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Synthesis and antibacterial activity evaluation of some novel 7-chloro-4-aminoquinoline derivatives

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Abstract: Some new 7-chloro-4-aminoquinoline derivatives were prepared by modification at C-2 position of six-membered 1,3-thiazinan-4-one ring system attached at the terminal propyl side chain of 7-chloro-4-aminoquinoline nucleus. The synthesized compounds were characterized by their physical, analytical (CHN) and spectral data (UV-Visible, IR, ^{1}H NMR, ^{13}C NMR and MS). In addition to evaluation of antimalarial activity, the synthesized compounds were evaluated for antibacterial activity against six different strains of Gram positive (*Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*) and Gram negative bacteria (*Eschericia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) at two different tested doses viz. 25 µg/disc and 50 µg/disc by disc diffusion method. All the compounds were found to be active against the tested organisms, but were less active as compared to standard drug ofloxacin (5 µg/disc). The compounds with aromatic bulky substituents such as 2-fluorophenyl-, 3-hydroxyphenyl-, 4-methoxyphenyl-, furan-2-yl, 4-(dimethylamino)phenyl-, 5-methylthiophen-2-yl at C-2 position of 1,3-thiazinan ring system showed better antibacterial activity than that of the compounds with aliphatic alkyl (ethyl) substituent. It indicates that aromatic bulky substituents have greater contributing effect to the antibacterial activity of the 7-chloro-4-aminoquinoline derivatives as compared to aliphatic non-bulky group.

Key words: 7-chloro-4-aminoquinoline, Antibacterial activity, Bulky substituent.

Introduction

The incidence of microbial infections has been increasing worldwide over the past two decades because of widespread emergence of bacterial resistance to the currently available beta-lactam antibiotics, quinolones, macrolids etc [1]. A matter of concern in the treatment of microbial infection is the limited number of efficacious antimicrobial agents, which clearly highlights the urgent need of novel antimicrobial agents.

A large variety of synthetic compounds having therapeutic use in some other ailments possess antibacterial activity. The medicinal properties of imidazole drugs include antibacterial [2], antifungal [3], alongwith antimalarial [4]. On the basis of this premise, few 7-chloro-4-aminoquinoline analogues synthesized and tested for antimalarial activity were also subjected to antibacterial activity screening. The present study was aimed at evaluation of antibacterial activity of 7-chloro-4-aminoquinoline analogues with substituted heterocyclic ring at the side chain using 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one as lead compound in the development of a new series of antibacterial agents.

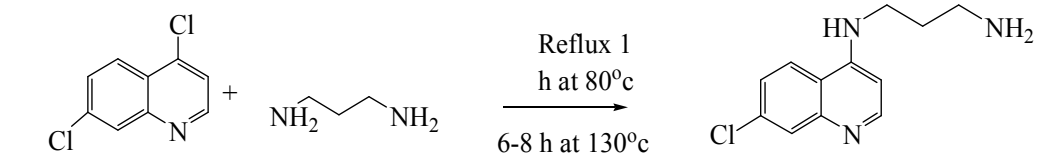
Materials and Methods

All chemicals and reagents were procured from Sigma-Aldrich Corporation (USA), Merck (Germany) or Spectrochem Pvt. Ltd. (India) and were used without further purification unless otherwise stated. 4,7-dichloroquinoline was obtained from M/s. Mangalam Drug & Organics, Mumbai, India. Melting points (mp) were taken in open capillaries on a Veego-MPI melting point apparatus and are uncorrected. The progress of reactions and purity of synthesized compounds were checked on silica gel-G TLC plate using various solvent combinations of different polarity. The spots were detected with iodine vapors on UV-light (254 nm). The UV-visible spectra (λ_{max}, nm) of synthesized compounds were obtained on *Shimadzu UV-1700* UV-visible spectrophotometer. Infrared (IR) spectra were recorded on a FT-IR *Perkin-Elmer Spectrum RX-I* spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a *Bruker AC-F 300* FT-NMR spectrometer using $CDCl_3$ as solvent. Chemical shifts (δ in ppm) are reported with tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained with a LC-MS *Water 4000 ZQ* instrument using atmospheric pressure ionization (API). Elemental microanalyses (CHN) were performed on a *Perkin Elmer 2400 Series II* CHNS/O analyzer and values were within the acceptable limits of the calculated values.

The intermediate reaction product N^1-(7-chloroquinolin-4-yl)-propane-1,3-diamine, I (Scheme 1) was prepared according to the method reported by Madrid *et al.* [5,6]. 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives, IIa-g (Scheme 2) were prepared as per the method designed by Solomon *et al.* [7,8].

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(2-fluorophenyl)-1,3-thiazinan-4-one (IIa)

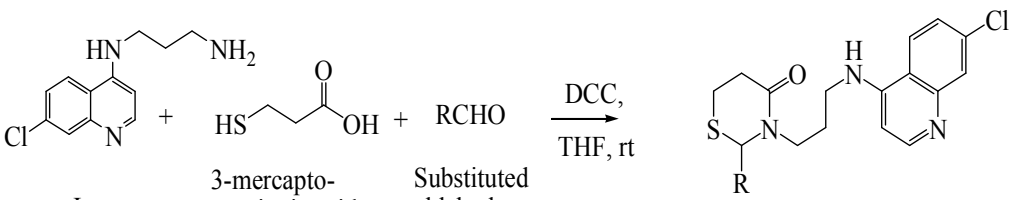
Light yellow gummy solid, 73% yield; R_f: 0.55 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm) : 262.0, 364.5, 428.0. IR spectrum (chloroform), υ, cm^{-1}: 3340 (N-H str., >NH); 1698 (C=O str.); 1371, 1275 (C-N str.); 1097 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.73–1.85 (t, 2H, J=17.4 Hz, CH_2), 2.57–2.61 (t, 2H, J=6.0 Hz, CH_2); 2.67–2.84 (m, 2H, CH_2); 3.16–3.37 (m, 2H, CH_2); 5.70 (s, 1H, NH), 6.22–6.23 (d, 1H, J=4.5 Hz, quinoline-H_3); 6.82–7.11 (m, 4H, C_6H_4–); 7.49–7.55 (dd 1H, J=8.7 Hz, 5.1 Hz, quinoline-H_6); 7.73–7.79 (dd 1H, J=7.5, 4.8 Hz, quinoline-H_5); 7.98–8.00 (d, 1H, J=6.9 Hz, quinoline-H_8); 8.23–8.24 (d, 1H, J=4.5 Hz, 2H quinoline). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 25.74 (CH_2), 29.59 (CH_2), 34.37 (CH_2), 39.85 (CH_2), 44.78 (CH_2), 55.73 (CH), 115.85 (C-2, quinoline), 116.58 (C-4a, quinoline), 123.07 (C-5, quinoline), 124.08, 124.64, 125.95, 126.63 (Ar-C), 127.63 (C-6, quinoline) 128.68 (Ar-C), 130.30 (C-8, quinoline), 132.67 (Ar-C), 136.37 (C-7, quinoline, C-Cl), 148.16 (C-8a, quinoline), 151.94 (C-2, quinoline), 158.28 (C-4, quinoline), 160.76 (C-F), 170.70 (C=O). MS (API), m/z (%): 430.2 (100), $[M+H]^+$; 431.1 (25.67), 432.1 (36.45), 433.2 (10.35). Anal. cacld. (%) for $C_{22}H_{21}N_3OSClF$: C, 61.46; H, 4.92; N, 9.77; found (%): C, 58.59 ; H, 5.65; N, 5.28.



4,7-dichloroquinoline 1,3-Diaminopropane

N^1-(7-chloroquinolin-4-yl)propane-1,3diamine (I)

Scheme 1



I 3-mercapto-propionic acid Substituted aldehyde

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-substituted-1,3-thiazinan-4-one (II_{A-D})

Scheme 2

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(3-hydroxyphenyl)-1,3-thiazinan- 4-one (IIb)

Light yellow gummy solid, 62% yield; R_f: 0.51 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 264.5, 388.0, 416.0. IR spectrum (chloroform), υ, cm-^{1}: 3530 (O-H str., bonded OH); 3430 (N-H str., >NH); 1310, 1283, (C-N str.), 1215 (C-O str.); 1083 (Ar. C-Cl.str.). ^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm): 1.73–1.81 (m, 2H, CH_2), 2.63–2.66 (t, 2H, J=48 Hz, CH_2), 2.67–2.77 (m, 2H, CH_2), 3.62-3.66 (t, 2H, J=72 Hz, CH_2), 5.35 (s, 1H, NH), 6.20-6.21 (d, 1H, J=4.5 Hz, quinoline-H_3); 6.57–6.59 (d, 1H, J=5.7 Hz, C_6H_4–), 6.75–6.77 (d, 1H, J=6.0 Hz, C_6H_4–), 7.20–7.22 (d, 1H, J=3.9 Hz, quinoline-H_6), 7.78 (s, 1H, OH), 7.88–7.90 (d, 1H, J=6.6 Hz, quinoline-H_5), 8.19–8.20 (d, IH, J=4.2 Hz, quinoline-H_8), 8.46 (bs, 1H, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm): 24.85 (CH_2), 29.66 (CH_2), 33.74 (CH_2), 39.96 (CH_2), 45.13 (CH_2), 62.25 (CH_2), 113.86 (C-3, quinoline); 115.47 (2C), 116.58 (C-4a, quinoline) 121.75 (Ar-C), 122.48 (C-5, quinoline), 126.29 (C-5, quinoline), 129.90 (C-8, quinoline), 130.10 (Ar-C), 136.94 (C-7, quinoline, C-Cl), 139.80 (Ar-C), 147.58 (C-8a, quinoline), 152.41 (C-2, quinoline), 153.76 (C-4, quinoline), 158,14 (Ar-C), 171.25 (C=O). MS (API), m/z (%): 428.2 (100), $[M+H]^+$; 429.2 (27.45%), 433.2 (40.50), 433.1 (10.75). Anal. cacld. (%) for $C_{22}H_{21}N_3O_2SCl$: C, 61.74; H, 5.18; N, 9.82; found (%): C, 62.67; H, 7.16; N, 4.43.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-ethyl-1,3-thiazinan- 4-one (IIc)

Light yellow gummy solid in 74% yield; R_f: 0.49 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 255.0, 350.0, 419.0. IR spectrum (chloroform), υ, cm^{-1}: 3422 (N-H str., >NH); 1719 (C= O str.); 1398, 1283 (C-N str.); 1074 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 0.96–0.98 (t, 3H, J=2.1 Hz, CH_3), 1.75–1.79 (m, 2H, CH_2), 1.91-1.96 (dd, 2H, J=5.1, 4.8 Hz, CH_2), 2.54–2.59 (m, 2H, CH_2), 2.60–2.77 (m, 2H, CH_2), 3.07–3.12 (dd, 2H, J=4.8, 4.8 Hz, CH_2), 3.65–3.68 (t, 2H, J=4.8 Hz, CH_2), 4.26–4.30 (t, 1H, J=5.4 Hz, CH), 6.35–6.37 (d, 1H, J=5.1 Hz, quinoline-H_3); 6.77 (bs, 1H, NH), 7.24–7.32 (dd, 1H, J=6.6, 17.7 Hz, quinoline-H_6); 7.88 (d, 1H, J=0.9 Hz, quinoline-H_5), 8.06 –8.09 (d, 1H, J=6.9 Hz, quinoline-H_8); 8.28–8.30 (d, 1H, J=4.8 Hz, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm): 11.45 (CH_3), 25.54 (CH_2), 27.78 (CH_2), 30.85 (CH_2), 36.07 (CH_2), 39.61 (CH_2), 40.56 (CH_2), 67.89(CH_2), 115.58 (C-3, quinoline), 120.87 (C-4a, quinoline), 123.90 (C-5, quinoline), 127.16 (C-6, quinoline), 138.62 (C-8, quinoline), 139.92 (C-7, quinoline, C-Cl), 143.97 (C-8a, quinoline), 154.52 (C-2, quinoline), 157.58 (C-4, quinoline), 170.41 (C=O). MS (API), m/z (%): 364.1 (100), $[M+H]^+$; 365.1 (22.95), 366.1 (41.25), 367.0 (8.72). Anal. cacld. (%) for $C_{18}H_{22}N_3OSCl$: C, 59.41; H, 6.09; N, 11.55; found (%): C, 52.13; H, 7371; N, 4.13.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(2-furyl)-1,3-thiazinan-4-one(IId)

Light yellow gummy solid, 65% yield; R_f: 0.54 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 257.0, 364.0, 426.0. IR spectrum (chloroform), υ, cm^{-1}: 3432 (N-H str., >NH); (C=O str.); 1375,1305, (C-N str.); 1091 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm): 1.75–1.87 (m, 2H, CH_2), 2.52–2.55 (t, 2H, J=4.8 Hz, CH_2), 2.70–2.73 (m, 2H, CH_2), 3.64–3.78 (m, 2H, CH_2), 5.49 (s, 1H, NH), 6.18 (bs, 1H, CH), 6.09-6.12 (m, 2H, furan-2-yl); 6.22–623 (d, 1H, J=1.2 Hz, quinoline-H_3); 7.25 (bs, 1H, furan–2–yl), 7.29–7.32 (d, 1H, J=8.4 Hz, quinoline-H_6), 7.60 -7.62 (d, 1H, J=7.2 Hz, quinoline-H_5), 7.97–8.04 (d, 1H, J=18.3 Hz, quinoline-H_8); (bs, 1H, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm): 25.47 (CH_2), 27.15 (CH_2), 35.47 (CH_2), 39.39 (CH_2), 40.19 (CH_2), 67.78 (CH_2), 106.99 (C_3, furan-2-yl), 110.60 (C_4, furan-2-yl), 112.67 (C-3, quinoline); 119.78 (C-4a, quinoline), 121.70 (C-5, quinoline), 127.17 (C-6, quinoline), 138.66 (C-7, quinoline, C-Cl), 142.33 (C_5, furan-2-yl), 148.31 (C-8a, quinoline), 151.69 (C-2, quinoline), 152.25 (C_2, furan-2-yl), 154.95 (C-4, quinoline), 170.67 (C=O). MS (API), m/z (%): 402.1 (100), $[M+H]^+$; 403.1 (24.30), 404.1 (41.40), 405.1 (9.00). Anal. cacld. (%) for $C_{20}H_{20}N_3O_2SCl$: C, 59.77; H, 5.02; N, 10.46; found: C, 51.63; H, 6.11; N, 3.06.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-methoxyphenyl)-1,3-thiazinan-4-one (IIe)

Light yellow gummy solid, 68% yield; R_f: 0.52 ($CHCl_3$: MeOH=3:1); UV-visible spectrum ($CHCl_3$), λ_{max} (nm)**:** 277.0, 368.0, 442.0. IR spectrum ($CHCl_3$), υ, cm^{-1}: 3435 (N-H str., >NH); 1734 (C=O str.); 1304, 1296 (C-N str.); 1161, 1046 (υ_{as} & υ_s C-O-C str.); 1080 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm): 1.73–1.88 (m, 2H, CH_2), 2.59–2.64 (m, 2H, CH_2), 2.66–2.78 (m, 2H, CH_2), 3.11–3.17 (m, 2H, CH_2), 3.28–3.41 (m, 2H, CH_2), 3.72 (s, 1H, OCH_3), 5.43 (s, 1H, NH), 6.24–6.26 (d, 1H, J=4.2 Hz, quinoline-H_3); 6.80–6.81 (m, 4H, C_6H_4-), 7.28–7.30 (d, 1H, J=1.2, 1.2 Hz, quinoline-H_6); 7.70–7.73 (d, 1H, J=10.2 Hz, quinoline-H_5); 7.89–7.91 (d, 1H, J=6.6 Hz, quinoline-H_8); 8.34–8.36 (d, 1H, J=4.2 Hz, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm) 25.59 (CH_2), 29.68 (CH_2), 33.92 (CH_2), 39.24 (CH_2), 44.35 (CH_2), 55.54 (OCH_3), 61.76 (CH_2), 113.95 (C-3, quinoline) 144.20 (2C), 117.49 (C-4a, quinoline), 122.20 (C-5, quinoline), 127.77 (C-5, quinoline), 124.34 (C-8, quinoline), 129.83 (2C), 131.99 (Ar-C), 135.13 (C-7, quinoline, C-Cl), 148.52 (C-8a,

quinoline), 151.20 (C-2, quionline), 157.17 (C-4, quinoline), 159.59 (Ar-C), 170.78 (C=O). MS (API), m/z (%): 442.2 (100), $[M+H]^+$. Anal. cacld. (%) for $C_{23}H_{24}N_3O_2SCl$: C, 62.50; H, 5.47; N, 9.51; found (%): C, 61.38; H, 6.94; N, 6.76.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-(dimethylamino)phenyl)-1,3-thiazinan- 4-one (IIf)

Reddish yellow gummy solid, 69% yield; R_f: 0.56 ($CHCl_3$: MeOH =3:1); UV-visible spectrum ($CHCl_3$), λ_{max} (nm): 279.0, 392.0, 447.0. IR spectrum ($CHCl_3$), υ, cm^{-1}: 3435 (N-H str. >NH); 1719 (C=O str.); 1336 (C-N str.), 1074 (Ar. C-Cl str.). ^1H NMR (300 MHz,$CDCl_3$), δ (ppm): 1.79–1.83 (t, 2H, J=5.4 Hz, CH_2), 2.50–2.57 (m, 2H, CH_2), 2.95 (s, 6H, NMe_2), 3.22-3.25 (t, 2H, J=4.5 Hz, CH_2), 3.30–3.47 (m, 2H, CH_2), 6.03 (bs, 1H, NH), 6.24–6.26 (d, 1H, J=6.3 Hz, quinoline-H_3), 6.67–6.69 (d, 1H, J=60 Hz, C_6H_4-), 6.86–6.88 (d, 1H, J=5.7 Hz, C_6H_4-), 7.26–7.28 (d, 1H, J=6.3 Hz, quinoline-H_6), 7.42–7.49 (dd, 1H, J=11.7, 3.3 Hz, quinoline-H_5), 7.79–7.87 (dd, 1H, J=5.7, 6.3 Hz, quinoline-H_8), 7.92–7.95 (t, 1H, J=5.1 Hz, quinoline-H_2). ^{13}C NMR (100 MHz,$CDCl_3$), δ (ppm): 20.88 (C_4H_2SMe), 26.88 (CH_2), 29.57 (CH_2), 36.52 (CH_2), 40.07 (CH_2), 44.65 (CH_2), 63.53 (CH_2), 102.79 (C-3, quinoline), 120.71 (C-4a, quinoline), 122.32 (C-5, quinoline, 125.99 (2C), 129.61 (C-6, quinoline), 132.20 (C-8, quinoline), 136.75 (C-7, quinoline), C-Cl), 139.47 (C_5, thiophen-2-yl), 141.77 (C_2, thiophen-2-yl), 148.37 (C-8a, quinoline), 151.87 (C-2, quinoline); 156.24 (C-4, quinoline), 174.37 (C=O). MS (API), m/z (%): 455.2 (100), $[M+H]^+$. Anal. cacld. (%) for $C_{24}H_{27}N_4OSCl$: C, 63.35; H, 5.98; N, 12.31; found (%): C, 58.92; H, 7.21; N, 5.36.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(5-methylthiophen-2-yl)-1,3-thiazinan- 4-one (IIg)

Reddish yellow gummy solid, 66% yield; R_f: 0.58 ($CHCl_3$: MeOH=3:1); UV-visible spectrum ($CHCl_3$), λ_{max} (nm): 282.0, 381.5, 422.0. IR spectrum ($CHCl_3$), υ, cm^{-1}: 3435 (N-H str. >NH); 1719 (C=O str.); 1390, (C-N str.); 1077 (Ar. C-Cl. str). ^1H NMR (300 MHz,$CDCl_3$), δ (ppm): 1.66–1.77 (t, 2H, J=9.3 Hz, CH_2), 2.25 (s, 3H, CH_3), 2.63–2.67 (t, 2H, J=4.8 Hz, CH_2), 2.79–2.82 (t, 2H, J=4.8 Hz, CH_2), 3.03–3.05 (d, 2H, J=5.4 Hz, CH_2), 3.44–3.3.47 (t, 2H, J=4.5 Hz, CH_2), 6.38 (bs, 1H, NH), 6.60–6.69 (dd, 1H, J=7.8 Hz, 12.6 Hz, quinoline-H_3), 6.75 (s, 2H, thiophen-2-yl), 7.37–7.49 (dd, 2H, J=18.6, 6.0 Hz, 6H quinoline), 7.60–7.89 (dd, 1H, J=29.1Hz, 36.0 Hz, quinoline-H_5), 8.04–8.15 (dd, 1H, J=6.9, 24.0 Hz, quinoline-H_8), 8.21–8.69 (dd, 1H, J=22.5, 82.8 Hz, quinoline-H_2). ^{13}C NMR (100 MHz,$CDCl_3$), δ (ppm): 25.38 (CH_2), 29.11(CH_2), 35.62 (CH_2), 39.80 (-NMe_2), 40.30 (CH_2), 66.72 (CH_2), 112.01 (C-3, quinoline), 116.20 (C-4a, quinoline), 115.51 (2C) 124.93 (C-5, quinoline), 127.43 (C-6, quinoline), 128.34 (C-8 quinoline), 131.75 (2C), 132.26 (C-7, quinoline C-Cl), 149.87 (C-8a, quinoline), 154.19 (C-2, quinoline), 157.63 (C-4, quinoline), 169.80 (C=O). MS (API), m/z (%): 432.1 (100), $[M+H]^+$. Anal. cacld. (%) for $C_{27}H_{27}N_4OSCl$: C, 58.29; H, 5.13; N, 9.73; found (%): C, 56.24; H, 6.50; N, 7.36.

Antibacterial activity testing:

All the synthesized compounds were screened for antibacterial activity by Kirby-Bauer disc diffusion method [9-11] against six different strains of Gram positive and Gram negative bacteria at two different tested doses viz. 25 μg/disc and 50 μg/disc. Three strains of Gram positive bacteria; *Bacillus subtilis* [(ATCC 11774), *Bacillus cereus* (ATCC 10876), *Staphylococcus aureus* (ATCC BAA 1026); and three strains of Gram negative bacteria [*Eschericia coli* (ATCC 10536)], *Klebsiella pneumoniae* (ATCC 33495), *Pseudomonas aeruginosa* (ATCC 10662)] were used for the study. All the bacterial strains were obtained from National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory (Council of Scientific & Industrial Research), Pune, India. The cultures of bacteria were maintained in their appropriate agar slants at 4°C throughout the study and used as stock cultures. Ofloxacin was used as reference standard drug. Studies were performed in triplicate; mean values with standard deviation were calculated

Results and Discussion

In this study, some new 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives were synthesized. The intermediate (I) and all the products (IIa-g) were obtained in good yield and purity. The analytical and spectral data confirms the structures of the purified compounds.

All the compounds in chloroform exhibited three characteristic absorption maxima (λ_{max}, nm) in the range between 220- 450nm. The shift of λ_{max} towards longer wavelength indicate the presence of strong chromophoric group such as quinoline structure, and C=O group in the molecule. The maxima in the lower wavelength range between 220-280 nm is due to the presence of substituted phenyl ring such as 2-fluorophenyl (IIa), 4-methoxyphenyl (IIe) etc. and hetero-aromatic ring system such as furan-2-yl (IId), 5-methylthiophen-2-yl (IIg) etc. The infrared spectral data as depicted in experimental section showed characteristic absorption bands for >NH (3340-3435 cm^{-1}); C=O (1693-1734 cm^{-1}); C-N (1275-1398 cm^{-1}); C-Cl (1074-1097 cm^{-1}); $>CH_2$ (υ_{as}: 2976-2930 cm^{-1} & υ_s: 2819-1863 cm^{-1}), and aromatic C=C (1432-1657 cm^{-1}) stretching which confirms the anticipated structure of the synthesized compounds, IIa-IIg. The

assignment of protons is fully supported by the characteristic chemical shift values for the 4-aminoquinoline nucleus as discussed in experimental section. The assignment of ^{13}C resonance for different carbon atoms of quinoline nucleus, $>CH_2$ group of side chain and C=O of 1,3-thiazinan-4-one ring system is in close agreement with the structures of the synthesized compounds. The prominent molecular ion peaks, $[M+H]^+$ for all the compounds are in accordance with the anticipated mass of IIa-IIg. The results of CHN analyses were within the acceptable limits of the calculated values. The elemental analyses data are shown in experimental section.

The results depicted in Table 1 clearly revealed that all the compounds at the tested dose showed antibacterial activity and were equally active with some degree of variations, but were less active as compared to standard drug ofloxacin (5 µg/disc). However, it is interesting to note that no obvious difference in susceptibility was found between Gram positive and Gram negative bacterial strains for all the test compounds. Among the synthesized compounds, compounds with aromatic bulky substituents such as 2-fluorophenyl- (IIa), 3-hydroxyphenyl- (IIb), furan-2-yl (IId), 4-methoxyphenyl- (IIe), 4-(dimethylamino)phenyl- (IIf), 5-methylthiophen-2-yl (IIg) are more active than that of compound with aliphatic alkyl substituent (ethyl in IIc) at C-2 position of 1,3-thiazinan ring system.

Table 1: Antibacterial activity data

Compd.	Strength (µg/disc)	Diameter of zone of inhibition (mm ± SD)*					
		Bacillus subtilis ATCC 11774	*Bacillus cereus* ATCC 10876	*Staphylococcus aureus* ATCC BAA 1026	*Eschericia coli* ATCC 10586	*Klebsiella pneumoniae* ATCC 33495	*Pseudomonas aeruginosa* ATCC 10662
IIa	50	23.66±0.57	24.26±0.28	23.93±0.11	24.36±0.30	2416±0.11	2480±0.20
	25	18.83±0.28	14.26±0.28	14.16±0.15	14.33±0.23	14.33±0.30	14.06±0.11
IIb	50	23.30±0.50	24.40±0.20	24.06±0.11	24.40±0.20	24.20±0.20	24.06±0.11
	25	14.16±0.28	1433±0.11	14.13±0.11	14.23±0.05	14.06±0.11	14.33±0.11
IIc	50	23.16±0.28	23.60±0.20	23.06±0.11	23.41±0.10	23.13±0.23	23.06±0.11
	25	13.06±0.11	13.53±0.11	12.93±0.11	13.66±0.11	13.23±0.05	13.46±0.11
IId	50	23.83±0.28	23.66±0.28	24.06±0.11	24.33±0.11	24.20±2.10	23.90±0.36
	25	13.83±0.28	14.06±0.11	14.26±0.23	13.93±0.11	14.00±0.20	13.86±0.11
IIe	50	23.30±0.50	24.40±0.20	24.06±0.11	24.40±0.20	24.20±0.20	24.06±0.11
	25	14.16±0.28	14.33±0.11	14.13±0.11	14.23±0.05	14.06±0.11	14.33±0.11
IIf	50	23.66±0.11	24.26±0.23	23.86±0.11	23.93±0.11	24.06±0.30	23.66±0.11
	25	14.26±0.30	14.00±0.20	13.86±0.11	14.26±0.30	14.06±0.30	13.73±0.11
IIg	50	23.93±0.11	24.23±0.20	23.93±0.23	24.13±0.23	23.93±0.11	23.73±0.11
	25	14.20±0.20	13.93±0.11	14.00±0.20	14.20±0.20	13.86±0.11	13.86±0.11
Ofloxacin#	5	20.66±0.25	20.33±0.57	21.66±0.57	21.50±0.50	20.33±0.57	20.83±0.28
DMSO@	-	Nil	Nil	Nil	Nil	Nil	Nil

*Values are mean inhibition zone (mm±SD) of three replicates

Ofloxacin disc 5 µg was used as a positive reference standard.

@ DMSO was used as vehicle control.

Conclusion

All the 7-chloro-4-aminoquinoline derivatives with substituted heterocyclic ring at the side chain possess antibacterial activity. It has also been observed that aromatic bulky substituents have greater contributing effect to the antibacterial activity of the new series of prepared derivatives as compared to aliphatic non-bulky group.

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