 53.34; H, 2.05; Cl, 31.09; N, 6.38

2,7- Dichloroquinoline-3-carbaldehyde (3b)

Light yellow solid; Yield 74%, MP: 201.7-202.9°C; IR (υmax, cm^{-1}): 3115, 2750 (aromatic, C-H), 1699 (C=O), 1604, 1488 (Ar. C=C), 1095 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.398 (d,1H, H-6), 7.592 (d,1H, H-H-5), 8.062 (s,1H, H-8), 8.692 (s,1H, H-4), 10.512 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 224.975 (M^+); Calculated for $C_{10}H_5Cl_2NO$: C, 53.13; H, 2.23; Cl, 31.37; N, 6.20 ; Found: C, 53.28; H, 2.06; Cl, 31.65; N, 6.02

2,6-Dichloroquinoline-3-carbaldehyde (3c)

Golden yellow solid; Yield 68%, MP: 206.9-207.8°C; IR (υmax, cm^{-1}): 3130, 2718 (aromatic, C-H), 1698 (C=O), 1598, 1501 (Ar. C=C), 1094 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.422 (d,1H, H-7), 7.762 (s,1H, H-5), 7.943(s,1H, H-8) 8.716 (s,1H,H-4), 10.478 (s,1H, CHO, D_2O exchangeable); EIMS m/z: 224.975 (M^+); Calculated for $C_{10}H_5Cl_2NO$: C, 53.13; H, 2.23; Cl, 31.37; N, 6.20; Found: C, 53.31; H, 2.01; Cl, 31.69; N, 6.06

2,7,8-Trichloroquinoline-3-carbaldehyde (3d)

Mustard yellow solid; Yield 55%, MP: 241.4-242.5°C; IR (υmax, cm^{-1}): 3126, 2709 (aromatic, C-H), 1704 (C=O), 1601, 1504 (Ar. C=C), 1098 (Ar. C-Cl) cm^{-1} ; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.539 (d,1H,H-5), 7.812 (d,1H,H-6), 8.768 (s,1H,H-4), 10.542 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 258.936 (M^+); Calculated for $C_{10}H_4Cl_3NO$: C, 46.11; H, 1.55; Cl, 40.83; N, 5.38; Found: C, 46.32; H, 1.28; Cl, 40.98; N, 5.23

2,6,8,-Trichloroquinoline-3-carbaldehyde (3e)

Golden yellow solid; Yield 78%, MP: 238.5-239.6°C; IR (υmax, cm^{-1}): 3127, 2714 (aromatic, C-H), 1702 (C=O), 1596, 1505 (Ar. C=C), 1096 (Ar. C-Cl) cm^{-1} ; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.531(s,1H,H-5), 8.305 (s,1H,H-7), 8.732 (s,1H,H-4), 10.582 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 258.936 (M^+); Calculated for $C_{10}H_4Cl_3NO$: C, 46.11; H, 1.55; Cl, 40.83; N, 5.38 ; Found: C, 46.09; H, 1.24; Cl, 40.95; N, 5.27

2,6,7-Trichloroquinoline-3-carbaldehyde (3f)

Light yellow solid; Yield 70%, MP: 245.7-246.8°C; IR (υmax, cm^{-1}): 3127, 2714 (aromatic, C-H), 1702 (C=O), 1596, 1505 (Ar. C=C), 1096 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.531(s,1H,H-5), 8.305 (s,1H,H-8), 8.732 (s,1H,H-4), 10.582 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 258.936 (M^+); Calculated for $C_{10}H_4Cl_3NO$: C, 46.11; H, 1.55; Cl, 40.83; N, 5.38 ; Found: C, 46.27; H, 1.69; Cl, 40.98; N, 5.45

2,5,7-Trichloroquinoline-3-carbaldehyde (3g)

Off white solid: Yield 56%, MP: 247.6-248.7°C; IR (υmax, cm^{-1}): 3120, 2710 (Aromatic, C-H), 1705 (C=O), 1602, 1498 (Ar. C=C), 1092 (Ar. C-Cl) cm^{-1} ; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.611 (s,1H,H-6), 8.068 (s,1H,H-8), 9.386 (s,1H,H-4), 10.523 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 258.936 (M^+); Calculated for $C_{10}H_4Cl_3NO$: C, 46.11; H, 1.55; Cl, 40.83; N, 5.38 ; Found: C, 46.32; H, 1.74; Cl, 40.88; N, 5.51

2-Chloro-8-ethylquinoline-3-carbaldehyde (3h)

Yellow solid; Yield 62%, MP: 244.5-245.6°C; IR (υmax, cm^{-1}): 3078, 2879, 2744 (Aromatic, C-H), 1706 (C=O), 1600, 1498 (Ar. C=C), 1093 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 1.245(t,3H,CH_3), 2.678 (q,2H,CH_2), 7.371 (d,1H,H-6), 7.654(d,1H,H-5), 7.887(s,1H,H-8), 8.329 (s,1H,H-4), 9.837 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 219.045 (M^+); Calculated for $C_{12}H_{10}ClNO$:C, 65.61; H, 4.59; Cl, 16.14; N, 6.38; Found: C, 65.45; H, 4.33; Cl, 16.45; N, 6.19

2-Chloro-7-ethylquinoline-3-carbaldehyde (3i)

Mustard yellow solid; Yield 56%, MP: 252.8-253.9°C; IR (υmax, cm^{-1}): 3089, 2878, 2757 (Aromatic, C-H), 1707 (C=O), 1596, 1505 (Ar. C=C), 1095 (Ar. C-Cl) cm^{-1} ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 1.245 (t,3H,CH_3), 2.592 (q,2H,CH_2), 7.297 (d,1H,H-6), 7.627 (d,1H,H-5), 8.724 (s,1H,H-4), 8.848 (s,1H, H-8), 10.689 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 219.045 (M^+); Calculated for $C_{12}H_{10}ClNO$:C, 65.61; H, 4.59; Cl, 16.14; N, 6.38; Found: C, 65.87; H, 4.69; Cl, 16.52; N, 6.32

2-Chloro-8-nitroquinoline-3-carbaldehyde (3j)

Light yellow solid; Yield 62%, MP: 267.5-268.6°C; IR (υmax, cm^{-1}): 3088, 2728 (Aromatic, C-H), 1699 (C=O), 1603, 1501 (Ar. C=C), 1556 (Asym. N=O), 1357 (Sym. N=O), 1087 (Ar. C-Cl), 859 (C-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.578 (t,1H,H-6), 7.888 (d,1H,H-5), 8.567 (d,1H,H-7), 9.043 (s,1H,H-4), 10.544 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 235.999 (M^+); Calculated for $C_{10}H_5ClN_2O_3$: C, 50.76; H, 2.13; Cl, 14.98; N, 11.84 ; Found: C, 50.58; H, 2.45; Cl, 14.76; N, 11.92

2-Chloro-7-nitroquinoline-3-carbaldehyde (3k)

Off white solid; Yield 58%; MP: 273.4-274.5°C; IR (υmax, cm^{-1}): 3094, 2736 (Aromatic, C-H), 1701 (C=O), 1601, 1500 (Ar. C=C), 1559 (Asym. N=O), 1352 (Sym. N=O), 1090 (Ar. C-Cl), 865 (C-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.867 (d,1H, H-5), 8.255 (d,1H, H-6), 8.898 (s,1H, H-4), 9.043 (s,1H, H-8), 10.582 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 235.999 (M^+); Calculated for $C_{10}H_5ClN_2O_3$: C, 50.76; H, 2.13; Cl, 14.98; N, 11.84 ; Found: C, 50.69; H, 2.32; Cl, 14.81; N, 11.98

2-Chloro-6-nitroquinoline-3-carbaldehyde (3l)

Light yellow solid; Yield 72%, MP: 278.4-279.6°C; IR (υmax, cm^{-1}): 3098, 2749 (Aromatic, C-H), 1702 (C=O), 1600,1502 (Ar. C=C), 1563 (Asym. N=O), 1345 (Sym. N=O), 1096 (Ar. C-Cl), 872 (C-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 8.334 (d,1H, H-8), 8.435 (d,1H,H-7), 8.667 (s,1H,H-5), 8.978 (s,1H, H-4), 10.454 (s,1H,CHO, D_2O exchangeable); EIMS m/z: 235.999 (M^+); Calculated for $C_{10}H_5ClN_2O_3$: C, 50.76; H, 2.13; Cl, 14.98; N, 11.84 ; Found: C, 50.65; H, 2.37; Cl, 14.87; N, 11.89

8-Chloroisoxazolo[5,4-b]quinoline (4a)

Potassium carbonate (3 mmol) was added in a refluxing solution of 2,7- dichloroquinoline-3-carbaldehyde (3a) (3 mmol) in ethanol (250 mL) and the solution was refluxed for 2–3 hours along with hydroxylamine hydrochloride (1-mmol). A concentrated reaction mixture was added to ice-cold water and the precipitate that resulted was washed with water, filtered, dried and recrystallized to yield 4a. Completion of the reaction was monitored *via* the use of TLC with mobile phase ethyl acetate: Benzene (9.5: 0.5).

The similar procedure was adopted to synthesize isoxazole derivatives (4b-4l) by using corresponding chloroaldehyde derivatives of quinoline (3b-3l).

Opal white solid; Yield 45.3%, MP: 251.9-252.9°C; IR (υmax, cm^{-1}): 3120 (Aromatic, C-H), 1596, 1499 (Ar. C=C), 1227(C-O-N) , 1091 (Ar. C-Cl) cm^{-1}; 1H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.169 (t,1H,H-6), 7.356 (d,1H,H-5), 7.676 (d,1H,H-7), 7.911 (s,1H,H-4), 8.123 (s,1H,isoxazole); EIMS m/z: 204.009 (M^+); Calculated for $C_{10}H_5ClN_2O$: C, 58.70; H, 2.46; Cl, 17.33; N, 13.69 ; Found: C, 58.62; H, 2.32; Cl, 17.57; N, 13.45

7-Chloroisoxazolo[5,4-b]quinoline (4b)

White solid; Yield 56.7%, MP: 255.6-256.8°C; IR (υmax, cm^{-1}): 3117 (Aromatic, C-H), 1599, 1497 (Ar. C=C), 1229 (C-O-N) , 1094 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.398 (d,1H,H-6), 7.510 (d,1H,H-5), 7.712 (s,1H,H-8), 7.918 (s,1H,H-4), 8.112 (s,1H, isoxazole); EIMS m/z: 204.009 (M^+); Calculated for $C_{10}H_5ClN_2O$: C, 58.70; H, 2.46; Cl, 17.33; N, 13.69 ; Found: C, 58.62; H, 2.32; Cl, 17.57; N, 13.45

6-Chloroisoxazolo[5,4-b]quinoline (4c)

White solid; Yield 68.4%, MP: 258.9-259.8°C; IR (υmax, cm^{-1}): 3123 (Aromatic, C-H), 1604, 1495 (Ar. C=C), 1228 (C-O-N), 1095 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.298 (s,1H,H-5), 7.484 (d,1H,H-7), 7.692 (d,1H,H-8), 7.898 (s,1H,H-4), 8.124 (s,1H,isoxazole); EIMS m/z: 204.009 (M^+); Calculated for $C_{10}H_5ClN_2O$: C, 58.70; H, 2.46; Cl, 17.33; N, 13.69 ; Found: C, 58.53; H, 2.25; Cl, 17.61; N, 13.51

7,8-Dichloroisoxazolo[5,4-b]quinoline (4d)

Off white solid; Yield 70.8%, MP: 290.4-291.8°C; IR (υmax, cm^{-1}): 3114 (Aromatic, C-H), 1599, 1503 (Ar. C=C), 1234 (C-O-N) , 1096 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.389 (d,1H,H-6), 7.548 (d,1H,H-5), 7.778 (s,1H,H-4), 8.112 (s,1H,isoxazole); EIMS m/z: 237.970 (M^+); Calculated for $C_{10}H_4Cl_2N_2O$: C, 50.24; H, 1.69; Cl, 29.66; N, 11.72 ; Found: C, 50.43; H, 1.56; Cl, 29.89; N, 11.54

6,8-Dichloroisoxazolo[5,4-b]quinoline (4e)

White solid; Yield 58.5%, MP: 286.9-287.8°C; IR (υmax, cm^{-1}): 3119 (Aromatic, C-H), 1597, 1507 (Ar. C=C), 1232 (C-O-N) , 1094 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.216 (s,1H,H-5), 7.497 (s,1H,H-7), 8.076 (s,1H,H-4), 8.163 (s,1H,isoxazole); EIMS m/z: 237.970 (M^+); Calculated for $C_{10}H_4Cl_2N_2O$: C, 50.24; H, 1.69; Cl, 29.66; N, 11.72 ; Found: C, 50.48; H, 1.45; Cl, 29.91; N, 11.78

6,7-Dichloroisoxazolo[5,4-b]quinoline (4f)

Opal white solid; Yield 60.7%, MP: 298.4-299.7°C; IR (υmax, cm^{-1}): 3113 (Aromatic, C-H), 1606, 1503 (Ar. C=C), 1237 (C-O-N), 1095 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.548 (s,1H,H-5), 7.667(s,1H,H-8), 8.011 (s,1H,H-4), 8.181 (s,1H,isoxazole); EIMS m/z: 237.970 (M^+); Calculated for $C_{10}H_4Cl_2N_2O$: C, 50.24; H, 1.69; Cl, 29.66; N, 11.72 ; Found: C, 50.06; H, 1.48; Cl, 29.79; N, 11.61

5,7-Dichloroisoxazolo[5,4-b]quinoline (4g)

Off white solid; Yield 54.5%, MP: 282.8-283.9°C; IR (υmax, cm^{-1}): 3109 (Aromatic, C-H), 1604, 1506 (Ar. C=C), 1235 (C-O-N), 1093 (Ar. C-Cl) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.571 (s,1H,H-6), 7.787 (s,1H,H-8), 7.937 (s,1H,H-4); 8.121 (s,1H,isoxazole); EIMS m/z: 237.970 (M^+); Calculated for $C_{10}H_4Cl_2N_2O$: C, 50.24; H, 1.69; Cl, 29.66; N, 11.72 ; Found: C, 50.01; H, 1.78; Cl, 29.81; N, 11.64

8-Ethylisoxazolo[5,4-b]quinoline (4h)

White solid; Yield 57.8%, MP: 233.5-234.7°C; IR (υmax, cm^{-1}): 3126, 2894 (Aromatic, C-H), 1603, 1501 (Ar. C=C), 1241 (C-O-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 1.243 (t,3H,CH_3), 2.578 (q,2H,CH_2), 7.354 (d,1H,H-7), 7.571 (t,1H,H-6), 7.787 (d,1H,H-5), 7.909 (s,1H,H-4), 8.137 (s,1H,isoxazole); EIMS m/z: 198.079 (M^+); Calculated for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13 ; Found: C, 72.65; H, 5.32; N, 14.27

7-Ethylisoxazolo[5,4-b]quinoline (4i)

Opal white solid; Yield 57.9%, MP: 248.4-249.7°C; IR (υmax, cm^{-1}): 3058, 2978 (Aromatic, C-H), 1601, 1497 (Ar. C=C), 1245 (C-O-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 1.249 (t,3H, CH_3), 2.594 (q,2H,CH_2), 7.291 (d,1H,H-6), 7.628 (d,1H,H-5), 7.834 (s,1H,H-8), 7.998 (s,1H,H-4), 8.154 (s,1H,isoxazole); EIMS m/z: 198.079 (M^+); Calculated for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13 ; Found: C, 72.58; H, 5.21; N, 14.34

8-Nitroisoxazolo[5,4-b]quinoline (4j)

Off white solid; Yield 68.4%, MP: 290.7-291.9°C; IR (υmax, cm^{-1}): 3072 (Aromatic, C-H), 1600, 1504 (Ar. C=C), 1578 (Asym. N=O), 1360 (Sym. N=O), 1236 (C-O-N) , 867 (C-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.397 (t,1H,H-6), 7.475 (d,1H,H-5), 7.777 (d,1H,H-7), 7.949 (s,1H,H-4), 8.184 (s,1H,isoxazole); EIMS m/z: 215.033 (M^+); Calculated for $C_{10}H_5N_3O_3$: C, 55.82; H, 2.34; N, 19.53; Found: C, 55.98; H, 2.12; N, 19.27

7-Nitroisoxazolo[5,4-b] quinoline (4k)

White solid; Yield 76.3%, MP: 283.3-284.6°C**;** IR (υmax, cm^{-1}): 3084 (Aromatic, C-H), 1603, 1501 (Ar. C=C), 1562 (Asym. N=O), 1357 (Sym. N=O), 1239 (C-O-N), 868 (C-N) cm^{-1}**;** ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 7.267 (d,1H,H-5), 8.135 (s,1H,isoxazole), 8.388 (s,1H,H-4),8.564 (d,1H,H-6), 9.031 (s,1H,H-8)**;** EIMS m/z: 215.033 (M^+); Calculated for $C_{10}H_5N_3O_3$: C, 55.82; H, 2.34; N, 19.53; Found: C, 55.95; H, 2.48; N, 19.23

6-Nitroisoxazolo[5,4-b] quinoline (4l)

Off white solid; Yield 72.2%, MP: 280.9-281.6°C; IR (υmax, cm^{-1}): 3092 (Aromatic, C-H), 1604, 1578 (Ar. C=C), 1520 (Asym. N=O), 1356 (Sym. N=O), 1241 (C-O-N), 872 (C-N) cm^{-1}; ^{1}H-NMR [400MHz, $CDCl_3$] δ [ppm]: 8.102 (s,1H,isoxazole), 8.288 (d,1H,H-8), 8.313 (s,1H,H-4), 8.435 (d,1H,H-7), 8.796 (s,1H,H-5); EIMS m/z: 215.033 (M^+); Calculated for $C_{10}H_5N_3O_3$: C, 55.82; H, 2.34; N, 19.53; Found: C, 55.75; H, 2.43; N, 19.29

Biological Activities

Antibacterial Activity

The antibacterial activities of newly synthesized compounds were tested against the following bacterial strains using the disc diffusion method on nutritive agar medium: *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Escherichia coli* (ATTC-35210) and *Pseudomonas aeruginosa* (ATCC-27853) (Gram-negative).

In the disc diffusion approach, paper discs were impregnated with compounds dissolved in DMF at 25, 50, and 100 µg/mL concentrations. Discs that had been saturated with DMF were used as a solvent control for the antibacterial activity since the test compounds were

Table 1: Antibacterial activity of the synthesized compounds

Compound No.	Zone of Inhibition in mm					
	S. aureus (ATCC 6538)			*B. subtilis (ATCC 6633)*		
	25 µg/mL	*50 µg/mL*	*100 µg/mL*	*25 µg/mL*	*50 µg/mL*	*100 µg/mL*
4a	6.34 ± 0.30	9.08 ± 0.75	12.77 ± 0.54	9.20 ± 0.46	10.81 ± 0.75	12.60 ± 0.81
4b	5.98 ± 0.32	7.87 ± 0.91	9.20 ± 0.76	9.83 ± 0.76	18.73 ± 0.46	20.27 ± 0.91
4c	5.78 ± 0.40	10.67 ± 0.46	17.67 ± 0.87	8.43 ± 0.81	11.23 ± 0.56	13.07 ± 0.46
4d	6.56 ± 0.35	8.03 ± 0.56	13.13 ± 0.76	6.30 ± 0.45	14.83 ± 0.87	14.48 ± 0.98
4e	7.44 ± 0.61	13.60 ± 0.91	17.87 ± 0.78	7.07 ± 0.43	9.09 ± 0.21	13.32 ± 0.75
4f	9.20 ± 0.64	15.63 ± 0.45	19.07 ± 0.34	12.86 ± 0.91	20.83 ± 0.45	24.67 ± 0.98
4g	7.23 ± 0.31	13.43 ± 0.76	12.46 ± 0.56	11.80 ± 0.98	16.73 ± 0.67	16.07 ± 0.72
4h	3.32 ± 0.40	6.26 ± 0.67	8.56 ± 0.81	2.83 ± 0.87	6.76 ± 0.98	7.89 ± 0.46
4i	2.47 ± 0.56	4.76 ± 0.78	7.67 ± 0.67	2.89 ± 0.67	4.14 ± 0.88	8.34 ± 0.89
4j	6.76 ± 0.45	9.45 ± 0.35	21.67 ± 0.68	6.53 ± 0.56	11.76 ± 0.55	18.55 ± 0.48
4k	5.87 ± 0.57	8.89 ± 0.46	20.86 ± 0.59	7.56 ± 0.34	12.98 ± 0.57	16.78 ± 0.72
4l	6.28 ± 0.34	10.01 ± 0.79	19.98 ± 0.67	8.89 ± 0.38	13.78 ± 0.89	15.09 ± 0.84
Ciprofloxacin	-	10.05 ± 0.58	-	-	14.07 ± 0.24	-
Control	-	-	-	-	-	-

Data are given as mean S.D (n=3); S.D = Standard Deviation

Table 2: Antibacterial activity of the synthesized compounds

Compound No. 25 µg/mL	Zone of Inhibition in mm					
	E. coli (ATCC 35210)			*P. aeruginosa (ATCC 27853)*		
	50 µg/mL	*100 µg/mL*	*25 µg/mL*	*50 µg/mL*	*100 µg/mL*	
4a	10.20 ± 0.25	12.63 ± 0.45	15.62 ± 0.47	9.72 ± 0.84	17.30 ± 0.93	18.20 ± 0.72
4b	9.60 ± 0.54	11.92 ± 0.67	17.73 ± 0.58	12.00 ± 0.53	20.83 ± 0.84	19.40 ± 0.64
4c	16.03 ± 0.42	21.60 ± 0.89	24.26 ± 0.59	18.43 ± 0.67	23.62 ± 0.85	28.43 ± 0.85
4d	8.66 ± 0.75	11.65 ± 0.24	15.70 ± 0.13	9.60 ± 0.84	13.43 ± 0.92	17.18 ± 0.98
4e	9.14 ± 0.62	12.54 ± 0.34	13.60 ± 0.15	9.05 ± 0.63	17.68 ± 0.19	18.80 ± 0.97
4f	9.28 ± 0.14	15.30 ± 0.45	14.20 ± 0.27	9.30 ± 0.42	14.73 ± 0.38	18.46 ± 0.89
4g	17.83 ± 0.26	22.73 ± 0.16	25.62 ± 0.38	10.26 ± 0.81	12.23 ± 0.47	14.04 ± 0.78
4h	3.16 ± 0.35	4.60 ± 0.47	7.80 ± 0.37	1.43 ± 0.75	5.66 ± 0.72	7.26 ± 0.69
4i	2.46 ± 0.54	5.53 ± 0.56	9.71 ± 0.49	1.23 ± 0.64	3.43 ± 0.83	5.76 ± 0.94
4j	9.01 ± 0.45	11.98 ± 0.26	26.89 ± 0.18	8.90 ± 0.55	18.56 ± 0.44	21.68 ± 0.43
4k	8.08 ± 0.36	10.67 ± 0.37	26.66 ± 0.37	9.45 ± 0.42	16.98 ± 0.53	22.22 ± 0.55
4l	7.90 ± 0.37	11.78 ± 0.27	27.84 ± 0.61	6.54 ± 0.82	10.87 ± 0.82	25.02 ± 0.81
Ciprofloxacin	-	12.50 ± 0.65	-	-	20.18 ± 0.45	-
Control	-	-	-	-	-	-

Data are given as mean S.D (n=3); S.D = Standard Deviation

easily soluble. After the microorganism culture had been distributed over nutritional agar media in petri dishes, the disc immersed with the solution was then located on the surface of the medium inoculated well with bacterial strain. The plates were then incubated for 24 hours at 35°C for bacterial cultures. After incubation, the disc's zone of inhibition was observed.[32]

The zone of inhibition shows that the compounds prevent microbial growth. Each test was performed three times. Ciprofloxacin was selected as the standard for antibacterial activity at a concentration of 50 µg/mL. For the compounds 4a-4l the zone of inhibition was identified.

Antifungal Activity

On nutritional medium, the disc diffusion method was used to investigate the antifungal activity of newly synthesized compounds against the fungal strains, namely: *Candida albicans* (ATCC-10261) and *Aspergillus niger* (IMI-9643)

Table 3: Antifungal activity of synthesized compounds

Compound No. 25 µg/mL	Zone of Inhibition in mm					
	C. albicans (ATCC-10261)			*A. niger (IMI-9643)*		
	50 µg/mL	*100 µg/mL*	*25 µg/mL*	*50 µg/mL*	*100 µg/mL*	
4a	10.20 ± 0.28	12.63 ± 0.45	15.62 ± 0.47	9.72 ± 0.84	13.30 ± 0.93	18.20 ± 0.72
4b	9.60 ± 0.58	11.92 ± 0.67	17.73 ± 0.58	11.00 ± 0.53	15.23 ± 0.84	19.40 ± 0.64
4c	9.03 ± 0.45	14.60 ± 0.89	24.26 ± 0.59	18.43 ± 0.67	21.62 ± 0.85	25.43 ± 0.85
4d	8.66 ± 0.75	13.65 ± 0.24	15.70 ± 0.13	9.60 ± 0.84	13.43 ± 0.92	17.18 ± 0.98
4e	9.14 ± 0.62	12.64 ± 0.34	13.60 ± 0.15	9.05 ± 0.63	17.68 ± 0.19	18.80 ± 0.97
4f	8.90 ± 0.14	15.30 ± 0.45	14.20 ± 0.27	9.30 ± 0.42	14.73 ± 0.38	18.46 ± 0.89
4g	9.67 ± 0.26	11.73 ± 0.16	16.62 ± 0.38	11.26 ± 0.81	12.23 ± 0.47	14.04 ± 0.78
4h	2.16 ± 0.35	5.60 ± 0.47	7.80 ± 0.37	1.43 ± 0.75	2.66 ± 0.72	3.26 ± 0.69
4i	1.46 ± 0.59	1.53 ± 0.56	2.71 ± 0.49	3.23 ± 0.64	4.43 ± 0.83	7.76 ± 0.94
4j	8.01 ± 0.75	10.98 ± 0.26	12.89 ± 0.18	6.90 ± 0.65	13.56 ± 0.94	15.68 ± 0.93
4k	6.08 ± 0.36	9.67 ± 0.37	13.66 ± 0.37	7.45 ± 0.92	11.98 ± 0.93	13.22 ± 0.85
4l	7.90 ± 0.67	9.78 ± 0.27	12.44 ± 0.61	6.54 ± 0.82	12.87 ± 0.82	18.02 ± 0.81
Fluconazole	-	12.22 ± 0.34	-	-	15.28 ± 0.67	-
Control	-	-	-	-	-	-

Data are given as mean S.D (n=3); S.D = Standard Deviation

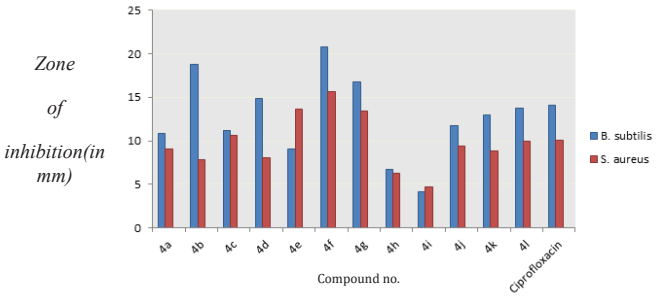


Fig. 1: Graph plotted between zone of Inhibition and synthesized compounds showing antibacterial activity

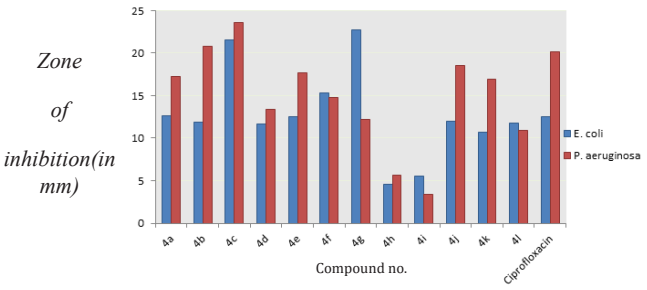


Fig. 2: Graph plotted between zone of Inhibition and synthesized compounds revealing antibacterial activity

The disc diffusion method employed paper discs impregnated with substances dissolved in DMF at concentrations of 25, 50, and 100 µg/mL. Discs that were impregnated with DMF were used as a solvent control for the antifungal activity since the test compounds were easily soluble. After the microorganism culture had been distributed over nutritional agar media in petri dishes, the

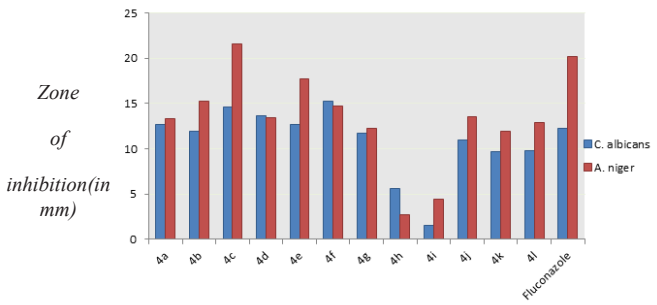


Fig. 3: Graph plotted between zone of Inhibition and synthesized compounds revealing antifungal activity

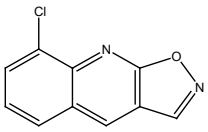
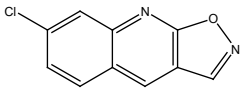
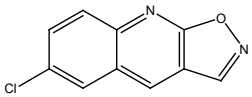
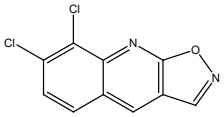
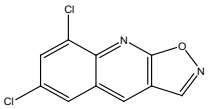
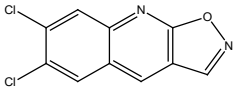
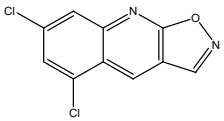
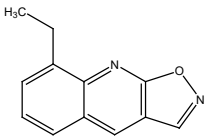
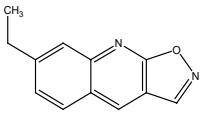
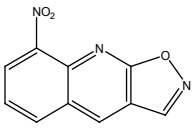
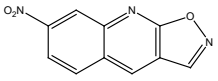
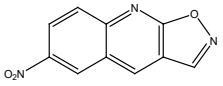
disc immersed with the solution was therefore spread on the top of the medium inoculated with the fungal strain. The plates were incubated for 48 hours at 25°C with fungal strains. The disc's surrounding zone of inhibition was observed after incubation.[28]

The zone of inhibition shows that the compounds prevent microbial growth. Each test was performed three times. Fluconazole was selected as the standard for antifungal activity at a concentration of 50 µg/mL. For the compounds 4a-4l, the zone of inhibition was identified.

Result And Discussion

In the introduction it has been observed that several quinoline derivatives and isoxazole derivatives were active as antibacterial and antifungal agents. The above observations prompted us to study on some quinoline fused isoxazole derivatives. Looking at the wide range of biological activities of quinolines, various quinoline derivatives were synthesized and hybridized with

Table 4: Structure of 4a-4l derivatives

Compound No.	Structure	% Yield	Melting Point (°C)
4a		45.3	251.9–252.9
4b		56.7	255.6–256.8
4c		68.4	258.9–259.8
4d		70.8	290.4–291.8
4e		58.5	286.9–287.8
4f		60.7	298.4–299.7
4g		54.5	282.8–283.9
4h		57.8	233.5–234.7
4i		57.9	248.4–249.7
4j		68.4	290.7–291.9
4k		76.3	283.3–284.6
4l		72.2	280.9–281.6

isoxazole moiety and screened for antibacterial and antifungal activities.

A total of 12 new compounds were synthesized and characterized by spectral interpretation.

Acetanilide derivatives (2a-2l) were synthesized by the reaction of substituted anilines (1a-1l) with acetyl chloride. Acetanilide derivatives (2a-2l) were treated with Vilsmeier Haack reagent prepared from dimethyl formamide and phosphorus oxychloride resulted in the formation of substituted 2-chloroquinoline-3-carbaldehyde (3a-3l) showing a proton singlet between δ 9.837 -10.689 ppm in the NMR spectrum for CHO (D_2O exchangable) and the FTIR for C=O absorption of aldehyde appeared between 1694–1705 cm^{-1} .α-β unsaturation reduces the frequency of carbonyl group and the C-Cl absorption band was observed between 1086–1098 cm^{-1} region. A solution of 3a-3l in ethanol was refluxed with hydroxylamine hydrochloride and potassium carbonate yielded Isoxazolo[5,4-b]quinoline analogues (4a-4l) that showed a proton singlet between δ 8.102–8.184 ppm in NMR spectrum and FTIR for aromatic and aliphatic C-H stretching vibrations were observed at 3045–3136 cm^{-1} and 2840–2983 cm^{-1} respectively and the band at 1225–1245 cm^{-1} was assigned to C-O-N for compounds 4a-4l. Bands between 1521–1578 cm^{-1} and 1338–1365 cm^{-1} was assigned to N-O (asymmetric) and N-O (symmetric) for compound 3j-3l and 4j-4l. Conjugation in nitro group lowers the frequency of both bands. The synthesized compounds were analyzed by TLC and melting point.

Antibacterial Activity

Using the disc diffusion method, the newly synthesised compounds were tested for *in-vitro* antibacterial activity. All synthetic compounds were tested for their antibacterial efficacy against the pathogenic bacterial strains *S. aureus, B. subtilis* (gramme positive), *E. coli*, and *P. aeruginosa* (gram negative). An antibiotic zone reader was used to measure the zone of inhibition.

The results revealed that compounds 4f and 4g showed potent antibacterial activity with 13.60 and 15.63 mm zone of inhibition respectively against *S. aureus* when given at concentration 50 µg/mL whereas under identical conditions standard drug ciprofloxacin showed 10.05 mm zone of inhibition. Compounds 4b and 4f showed potent antibacterial activity with 18.73 and 20.83 mm zone of inhibition, respectively against *B. subtilis* when given at concentration 50 µg/mL whereas under identical conditions ciprofloxacin showed 14.07 mm zone of inhibition as shown in Table 1 and Fig. 1.

Compounds 4c and 4g showed potent antibacterial activity with 21.60 and 22.73 mm zone of inhibition, respectively against *E. coli* when given at concentration 50 µg/mL whereas under identical conditions ciprofloxacin showed 12.50 mm zone of inhibition. Compound 4c showed potent antibacterial activity with 23.62 mm zone of inhibition, respectively against *P. aeruginosa* when given at concentration 50 µg/mL whereas under identical conditions ciprofloxacin showed 20.18 mm zone of inhibition as depicted in Table 2 and Fig. 2.

Antifungal Activities

The newly synthesized compounds were screened for *in-vitro* antifungal activity using disc diffusion method. The following fungal strains were used: *C.albicans* and *A. niger*. The results revealed that the newly synthesized compounds 4f showed potent antifungal activity with 15.30 mm zone of inhibition respectively against *C. albicans* when given at a concentration 50 µg/mL whereas under identical conditions, standard drug fluconazole showed 12.22 mm zone of inhibition. Compound 4c showed potent antifungal activity with 21.62 mm zone of inhibition respectively against *A. niger* when given at a concentration 50 µg/mL whereas fluconazole showed 15.28 mm zone of inhibition under identical conditions as revealed in Table 3 and Fig. 3.

The results reveal that the compounds 4b, 4c, 4f and 4g are most active against bacterial and fungal strains as they possess chloro groups at position C-5, C-6 and C-7.

The assessment of the results of the electron-withdrawing compounds was made in terms of (i) an electronic consideration, expressed by the Hammett substituent constant σ and inductive substituent constant σ_I (ii) a steric, expressed by the molar refractivity *MR*, the Taft's constant *Es* and the Charton steric parameter σ_v and (iii) a hydrophobic, expressed by cLog*P* and π, the Hansch substituent constant and led to the conclusion that the single most important physicochemical property that could explain the variance in the zone of inhibition of these compounds is the Hammett substituent constant σ.

Conclusion

Quinoline is present in many hybrid compounds with antibacterial and antifungal properties. Numerous reports of hybrid compounds with good biological activity contain quinoline. When compared to the individual agents, isoxazole-quinoline hybrid compounds showed good antibacterial and antifungal efficacy. However, some of the hybrid molecules were discovered to be less efficient than the individual drugs. Without a doubt, the research of quinoline heterocyclic compounds will continue to advance, forming stronger antibacterial and antifungal agents that will help combat the widespread drug resistance that now exists among antimicrobials.

The Lipinski rule of 5 is applied to quinoline hybrid compounds. The "rule of five" or Lipinski's rule, which was put forth for drug-likeness, states that a compound will have poor permeability if its hydrogen-bond donors total more than five, its molecular mass exceeds 500 with a calculated log P greater than five and its sum of nitrogen and oxygen atoms exceeds ten.

Supporting Information Summary

Details of characterization data for synthesized compounds, FTIR, ^{1}H NMR and Mass spectra have been provided in the supporting information file.

Acknowledgment

The authors express sincere gratitude to the Department of Chemistry, Rajiv Academy for Pharmacy, Mathura, Uttar Pradesh for providing the laboratory facilities.

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HOW TO CITE THIS ARTICLE: Snehi V, Pathak D. Synthesis, Characterization and Biological Evaluation of Novel Isoxazolo [5,4-b] Quinolines as Potent Antimicrobial Agents. Int. J. Pharm. Sci. Drug Res. 2022;14(6):725-733. **DOI:** 10.25004/IJPSDR.2022.140609