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Synthesis, characterization, antibacterial and antioxidant studies of oxetoquinolines

Abstract

A series of 2*H*-oxeto[2,3-b]quinolines have been synthesized involving the simple steps of oxidation, reduction and cyclization of 2-chloro-3-formyl quinolines. All the synthesized compounds were evaluated for their antibacterial screening and anti oxidant studies. Most of the compounds showed moderate to good activity against almost all the tested pathogens. In particular, compound 1e showed good antibacterial and antioxidant activity.

Keywords: 2-chloro-3-formyl quinolines, cyclization, Oxetoquinolines, antibacterial, antioxidant studies

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Muthukumar K,[1] Velmurugan K,[1] Derin TD,[1] Rajesh P,[2] Rajesh Kannan V,[2] Nandhakumar R[1]
[1]Department of Chemistry, Karunya Institute of Technology and Sciences, India
[2]Department of microbiology, Bharathidasan University, India

Correspondence: Nandhakumar R, Department of Chemistry, Karunya Institute of Technology and Sciences (Deemed to be University), Coimbatore-641 114, Tamil Nadu, India, Tel 80984 70837, Email nandakumar@karunya.edu

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Introduction

Mounting infectious diseases and the developing number of multi-drug resistant microbial pathogens still make the treatment of particular diseases an important and serious global problem. Therefore, an extensive research for the discovery and synthesis of new classes of antimicrobial agents is needed. The quinoline derivatives have been known to possess wide spectrum of pharmacological properties. They are the backbone in numerous commercial products such as perfumes, dyes including pharmaceuticals. Quinoline derivatives viz., ofloxacin, norfloxacin, ciprofloxacin, chloroquine, etc., have been used as efficient drugs till date. The derivatives of quinoline exhibit diverse biological and physiological activities such as antimicrobial, antituberculosis, antimalarial, antiinflammatory, anticancer, antihypertensive and anti-HIV.[1–5] Recently, quinoline has been employed in the study of bioorganic and bioorganometallic processes.[6]

The chemistry of quinolines is well established in the field of pharmacological activity. This system has proved to be a very attractive scaffold for medicinal chemist in recent years. However, quinoline derivatives were extensively studied as bioactive compounds, such as pyrazoloquinolines, diazepinoquinolines, thiadiazepinoquinolines[7–9] and known to possess remarkable biological activities. For many of the activities the molecular mode of action is known. Recent research efforts have also highlighted the ability of agents based on pyrazoloquinoline skeleton to modulate adenosine A3 receptors and the phosphodiesterase receptors.[10] Literature shows the annulations of pyridines to Quinoline[11] to create functionalized quinoline derivatives. Based on above facts and in search of newer drugs, among heterocyclic origin, we followed the—annulation of the oxeto ring onto a quinoline scaffold‖ approach. To the best of our knowledge, it is new and literature reports show about oxetoquinolines are not yet in the field of quinoline derivatives. Herein, we report the synthesis and chemistry of oxetoquinoline derivatives via the Vilsmeier-Haack reactions and its antibacterial and antioxidant studies.

Results and discussion

Over the years, 2-chloroquinoline-3-carbaldehydes,[12] prepared by a Vilsmeier Haack Reaction on acetanilides and their derivatives have attracted much attention due to their wide spectrum of biological and pharmacological activities such as antimicrobial,[13–19] anti-inflammatory[20,21] antimalarial[22] and antiviral activities.[23] They occupy a prominent position in the intermediate category as they can be utilized for further *[b]*annelation of many heterocyclic ring systems and for various functional group interconversions. On continuation of our research[24] on heterocyclic compounds and in search of newer derivatives of quinolines as potential biological molecules, we have realized the title compounds in a two step synthetic protocol.

The reaction of 2-chloroquinoline-3-carbaldehyde 2 with 4N hydrochloric acid afforded the oxo derivative of the quinoline aldehyde 3.[25,26] Subsequently, the sodiumborohydride reduction of the oxo derivative in a co-solvent of Tetrahydrofuran and ethanol yielded the alcohol derivative 4. The compound 4 under reflux conditions with glacial acetic acid for 4hours obtained the title compound oxetoquinoline 1. The reaction was diluted with water and extracted with ethyl acetate, dried over sodium sulphate, concentrated and column purified (Figure 1).

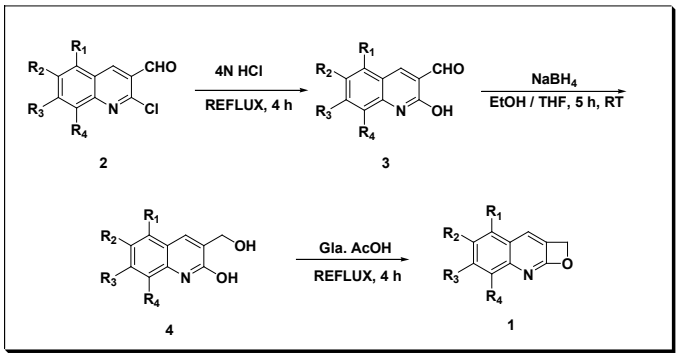

Figure 1 R_1=R_2=R_3=R_4=H, 4h, 80% yield; b: R_2=CH_3; R_1=R_3=R_4=H, 3.5h, 83% yield; c: R_2=OCH_3; R_1=R_3=R_4=H, 3h, 77% yield; d: R_2=R_4=CH_3; R_1=R_3=H, 3h, 78% yield; e: R_2=Cl; R_1=R_3=R_4=H, 4h, 72% yield

Its IR spectrum showed strong absorption peaks at 1643 & 1258cm^{-1} for C=N and C-O stretching frequencies respectively. The

^{1}H-NMR spectrum revealed a fine splitting pattern of the aromatic protons as δ 7.80 (s, ^{1}H, C_4-H), δ 7.58-7.60 (d, ^{1}H, C_8-H), δ 7.20-7.22 (d, 1H, C_5-H), δ 7.37-7.41 (t, 1H, C_7-H), δ 7.08-7.12 (t, 1H, C_6-H). In addition, it showed a sharp singlet at δ 4.86 which accounts for two proton methylene group (-CH_2-). It is worthy to note that there is a sharp downfield shift from δ 4.28 to δ 4.86 due to the cyclization reaction towards the formation of oxeto ring system. At the same time the peaks for the aromatic hydroxy and the primary hydroxyl groups are missing. The above details are further advocated by the mass spectra, which showed the prominent mass peak at (m/z) 158 [M^++1]. All the above spectral details supported the compound (1a) as 2H-oxeto[2,3-b]quinoline. The reaction was also extended to its methyl, methoxy, dimethyl and chloro derivatives.

Biological evaluation

Antibacterial activity

The newly synthesized 2*H*-oxeto[2,3-b]quinolines were screened for their in vitro antibacteiral activities against the seven different types of pathogens namely, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Escherichia coli*, *Klesiella pneumonia*, *Salmonella paratyphi*, *Salmonella typhi* and *Mycobacterium butyricum* by the agar well diffusion method using Ofloxacin as control drug. The pathogens were cultured on the nutrient agar medium and DMSO was used as solvent and as negative control. The diameter of zone of inhibition measured in mm is compared to the current antimicrobial drug Ofloxacin as shown in Table 1. The susceptibility was assessed on the basis of the diameter of zone of inhibition against the bacterial strains. The antibacterial activity results revealed that the majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. It was found that compounds 1c and 1e exhibited good inhibition towards almost all the pathogens and comparable to that of the standard Ofloxacin. Compounds 1a and 1b showed least activity whereas compound 1d showed moderate activity with the inhibition zone ranging between 2–6mg/disc with all the tested pathogens. This notable difference among the synthesized compounds towards the antibacterial activity may be due to substituent present at C_6-position, which plays a key role in the efficacy of the compound.

Antioxidant activity using FRAP assay

FRAP assay usually determines the reduction of ferric ion Fe^{3+} to ferrous ion Fe^{2+} in the presence of antioxidants. The reducing capacity of a compound may serve as a significant indicator of its potential antioxidant activity. It can be concluded from the Table 2 that the compound 1e shows the higher ferric reducing power than its other analogs 1(a-d). The reducing power of the compound 1e was comparable to that of the standard BHT. The other remaining compounds 1a-d, showed good to moderate antioxidant activity. From the values it is assumed that in this assay the substitutions at the C_6 position in the quinoline moiety as well as the hetero atoms might play substantial role in suppressing the radicals.

Table 1 In vitro antibacterial activity of 2H-oxeto[2,3-b]quinolines(1a–e) (mg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition (mm)															
	1a (mg/disc)			1b (mg/disc)			1c (mg/disc)			1d (mg/disc)			1e (mg/disc)			A
	10	50	100	10	50	100	10	50	100	10	50	100	10	50	100	10
Staphylococcus aureus	-	-	1	-	1	2	-	2	5	-	2	4	2	5	7	9
Aeromonas hydrophila	1	3	5	1	2	4	1	4	9	1	3	6	2	5	11	14
Escherichia coli	-	-	-	-	-	2	-	2	6	-	-	3	1	4	9	8
Klesiella pneumoniae	-	-	1	-	-	2	-	1	4	-	-	3	-	1	5	7
Salmonella paratyphi	-	-	2	-	-	3	-	1	3	-	-	2	-	1	4	6
Salmonella typhi	-	1	3	1	2	4	2	5	8	1	3	5	3	7	13	15
Mycobacterium butyricum	-	-	3	-	1	3	1	2	4	-	-	2	-	1	3	5

A, Ofloxacin, _—‘ no inhibition.

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Table 2 Anti-oxidant Activity of 2H-oxeto[2,3-b]quinolines(1a–e) - The ferric reducing/antioxidant power (FRAP)

Compound	The ferric reducing/antioxidant power (mg/mL)	
	1mg/mL	10mg/mL
1a	0.015	0.156
1b	0.018	0.183
1c	0.02	0.23
1d	0.01	0.196
1e	0.197	1.579
BHT	0.243	2.487

Experimental section

General

Thin layer chromatography was used to access the reactions and the purity of products. Melting points were determined on a Boetius Micro heating Table (Japan) and are uncorrected. IR spectra were recorded with a Shimadzu–8201FT instrument (Japan) in KBr discs and only noteworthy absorption levels (reciprocal centimeter) are listed. ^{1}H NMR spectra were recorded with a Bruker - AMX-400MHz spectrometer (US) in $CDCl_3$ solution; chemical shifts are expressed in ppm (δ) relative to TMS, coupling constants (J) in Hz. Signal multiplicities are represented by bs (broad singlet), s (singlet), d (doublet), t (triplet) and m (multiplet). ^{13}CNMR spectra were recorded on Bruker - AMX-100MHz spectrometer (US) in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded using a Jeol –D- 300 mass spectrometer (70eV) (Japan). C, H, N analyses were carried out on Perkin-Elmer Model 240 analyzers (UK).

Synthesis of 3-(hydroxymethyl)quinolin-2-ol (4a):

2-hydroxyquinoline-3-carbaldehyde, (3a) 2.1g, (0.013mol) was taken into the round bottom flask and completely dissolved in a co solvent of ethanol/tetrahydrofuran (80:20) and sodium borohydride 0.49g, (0.013mol) was added. The reaction mixture was stirred for 4hours. The product formation was monitored by the TLC. After the reaction completion the reaction mixture was poured into the ice cold water. The solid product formed was filtered and recrystallized from methanol.

IR (KBr): 1658 (C=O), 1599 (C=N) and 3291 (-OH) cm^{-1}; ^{1}H-NMR (400MHz , $CDCl_3$); δ 11.75 (bs, 1H, -Ar-OH), 7.73 (s, 1H, C_4-H), 7.56-7.58 (d, 1H, C_8-H), 7.19-7.21 (d, ^{1}H, C_5-H), 7.33-7.37 (t, 1H, C_7-H), 7.05-7.08 (t, 1H, C_6-H), 5.10-5.14 (t, 1H, -CH_2-OH), 4.28-4.30 (d, 2H,-CH_2-OH) ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 54.5, 121.8, 123.7, 124.4, 126.8, 127.7, 136.5, 144.9, 163.6 ppm. Anal. calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00; found: C, 68.50; H, 5.22; N, 8.02.

Synthesis of 3-(hydroxymethyl)-6-methylquinolin-2-ol (4b)

It was prepared similar to 4a. m.p. 265°C; IR (KBr): 1656 (C=O), 1595 (C=N), 3286 (-OH) cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 11.73 (bs, 1H, Ar-OH), 7.70 (s, 1H, C4-H), 7.54-7.56 (d, 1H, C8-H), 7.17-7.20 (d, 1H, C5-H), 7.32-7.34 (d, 1H, C_7-H), 5.08-5.12 (t, 1H, -CH_2-OH), 4.25-4.27 (d, 2H, -CH_2- OH), 2.3 (s, 3H, CH_3) ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 24.3, 57.4, 121.3, 123.70, 123.6, 125.7, 126.9, 133.7, 143.3,164.5ppm. Anal. calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40; found: C, 69.76; H, 5.89; N, 6.44.

Synthesis of 3-(hydroxymethyl)-6-methoxyquinolin-2-ol (4c)

It was prepared similar to 4a. m.p. 290°C; IR (KBr): 1650 (C=O), 1590 (C=N) and 3284 (-OH) cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 11.79 (bs, 1H, Ar- OH), 7.77 (s, 1H, C_4-H), 7.59-7.61 (d, 1H, C_8-H), 7.22- 7.24 (d, 1H, C_5-H), 7.35-7.40 (t, 1H, C7-H), 5.15-5.19 (t, 1H, -CH_2-OH), 4.31-4.34 (d, 2H, -CH_2-OH), 3.91 (s, 3H, -OCH_3) ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 53.9, 58.5, 121.8, 122.3, 124.7, 134.7, 141.5, 154.8, 164.4ppm. Anal. calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; found: C,64.31; H, 5.45; N, 6.85.

Synthesis of 3-(hydroxymethyl)-6,8-dimethylquinolin-2-ol (4d)

It was prepared similar to 4a. m.p 291°C; IR (KBr): 1649 (C=O), 1588 (C=N) and 3280 (-OH) cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 11.72 (bs, 1H, -Ar-OH), 7.68 (s, 1H, C4-H), 7.15-7.17 (d, 1H, C5-H), 7.28- 7.33 (t, 1H, C7-H), 5.04-5.08 (t, 1H, -CH_2-OH), 4.22-4.24 (d, 2H, -CH_2-OH), 2.46 (s, 3H, - CH_3), 2.42 (s, 3H, -CH_3)ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 21.4, 25.2, 58.6, 120.9, 123.4, 124.7, 131.4, 134.4, 136.8, 150.7, 164.7ppm. Anal. calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; found: C, 70.86; H, 6.48; N, 6.92.

Synthesis of 6-chloro-3-(hydroxymethyl)quinolin-2-ol (4e)

It was prepared similar to 4a. m.p. 226°C; IR (KBr):1660 (C=O), 1600 (C=N), 3291 (-OH)cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 11.81 (bs, 1H, -Ar-OH), 7.79 (s, 1H, C_4-H), 7.60-7.62 (d, 1H, C_8-H), 7.24-7.26 (d, 1H, C_5-H), 7.32-7.36 (t, 1H, C7-H), 5.16-5.20 (t, 1H, -CH_2-OH), 4.32-4.34 (d, 2H, -CH_2-OH)ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 58.3, 122.4, 124.6, 128.7, 130.8, 131.8, 135.1, 142.2, 166.3 ppm. Anal. calcd. for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68; found: C,57.27; H, 3.87; N, 6.69.

Synthesis of 2H-oxeto[2,3-b]quinoline (1a)

0.070g, (0.0003mol) was refluxed in glacial acetic acid (10ml) for four hours. The completion of the reaction was checked by TLC. The reaction was diluted with water and extracted with ethyl acetate, dried over sodium sulphate and concentrated. Column chromatography of the crude mixture as ethyl acetate and hexane as eluents yielded the desired title compound in good yields. Further the product is recrystallized from methanol (Figure 2–4).

Figure 2 ^{1}H-NMR spectrum of compound (1a)

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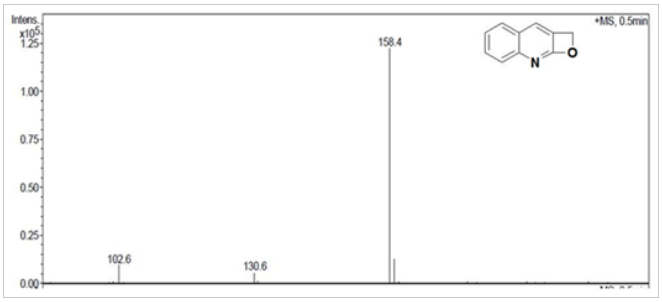

Figure 3 Mass spectrums (LC-MS) of compound (1a)

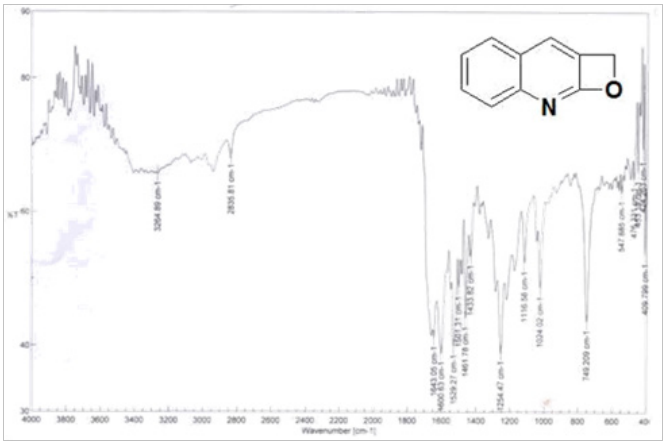

Figure 4 IR-spectrum of compound (1a)

IR (KBr): 1643 (C=N), 1258 (C-O)cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 7.8 (s, 1H), 7.57-7.59 (d, 1H), 7.36-7.40 (t, 1H), 7.19-7.21 (d, 1H), 7.06-7.09 (t, 1H), 4.86 (s, 2H)ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 34.03 (CH_2), 118.2, 120.1, 126.3, 132.5, 134.3, 138.2, 142.8, 144.3, 162.3ppm; LC-MS (m/z)=158 [M^++1]. Anal. calcd. for $C_{10}H_7NO$: C, 76.42; H, 4.49; N, 8.91; found: C,76.36; H, 4.52; N, 8.94.

Synthesis of 5-methyl-2H-oxeto[2,3-b]quinoline (1b)

It was prepared similar to 1a. m.p. 160°C; IR (KBr): 1638 (C=N), 1235 (C-O)cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 7.6 (s, 1H), 7.55 (s, 1H), 7.17-7.20 (d, 1H), 7.04-7.08 (d, 1H), 4.83 (s, 2H), 2.41(s, 3H)ppm; ^{13}C-NMR (100MHz, $CDCl_3$) δ : 22.4, 34.01 (CH_2), 118.0, 119.9, 126.1, 132.3, 134.1, 138.0, 142.7, 144.2, 162.1 ppm; LC-MS (m/z)=172 [M^++1]. Anal. calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18; found: C,77.13; H, 5.32; N, 8.20.

Synthesis of 5-methoxy-2H-oxeto[2,3-b]quinoline (1c)

It was prepared similar to 1a. m.p. 182°C; IR (KBr): 1641 (C=N), 1253 (C-O) cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 8.1 (s, 1H), 7.59 (s, 1H), 7.39-7.41 (d, 1H), 7.22-7.24 (d, 1H), 4.89 (s, 2H), 3.92 (s, 3H) ppm; ^{13}CNMR (100MHz, $CDCl_3$); δ 54.8, 34.05 (CH_2), 118.3, 120.2, 126.6, 132.6, 134.5, 138.4, 143.0, 144.5, 162.6 ppm; LC-MS (m/z)= 188 [M^++1]. Anal. calcd. for $C_{11}H_9NO_2$: C, 70.51; H, 4.80; N, 7.48; found: C, 70.45; H, 4.82; N, 7.52.

Synthesis of 5,7-dimethyl-2H-oxeto[2,3-b]quinoline (1d)

It was prepared similar to 1a. m.p 184°C; IR (KBr): 1640 (C=N), 1250 (C-O)cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$); δ 7.4 (s, 1H), 7.53 (s, 1H), 7.14 (s, 1H), 4.80 (s, 2H), 2.5 (s, 3H), 2.2 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$); δ 22.7, 22.3, 33.9 (CH_2), 117.9, 119.6, 125.9, 132.0, 133.9, 137.9, 142.5, 144.0, 161.9; LC-MS (m/z)=186 [M^++1]. Anal. calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56; found: C, 77.75; H, 6.03; N, 7.59.

Synthesis of 5-chloro-2H-oxeto[2,3-b]quinoline (1e)

It was prepared similar to 1a. m.p. 183°C; IR (KBr): 1640 (C=N), 1252 (C-O); 691 (C-Cl)cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.5 (s, 1H), 7.61 (s, 1H), 7.25-7.27 (d, 1H), 7.13-7.16 (d, 1H), 4.92 (s, 2H)ppm; ^{13}C-NMR (100MHz, $CDCl_3$); δ 34.08 (CH_2), 118.6, 120.5, 126.9, 132.9, 134.7, 138.7, 143.3, 144.8, 162.8ppm; LC-MS (m/z)=192 [M^+], 194 [M^++2]. Anal. calcd. for $C_{10}H_6ClNO$: C, 62.68; H, 3.16; N, 7.31; found: C, 62.66; H, 3.17; N, 7.32.

Antibacterial activity by Agar well diffusion method

The antibacterial activity of the synthesized compounds 4 (a-e) was performed on agar well diffusion method. Each chemical compound was mixed with the equal amount of dimethyl sulfoxide (DMSO) *i.e.,* 1 µl of DMSO contains 1mg of chemical compound and considered as the stock solution. The synthesized active chemical compounds were then subjected to the antimicrobial activity against the human pathogenic bacteria isolated from Hospital clinical samples which was collected by the Rhizosphere Biology Laboratory, Bharathidasan University, Tiruchirappalli, Tamil Nadu, India. The procured pathogenic bacteria namely *Staphylococcus aureus*, *Aeromonoas hydrophila*, *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella paratyphi*, *Salmonella typhi* and *Mycobacterium butyricum* (MTCC 940) were cultured in nutrient agar medium and incubated as well as maintained at 37ºC for at 24h. The medium was further used for the antimicrobial activity studies with the synthesized chemical compounds by the agar well diffusion method. Each compound 4 (a-e) were poured and checked for their antibacterial activity against the seven collected strains with different concentrations like 10g/10µl, 50mg/50µl and 100mg/100µl. The zone of inhibition was found after the incubation period of 24h at 37ºC and the measurements were reported as diameters in millimeters. The higher zone of inhibition was considered as significant activity of the synthesized chemical compound against the virulent human pathogenic bacteria (Figure 5) (Figure 6).[27–29]

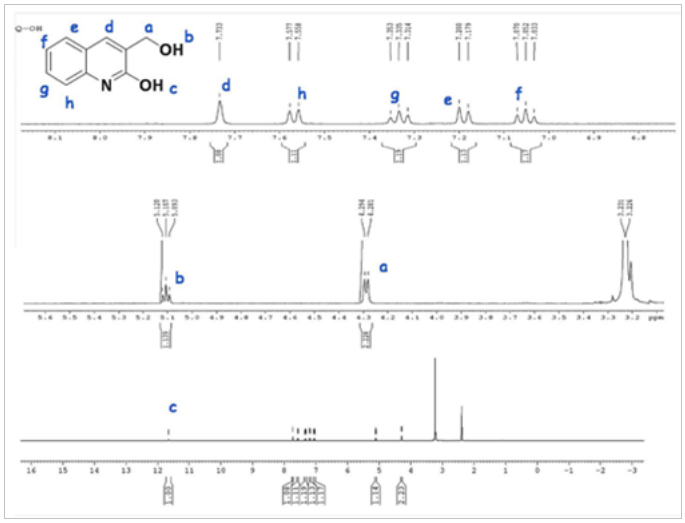

Figure 5 ^{1}H-NMR spectrum of compound (4a)

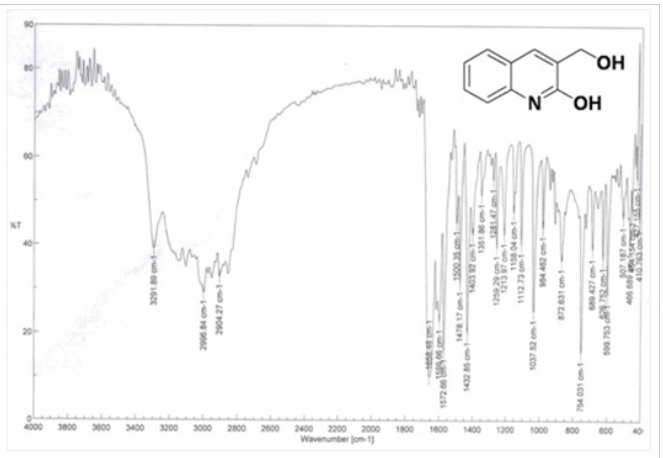

Figure 6 IR-spectrum of compound (4a)

Antioxidant activity using FRAP assay

The total antioxidant potential of a sample was determined using the ferric reducing ability of plasma FRAP assay as a measure of antioxidant potential. A potential antioxidant will reduce the ferric ion (Fe^{3+}) to the ferrous ion (Fe^{2+}); the latter forms a blue complex (Fe^{2+}/TPTZ), which increases the absorption at 593nm. Briefly, FRAP reagent was prepared by mixing acetate buffer (300M, pH 3.6), a solution of 10µM TPTZ in 40µM HCl and 20µM $FeCl_3$ at 10:1:1 (v/v/v). The reagent (300µl) and sample solutions (10µl) were added to each well and mixed thoroughly. The absorbance was taken at 593nm after 10min. Standard curve was prepared using different concentrations of trolox. All the solutions were used on the day of preparation and the results were corrected for dilution and expressed in µM trolox per 100g dry weight (dw) and all determinations were performed in triplicates. The stock solutions of the each synthesized chemical compound individually mixed with double distilled water about 1mg/mL and variant concentration about 10mg/mL was prepared and proceeded the above procedure to react with the FRAP reagents and taken the Optical density level at 593nm in UV visible spectroscopy. The Optical density was noted and the strength meant its antioxidant potential to control the free radical scavenging activity through standard curve.[30–31]

Conclusion

In summary some suitable and elegant methods have been chosen for the synthesis of novel heterocyclic compounds such as—Hydrogenated oxetoquinolines‖ though the annulation of the oxeto ring onto a quinoline scaffolds methodology. The key intermediate, 2-chloro-3-formyl quinolines were synthesized by the Vilsmeier Haack and further explored toward the synthesis of oxetoquinolines. The novel 2*H*-oxeto[2,3-b]quinoline and its derivatives were studied for its anti bacterial and antioxidant studies. All the compounds were found to be active against all the pathogens though they did not reach the effectiveness of the standards. In addition compound 1e showed good anti oxidant activity compared to other synthesized compounds.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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