European Journal of Chemistry 4 (4) (2013) 329-335

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis and biological evaluation of novel β-hydroxy benzimidazolyl sulfone fluoroquinolones by selective oxidation using ammonium molybdate catalysed H_2O_2

Batthini Guruswamy [a,*], Rama Krishnan Arul [a], Muggu Venkata Satya Rama Krishna Chaitanya [b] and Sai Subrahmanya Praveen Kumar Darsi [b]

[a] *Neuland Laboratories Research and Development Center, Bonthapally, Medak, Andhra Pradesh-500313, India*
[b] *Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Kukatpally, Hyderabad-500085, India*

**Corresponding author at: Neuland Laboratories Research & Development Center, Bonthapally, Medak, Andhra Pradesh-500313, India. Tel.: +91.086.54392608; fax: +91.086.54392600. E-mail address: guruswamy2748@gmail.com (B. Guruswamy).*

ARTICLE INFORMATION

Received: 05 April 2013
Received in revised form: 12 July 2013
Accepted: 12 July 2013
Online: 31 December 2013

KEYWORDS

Levofloxacin
Epichlorohydrine
Antimicrobial activity
Ammonium molybdate
β-Hydroxy benzimidazolyl sulfones
Chiral benzoxazole fluoroquinolones

ABSTRACT

Synthesis of new β-hydroxy benzimidazolyl sulfides (**4a-e**) and β-hydroxy benzimidazolyl sulfones (**5a-e**) containing 7-piperazine fluoroquinolones have been described and evaluated for their antimicrobial activity. Benzoxazine fluoroquinolone carboxylic acid, **1**, on reaction with piperazine in presence of triethylamine in acetonitrile under reflux resulted 7-piperazine bezoxazole fluoroquinolone, **2**. The latter is reacted with epichlorohydrine in presence of NaOH in acetone yielded corresponding *N*-substituted epoxide, **3**, with retained chirality, which on treatment with 5-substituted-2-mercaptobenzimidazoles given the corresponding β-hydroxy bezimidazolyl sulfides (**4a-e**). Further compounds **4a-e** on treatment with H_2O_2 and ammonium molybdate in dichloromethane yielded the β-hydroxy bezimidazolyl sulfones, **5a-e**. The antimicrobial activity of newly synthesized compounds along with levofloxacin (reference drug) were evaluated against different microorganisms and found many of the evaluated compounds have been exhibited remarkable activity.

1. Introduction

Fluoroquinolones are compounds which posses a wide variety of therapeutically interesting antibacterial activity against various Gram-positive and Gram-negative bacteria [1,2]. The board spectrum of antibiotic activity of these compounds is mainly due to the presence of a fluorine atom at position C-6, chemical modification at position C-7 (piperazine moiety) of fluroquinolones ring system [3-6]. Literature survey and Structure activity relationship (SAR) analysis reveals that the substitution/modifications at C-7 position of fluroquinolones nucleus lead to the synthesis of new and improved fluoroquinolones antibacterials [7,8] with enhanced activity similar to antibiotics like levofloxacin, moxifloxacin, ciprofloxacin, ofloxacin and enrofloxacin (Figure 1). Fluoroquinolones impair DNA gyrase, type IV topoisomerase enzymes and inhibit the DNA replication [9,10]. The main objective in fluroquinolone research include improving the potency and activity against resistant microorganisms [11,12].

Mercaptobenzimidazoles and its derivatives are heterocyclic compounds that exhibit a wide range of medicinal uses such as anti-cancer [13], anti-microbial [14], anti-viral [15] and anti-fungal [16] activity. These also been found to be an integral part of Vitamin B_{12} [17] in the form of 5,6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole. The medicinal importances of both 7-piperazine fluoroquinolones and substituted mercaptobenzimidazoles have prompted us to synthesize a series of novel β-hydroxy benzimidazolyl sulfides. Further on selective oxidation using ammonium molybdate dissolved in H_2O_2 [18], yielded novel β-hydroxy benzimidazolyl sulfones containing 7-piperazine fluroquinolones.

In view of these reports, it was thought worthwhile to synthesize and investigate the novel 7-piperazinyl fluoroquinolones. Present work is concerned with the synthesis of mercaptobenzimidazolyl substituted 7-piperazine fluoroquinolones having the objective of discovering novel antimicrobial agents.

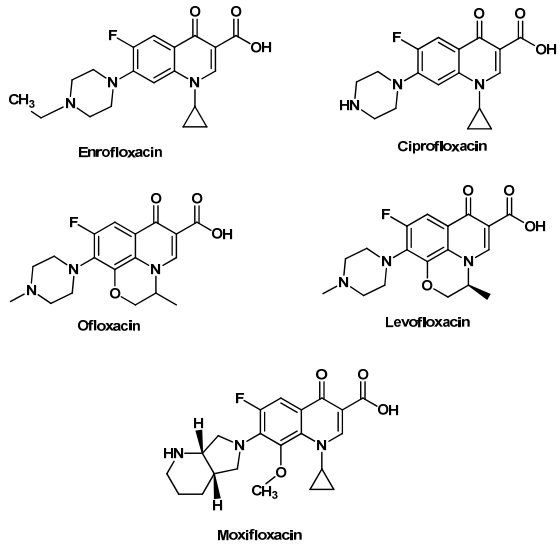
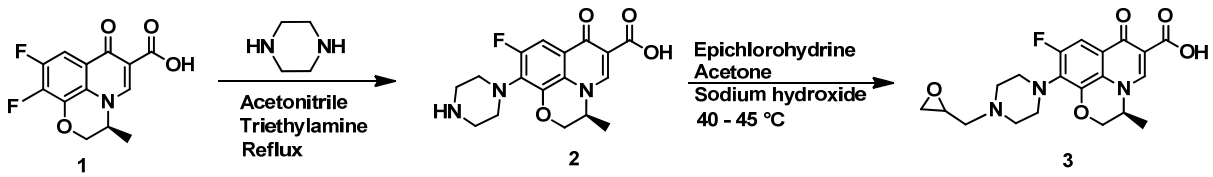


Figure 1. Fluroquinolone antibacterial agents.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.4.4.329-335.792



Scheme 1

2. Experimental

2.1. Instrumentation

All the reagents and solvents were used analytical grade and without further purification unless otherwise mentioned. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F_{254} (Merck). TLC Plates were inspected under UV light. Elemental analyses data were obtained by employing a Perkin-Elmer 240c analyzer. IR spectra (KBr pellets) were recorded with a Perkin-Elmer-1700 spectro photo meter. ^{1}H NMR and ^{13}C NMR spectra were measured on avance Bruker-300 MHz spectrometer. Mass spectrum was recorded on Varian 300-MS spectrometer and melting points were recorded on a Polmon MP96. Specific optical rotation performed on Rudolf model number 420766APR/6W polarimeter.

2.2. Synthesis

2.2.1. (S)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-10-(piperazin-1-yl)-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (2)

To a solution of compound **1** (100.0 g, 356 mmol) in acetonitrile (500 mL) and piperazine (45.92 g, 534 mmol) was stirred for 30 min at 25-30 °C, added triethylamine (107.86 g, 1068 mmol) and heated the reaction mass to reflux, maintained for 12 h, progress of the reaction was monitored by TLC. The reaction mass was cooled to 25-30 °C, stirred for 1 h, filtered the isolated compound and washed with acetonitrile. The crude solid was recrystallized from methanol to obtain pure compound **2** (Scheme 1). Yield: 106.19 g (86%). Color: pale yellow powder. M.p.: 263-265 °C. IR (KBr, *v*, cm^{-1}): 3412 (NH), 2814 (CH), 1728 (C=O), 1617 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.22-1.24 (d, 3H, CH_3, *J* = 6.0 Hz), 2.48-2.55 (m, 4H, 2×CH_2), 2.27 (s, 1H, NH, D_2O exchangeable), 3.56-3.62 (m, 4H, 2×CH_2), 3.97-4.00 (m, 1H, CH), 4.54-4.57 (m, 2H, CH_2), 7.48-7.32 (d, 1H, Ar-H, *J* = 12.0 Hz), 8.89 (s, 1H, C=CH), 15.17 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 18.39 (CH_3), 51.46 (2×CH_2), 54.32 (2×CH_2), 58.71 (CH), 60.31 (CH_2), 103.41 (CH), 107.62 (C), 120.34 (C), 125.41 (C), 131.08 (C), 140.36 (C), 146.54 (C), 154.31 (C), 157.29 (CH), 166.82 (C=O), 177.09 (C=O). Anal. calcd. for $C_{17}H_{18}FN_3O_4$: C, 58.78; H, 5.22; N, 12.10. Found: C, 58.64; H, 5.09; N, 12.01 %. MS (*m/z*): 348.07 (M^+). $[\alpha]_D^{25}$: -72.41 (c =1.0 in methanol:methylene chloride, 1:1).

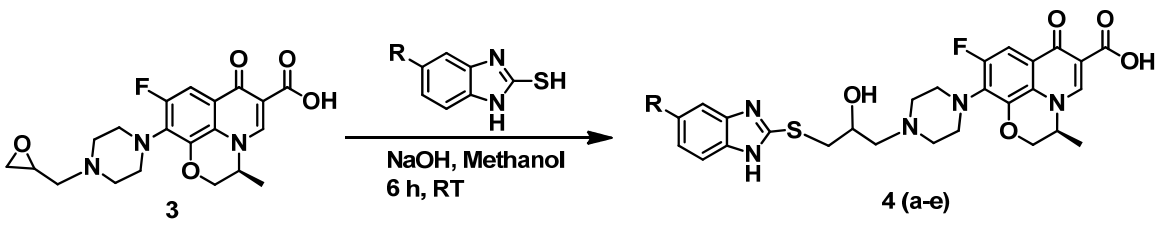
2.2.2. (S)-9-fluoro-3,7-dihydro-3-methyl-10-(4-((oxiran-2-yl) methyl)piperazin-1-yl)-7-oxo-2H-[1,4]oxazino[2,3,4-ij] quinoline-6-carboxylic acid (3)

To a solution of compound **2** (50.0 g, 123 mmol) in acetone (250 mL), added NaOH (12.3 g, 307 mmol) followed by epichlorohydrine (22.75 g, 0.246 mmol) and the reaction mixture was maintained for 4 h at 40-45 °C, at the end of this period, the reaction mixture was cooled to 25-30 °C and solvent was distilled off under vacuum. The residue was dissolved in water (50.0 mL) and adjusted the pH = 6.0-7.0 with dil. HCl. The separated solid was filtered, washed with water and dried. The crude solid was recrystallized from ethyl acetate to obtain pure compound **3** (Scheme 1). Yield: 47.40 g (81.6%). Color: Off white powder. M.p.: 210-213 °C. IR (KBr, *v*, cm^{-1}): 3042 (CH), 1708 (C=O), 1624 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.42-1.44 (d, 3H, CH_3, *J* = 6.0 Hz), 2.34-2.48 (m, 4H, 2×CH_2), 2.49-2.51 (m, 2H, CH_2), 3.23-3.32 (m, 4H, 2×CH_2), 3.51-3.54(d, 2H, CH_2, *J* = 6.2 Hz), 4.33-4.35 (d, 1H, CH, *J* = 6.0 Hz), 4.55-4.58 (d, 1H, CH, *J* = 6.0 Hz), 4.89-4.91 (d, 2H, CH_2, *J* = 6.0 Hz), 7.52-7.56 (d, 1H, Ar-H, *J* = 12.0 Hz), 8.94 (s, 1H, C=CH), 15.17 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.34 (CH_3), 45.29 (CH_2), 49.23 (CH_2), 50.72 (2×CH_2), 54.56 (2×CH_2), 55.25 (CH), 58.35 (CH), 61.61 (CH), 68.49 (CH_2), 107.32 (CH), 109.34 (C), 120.13 (C), 125.19 (C), 130.44 (C), 132.56 (C), 140.68 (C), 146.79 (C), 154.28 (CH), 166.45 (C=O), 176.77 (C=O). Anal. calcd. for $C_{20}H_{22}FN_3O_5$: C, 59.55; H, 5.50; N, 10.42. Found: C, 59.49; H, 5.60; N, 10.64 %. MS *(m/z)*: 404.02 (M^+). $[\alpha]_D^{25}$: -73.06 (c =1.0 in Methanol:Methylene chloride, 1:1).

2.2.3. General procedure for the synthesis of compounds 4a-e

To a solution of substituted mercaptobenzimidazoles (13.53 mmol) in methanolic NaOH (30.75 mmol) was added to compound **3** (5.0 g, 12.30 mmol) and the reaction mixture was stirred for 6 h at room temperature and monitored the reaction by TLC, upon completion of the reaction, methanol was distilled off under reduced pressure and the resulted residue was dissolved in water, adjusted the pH = 6.0-7.0 with dil. HCl and extracted the product in to dichloromethane. The organic layer was separated and washed with water followed by 20% sodium chloride solution, dried over anhydrous Na_2SO_4. The solvent was distilled off under vacuum to obtain crude **4a-e**. The crude compounds were recrystallized from ethylacetate to obtain the pure title compounds (Scheme 2).

(S)-10-(4-(3-(1H-benzo[d]imidazol-2-ylthio)-2-hydroxy propyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**4a**): Yield: 5.59 g (81.5%). Color: Off white powder. M.p.: 222-225 °C. IR (KBr, *v*, cm^{-1}): 3401 (OH), 1721 (C=O), 1619 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.39-1.41 (d, 3H, CH_3, *J* = 6.2 Hz) 2.52-2.58 (m, 4H, 2×CH_2), 2.71-2.73 (d, 2H, CH_2, *J* = 6.0 Hz), 3.26-3.28 (d, 2H, CH_2, *J* = 6.0 Hz), 3.53-3.60 (m, 4H, 2×CH_2), 3.62-3.66 (m, 1H, CH), 4.31-4.37 (m, 1H, CH), 4.49-4.51 (d, 2H, CH_2, *J* = 6.0 Hz), 4.96 (s, 1H, OH, D_2O exchangeable), 5.36 (s, 1H, NH, D_2O exchangeable), 7.03-7.08 (m, 2H, Ar-H), 7.36-7.37 (m, 2H, Ar-H), 7.47-7.50 (d, 1H, Ar-H, *J* = 12.0 Hz), 8.74 (s, 1H, C=CH), 15.16 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.39 (CH_3), 47.24 (CH_2), 49.04 (2×CH_2), 55.30 (2×CH_2), 60.43 (CH_2), 62.31 (CH), 64.51 (CH), 68.77 (CH_2), 107.24 (CH), 109.21 (C), 115.99 (CH), 120.96 (C), 124.05 (CH), 130.77 (C), 134.79 (C), 140.96 (C), 146.79 (C), 152.50 (C), 154.07 (CH), 166.39 (C=O), 176.83 (C=O). Anal. calcd. for $C_{27}H_{28}FN_5O_5S$: C, 58.58; H, 5.10; N, 12.56. Found: C, 58.46; H, 5.01; N, 12.49 %. MS (*m/z)*: 554.07 (M^+). $[\alpha]_D^{25}$: -91.68 (c =1.0 in methanol:methylene chloride, 1:1).



Scheme 2

(S)-10-(4-(3-(5-methyl-1H-benzo[d]imidazol-2-yl thio)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**4b**): Yield: 5.79 g (82.3%). Color: Off white powder. M.p.: 238-240 °C. IR (KBr, *v*, cm^{-1}): 3401 (OH), 1707 (C=O), 1624 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.43-1.45 (d, 3H, CH_3, *J* = 6.2 Hz), 2.43 (s, 3H, Ar-CH_3), 2.69-2.73 (m, 4H, 2×CH_2), 2.75-2.77 (d, 2H, CH_2, *J* = 6.0 Hz), 3.13-3.15 (d, 2H, CH_2, *J* = 6.0 Hz), 3.62-3.68 (m, 4H, 2×CH_2), 3.71-3.76 (m, 1H, CH), 4.35-4.39 (m, 1H, CH), 4.56-4.58 (d, 2H, CH_2, *J* = 6.0 Hz), 5.12 (s, 1H, OH, D_2O exchangeable), 5.54 (s, 1H, NH, D_2O exchangeable), 7.22-7.25 (d, 1H, Ar-H, *J* = 9.0 Hz), 7.31 (s, 1H, Ar-H), 7.45-7.61 (m, 2H, Ar-H), 8.97 (s, 1H, C=CH), 15.08 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.46 (CH_3), 26.8 (CH_3), 46.34 (CH_2), 50.26 (2×CH_2), 54.89 (2×CH_2), 60.52 (CH_2), 62.18 (CH), 64.49 (CH), 68.91 (CH_2), 107.51 (CH), 109.83 (C), 114.09 (CH), 120.33 (C), 124.18 (CH), 130.46 (C), 134.79 (C), 140.96 (C), 146.79 (C), 152.50 (C), 154.07 (CH), 166.39 (C=O), 176.83 (C=O). Anal. calcd. for $C_{28}H_{30}FN_5O_5S$: C, 59.25; H, 5.33; N, 12.34. Found: C, 59.12; H, 5.24; N, 12.20 %. MS (*m/z*): 568.10 (M^+). $[\alpha]_D^{25}$: -88.10 (c =1.0 in methanol:methylene chloride, 1:1).

(S)-10-(4-(3-(5-methoxy-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**4c**): Yield: 5.53 g (76.6 %). Color: Off white powder. M.p.: 234-238 °C. IR (KBr, *v*, cm^{-1}): 3399 (OH), 1708 (C=O), 1624 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.43-1.45 (d, 3H, CH_3, *J* = 6.2 Hz), 2.58-2.63 (m, 4H, 2×CH_2), 2.68-2.70 (d, 2H, CH_2, *J* = 6.0 Hz), 3.18-3.20 (d, 2H, CH_2, *J* = 6.0 Hz), 3.56-3.61 (m, 4H, 2×CH_2), 3.76-3.81 (m, 1H, CH), 3.86 (s, 3H, OCH_3), 4.41-4.45 (m, 1H, CH), 4.61-4.63 (d, 2H, CH_2, *J* = 6.0 Hz), 4.97 (s, 1H, OH, D_2O exchangeable), 5.31 (s, 1H, NH, D_2O exchangeable), 7.00-7.03 (d, 1H, Ar-H *J* = 9.0 Hz), 7.10 (s, 1H, Ar-H), 7.53-7.63 (m, 2H, Ar-H), 8.98 (s, 1H, C=CH), 15.14 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.41 (CH_3), 47.10 (CH_2), 51.24 (2×CH_2), 55.18 (2×CH_2), 58.36 (OCH_3), 60.56 (CH), 62.12 (CH), 64.56 (CH), 68.74 (CH_2), 102.21 (CH), 107.31 (CH), 108.31 (CH), 110.41 (C), 117.54 (CH), 125.31 (C), 129.47 (C), 135.27 (C), 141.07 (C), 146.53 (C), 149.11 (C), 152.28 (C), 154.32 (CH), 158.41 (C), 166.56 (C=O), 177.02 (C=O). Anal. calcd. for $C_{28}H_{30}FN_5O_6S$: C, 57.62; H, 5.18; N, 12.00. Found: C, 57.56; H, 5.07; N, 11.87 %. MS (*m/z*): 584.10 (M^+). $[\alpha]_D^{25}$: -64.80 (c = 1.0 in methanol:methylene chloride, 1:1).

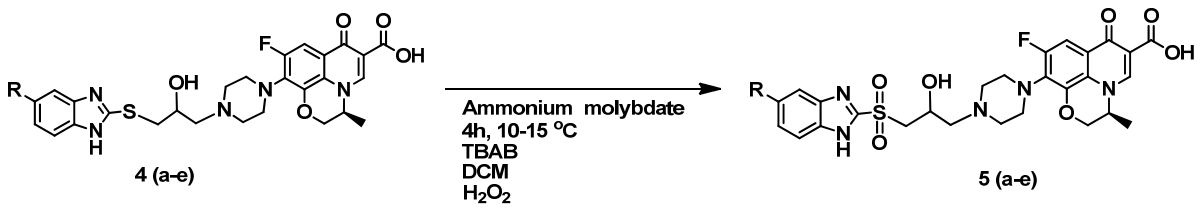
(S)-10-(4-(3-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**4d**): Yield: 6.41 g (74.8 %). Color: Off white powder. M.p.: 222-225 °C. IR (KBr, *v*, cm^{-1}): 3400 (OH), 1709 (C=O), 1623 (C=O). ^1H-NMR (300 MHz, DMSO-d_6, δ, ppm): 1.43-1.45 (d, 3H, CH_3, *J* = 6.2 Hz), 2.48-2.53 (m, 4H, 2×CH_2), 2.81-2.83 (d, 2H, CH_2, *J* = 6.0 Hz), 3.20-3.22 (d, 2H, CH_2, *J* = 6.0 Hz), 3.52-3.57 (m, 4H, 2×CH_2), 3.66-3.70 (m, 1H, CH), 4.37-4.41 (m, 1H, CH), 4.58-4.60 (d, 2H, CH_2, *J* = 6.0 Hz), 5.12 (s, 1H, OH, D_2O exchangeable), 5.53 (s, 1H, NH, D_2O exchangeable), 6.98 (m, 1H, Ar-H), 7.23-7.26 (m, 2H, Ar-H), 7.42 (s, 1H, CHF_2), 7.55-7.59 (d, 1H, Ar-H, *J* = 12.0 Hz), 8.98 (s, 1H, C=CH), 15.17 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.41 (CH_3), 47.48 (CH_2), 50.36 (2×CH_2), 55.11 (2×CH_2), 60.24 (CH_2), 62.31 (CH), 64.62 (CH), 68.56 (CH_2), 103.12 (CH), 108.09 (CH), 110.23 (CH), 110.85 (C), 118.61(CH), 120.34 (C), 130.41 (C), 133.45 (C), 142.56 (C), 148.35 (C), 152.36 (C), 154.60 (C), 158.62 (C), 166.84 (C=O), 177.26 (C=O). Anal. calcd. for $C_{28}H_{28}F_3N_5O_6S$: C, 54.28; H, 4.55; N, 11.30. Found: C, 54.13; H, 4.40; N, 11.18 %. MS (*m/z*): 588.05 (M^+). $[\alpha]_D^{25}$: - 36.10 (c =1.0 in methanol:methylene chloride, 1:1).

(S)-10-(4-(3-(5-chloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**4e**): Yield: 6.13 g (84.1%). Color: Off white powder. M.p.: 242-245 °C. IR (KBr, *v*, cm^{-1}): 3420 (OH), 1706 (C=O), 1623 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.43-1.45 (d, 3H, CH_3, *J* = 6.2 Hz), 2.61-2.67 (m, 4H, 2×CH_2), 2.72-2.74 (d, 2H, CH_2, *J* = 6.0 Hz), 3.32-3.24 (d, 2H, CH_2, *J* = 6.0 Hz), 3.61-3.67 (m, 4H, 2×CH_2), 3.68-3.73 (m, 1H, CH), 4.49-4.56 (m, 1H, CH), 4.66-4.68 (d, 2H, CH_2, *J* = 6.0 Hz), 5.07 (s, 1H, OH, D_2O exchangeable), 5.48 (s, 1H, NH, D_2O exchangeable), 7.28-7.31 (m, 1H, Ar-H), 7.53-7.60 (m, 3H, Ar-H), 8.97 (s, 1H, C=CH), 15.12 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.39 (CH_3), 47.36 (CH_2), 50.07 (2×CH_2), 54.91(2×CH_2), 60.43 (CH_2), 62.14 (CH), 64.51(CH), 68.77 (CH_2), 107.27 (CH), 109.43 (C), 113.57 (CH), 114.99 (CH), 120.96 (C), 125.19 (CH), 130.77 (C), 134.79 (C), 136.99 (C), 140.96 (C), 146.79 (C), 152.50 (CH), 166.39 (C=O), 176.83 (C=O). Anal. calcd. for $C_{27}H_{27}ClFN_5O_5S$: C, 55.15; H, 4.63; N, 11.91. Found: C, 54.96; H, 4.52; N, 11.79 %. MS (*m/z*): 588.65 (M^+). $[\alpha]_D^{25}$: -74.78 (c =1.0 in methanol: methylene chloride, 1:1).

2.2.4. General procedure for the preparation of 5a-e

To a solution of compounds **4a-e** (9.03 mmol) in dichloromethane (25 mL) and tetrabutyl ammonium bromide (0.1 g) was added to a solution of ammonium molybdate (0.2 g) in 30 % hydrogen peroxide (45.14 mmol) drop wise at 0-5 °C and maintained for 4 h at 10-15 °C and monitor the reaction by TLC. After completion of reaction organic layer was separated, washed with 20% NaCl solution (20 mL), dried over anhydrous Na_2SO_4 and the solvent was distilled off under vacuum to obtain a crude **5a-e**, the crude compounds were recrystallized from ethylacetate to obtain the pure title compounds (Scheme 3).

(S)-10-(4-(3-(1H-benzo[d]imidazol-2-yl sulfonyl)-2-hydroxy propyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**5a**): Yield: 4.40 g (83.4%). Color: Off white solid. M.p.: 200-203 °C. IR (KBr, *v*, cm^{-1}): 3418 (OH), 1718 (C=O), 1621 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.40-1.42 (d, 3H, CH_3, *J* = 6.2 Hz) 2.46-2.51 (m, 4H, 2×CH_2), 2.64-2.66 (d, 2H, CH_2, *J* = 6.0 Hz), 3.60-3.66 (m, 4H, 2×CH_2), 3.71-3.76 (m, 1H, CH), 3.83.85 (d, 2H, CH_2, *J* = 6.0 Hz), 4.41-4.46 (m, 1H, CH), 4.53-4.55 (d, 2H, CH_2, *J* = 6.0 Hz), 4.89 (s, 1H, OH, D_2O exchangeable), 5.24 (s, 1H, NH, D_2O exchangeable), 7.11-7.16 (m, 2H, Ar-H), 7.39-7.43 (m, 2H, Ar-H), 7.56-7.60 (d, 1H, Ar-H *J* = 12.0 Hz), 8.84 (s, 1H, C=CH), 15.12 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.41 (CH_3), 50.16 (2×CH_2), 54.51 (2×CH_2), 60.28 (CH_2), 62.41 (CH), 64.51 (CH), 65.78 (CH_2), 68.77 (CH_2), 108.23 (CH), 109.36 (C), 115.36 (CH), 119.48 (C), 123.92 (CH), 131.23 (C), 135.33 (C), 141.63 (C), 146.34 (C), 151.53 (C), 154.62 (CH),



Scheme 3

166.73 (C=O), 177.07 (C=O). Anal. calcd. for $C_{27}H_{28}FN_5O_7S$: C, 55.38; H, 4.82; N, 11.96. Found: C, 55.13; H, 4.71; N, 11.80 %. MS (*m/z*): 586.07 (M^+). Specific optical rotation: $[\alpha]_D^{25}$: -83.24 (c =1.0 in methanol:methylene chloride, 1:1).

(S)-10-(4-(3-(5-methyl-1H-benzo[d]imidazol-2-ylsulfonyl)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**5b**): Yield: 4.15 g (78.6%). Color: Off white solid. M.p.: 212-215 °C. IR (KBr, *v*, cm^{-1}): 3422 (OH), 1710 (C=O), 1619 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.41-1.43 (d, 3H, CH_3, *J* = 6.2 Hz), 2.47 (s, 3H, Ar-CH_3), 2.53-2.55 (m, 4H, 2×CH_2), 2.59-2.61 (d, 2H, CH_2, *J* = 6.0 Hz), 3.58-3.64 (m, 4H, 2×CH_2), 3.77-3.81 (m, 1H, CH), 3.85-3.87 (d, 2H, CH_2, *J* = 6.0 Hz), 4.56-4.60 (m, 1H, CH), 4.61-4.63(d, 2H, CH_2, *J* = 6.0 Hz), 4.94 (s, 1H, OH, D_2O exchangeable), 5.61 (s, 1H, NH, D_2O exchangeable), 7.18-7.21 (m, 1H, Ar-H), 7.24-7.27 (m,1H, Ar-H), 7.39-7.43 (m, 1H, Ar-H), 7.54-7.58 (d, 1H, Ar-H, *J* = 12.0 Hz), 8.91 (s, 1H, C=CH), 15.13 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.39 (CH_3), 26.73 (CH_3), 50.35 (2×CH_2), 54.33 (2×CH_2), 59.93 (CH_2), 62.26 (CH), 64.36 (CH), 66.03 (CH_2), 6.81 (CH_2), 108.41 (CH), 109.73 (C), 115.01 (CH), 119.96 (C), 123.56 (CH), 124.53 (CH), 130.95 (C), 134.76 (C), 140.68 (C), 145.53 (C), 152.26 (C), 154.58 (C), 166.58 (C=O), 176.83 (C=O). Anal. calcd. for $C_{28}H_{30}FN_5O_7S$: C, 56.08; H, 5.04; N, 11.68. Found: C, 55.93; H, 4.92; N, 11.58 %. MS (*m/z*): 600.12 (M^+). $[\alpha]_D^{25}$: -49.74 (c =1.0 in methanol:methylene chloride, 1:1).

(S)-10-(4-(3-(5-methoxy-1H-benzo[d]imidazol-2-ylsulfonyl)-2-hydroxypropyl) piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**5c**): Yield: 4.23 g (80.4%). Color: Off white powder. M.p.: 216-218 °C. IR (KBr, *v*, cm^{-1}): 3412 (OH), 1709 (C=O), 1618 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.40-1.42 (d, 3H, CH_3, *J* = 6.2 Hz), 2.49-2.55 (m, 4H, 2×CH_2), 2.72-7.74 (d, 2H, CH_2, *J* = 6.0 Hz), 3.62-3.66 (m, 4H, 2×CH_2), 3.71-3.75 (m, 1H, CH), 3.80-3.82 (d, 2H, CH_2, *J* = 6.0 Hz), 4.01 (s, 3H, OCH_3), 4.51-4.55 (m, 1H, CH), 4.58-4.60 (d, 2H, CH_2, *J* = 6.0 Hz), 5.07 (s, 1H, OH, D_2O exchangeable), 5.48 (s, 1H, NH, D_2O exchangeable), 7.11-7.13 (d, 1H, Ar-H, *J* = 9.0 Hz), 7.21-7.23 (m, 1H, Ar-H), 7.53-7.63 (m, 2H, Ar-H), 8.93 (s, 1H, C=CH), 15.12 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.41 (CH_3), 50.48 (2×CH_2), 54.76 (2×CH_2), 56.82 (CH_2), 58.42 (OCH_3), 62.34 (CH), 64.56 (CH), 66.50 (CH_2), 68.61(CH_2), 103.27 (CH), 108.72 (CH), 109.67 (CH), 110.38 (C), 118.66 (CH), 120.46 (C), 129.37 (C), 133.56 (C), 141.38 (C), 147.71 (C), 152.39 (C), 154.64 (C), 158.41 (C), 166.63 (C=O), 176.74 (C=O). Anal. calcd. for $C_{28}H_{30}FN_5O_8S$: C, 54.63; H, 4.91; N, 11.38. Found: C, 54.48; H, 4.80; N, 11.24 %. MS (*m/z*): 616.05 (M^+). $[\alpha]_D^{25}$: -44.80 (c =1.0 in methanol:methylene chloride, 1:1).

(S)-10-(4-(3-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylsulfonyl)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**5d**): Yield: 4.17 g (79.5%). Color: Off white solid. M.p.: 208-210 °C. IR (KBr, *v*, cm^{-1}): 3412 (OH), 1708 (C=O), 1619 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.38-1.40 (d, 3H, CH_3, *J* = 6.2 Hz), 2.56-2.61 (m, 4H, 2×CH_2), 2.79-2.81 (d, 2H, CH_2, *J* = 6.0 Hz), 3.55-3.61 (m, 4H, 2×CH_2), 3.71-3.74 (m, 1H, CH), 3.81-3.83 (d, 2H, CH_2, *J* = 6.0 Hz), 4.42-4.46 (m, 1H, CH), 4.62-4.64 (d, 2H, CH_2, *J* = 6.0 Hz), 4.99 (s, 1H, OH, D_2O exchangeable), 5.36 (s, 1H, NH, D_2O exchangeable), 7.02-7.03 (m, 1H, Ar-H), 7.34-7.38 (m, 2H, Ar-H), 7.41 (s, 1H, Ar-H), 7.57-7.61 (m, 1H, Ar-H), 8.86 (s, 1H, C=CH), 15.11 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.37 (CH_3), 50.41(2×CH_2), 54.68 (2×CH_2), 60.31 (CH_2), 62.18 (CH), 64.58 (CH), 66.50 (CH_2), 68.73 (CH_2), 102.31 (CH), 107.88 (CH), 109.43 (CH), 110.63 (C), 118.54 (CH), 119.94 (C), 129.81 (C), 133.01 (C), 142.62 (C), 148.35 (C), 152.17 (C), 154.38 (C), 158.49 (C), 164.28 (CHF_2), 166.52 (C=O), 176.79 (C=O). Anal. calcd. for $C_{28}H_{28}F_3N_5O_8S$: C, 51.61; H, 4.33; N, 10.75. Found: C, 51.48; H, 4.20; N, 10.62 %. MS (*m/z*): 652.11 (M^+). $[\alpha]_D^{25}$: -54.10 (c =1.0 in methanol:methylene chloride, 1:1).

(S)-10-(4-(3-(5-chloro-1H-benzo[d]imidazol-2-ylsulfonyl)-2-hydroxypropyl)piperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**5e**): Yield: 4.60 g (86.8 %). Color: Off white powder. M.p.: 197-199 °C. IR (KBr, *v*, cm^{-1}): 3416 (OH), 1708 (C=O), 1619 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.39-1.41 (d, 3H, CH_3, *J* = 6.2 Hz), 2.71-2.75 (m, 4H, 2×CH_2), 2.78-2.80 (d, 2H, CH_2, *J* = 6.0 Hz), 3.69-3.73 (m, 4H, 2×CH_2), 3.76-3.80 (m, 1H, CH), 3.84-3.86 (d, 2H, CH_2, *J* = 6.0 Hz), 4.53-4.57 (m, 1H, CH), 4.69-4.71 (d, 2H, CH, *J* = 6.0 Hz), 5.07 (s, 1H, OH, D_2O exchangeable), 5.48 (s, 1H, OH, D_2O exchangeable), 7.24-7.28 (m, 1H, Ar-H), 7.48-7.53 (m, 2H, Ar-H), 7.58-7.62 (d, 1H, Ar-H, *J* = 12.0 Hz), 8.89 (s, 1H, C=CH), 15.10 (s, 1H, COOH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6, ppm, δ): 18.39 (CH_3), 51.08 (2×CH_2), 54.84 (2×CH_2), 60.12 (CH_2), 62.49 (CH), 64.51 (CH), 66.24 (CH_2), 68.62 (CH_2), 108.18 (CH), 109.25 (C), 114.27 (CH), 114.99 (CH), 119.53 (C), 124.32 (CH), 131.21 (C), 134.76 (C), 137.26 (C), 141.14 (C), 146.52 (C), 152.32 (CH), 166.48 (C=O), 176.58 (C=O). Anal. calcd. for $C_{27}H_{27}ClFN_5O_7S$: C, 52.30; H, 4.39; N, 11.29. Found: C, 52.17; H, 4.24; N, 11.18 %. ES (*m/z*): 620.61 (M^+). $[\alpha]_D^{25}$: -61.29 (c =1.0 in methanol:methylene chloride, 1:1).

2.3. Biological evaluation

2.3.1. Antibacterial activity

The compounds **2**, **3**, **4a**-**e** and **5a**-**e** were assayed for antibacterial activity against three representative Gram-positive organisms *viz. Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Staphylococcus epidermidis* and three Gram-negative organisms *viz Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741) and *Klebsiella pneumoniae* (MTCC 618) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards [19]. Levofloxacin was used as reference standard**.** The minimum inhibitory concentration (MIC) values are presented in Table 1.

2.3.2. Antifungal activity

In vitro antifungal activity of the newly synthesized compounds ware studied against the fungal strains, *Candida albicans* (MTCC 227), *Candida rugosa* (NCIM 3467), *Aspergillus flavus* (MTCC 277) and *Saccharomyces cervisiae* (MTCC 36) of yeasts by Agar Well Diffusion Method [20] in 100 and 150 µg/mL concentrations.

Table 1. Minimum inhibitory concentration (MIC) values of compounds **2**, **3**, **4a-e** and **5a-e**.

Sample no	Test compounds	Microorganisms and minimum inhibitory concentration (MIC) µg/mL					
		B. subtilis	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
1	2	6.9	0.75	1.20	0.75	2.20	2.20
2	3	7.5	6.17	7.37	7.37	6.68	3.75
3	4a	2.64	0.66	0.84	7.22	2.16	4.32
4	4b	2.34	3.24	4.12	6.34	1.18	6.42
5	4c	1.58	0.92	0.62	1.58	0.88	1.58
6	4d	1.28	0.68	0.94	1.20	0.72	2.84
7	4e	2.28	1.74	1.20	1.58	0.58	4.62
8	5a	0.96	0.34	0.34	0.58	0.24	0.84
9	5b	1.34	0.34	0.42	0.78	0.58	0.68
10	5c	0.52	0.32	0.18	0.36	0.22	0.48
11	5d	0.84	0.34	0.18	0.28	0.18	0.74
12	5e	1.28	0.64	0.62	0.58	0.72	1.18
13	Levofloxacin	0.78	0.19	0.19	0.19	0.19	1.56

Table 2. Zone of inhibition of compounds **2**, **3**, **4a-e** and **5a-e** in mm at 100 and 150 µg/mL concentrations *.

Sample no	Test compounds	*C. albicans*	
		100 µg/mL	150 µg/mL
1	2	-	6
2	3	-	7
3	4a	-	4
4	4b	-	5
5	4c	-	5
6	4d	-	7
7	4e	-	7
8	5a	-	6
9	5b	-	7
10	5c	-	7
11	5d	-	9
12	5e	-	9
13	Levofloxacin	-	4

"-" = Not active.

The Potato Dextrose Agar (PDA) medium was suspended in distilled water (39 g in 1000 mL) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at pressure of 15 psi for 20 min. Agar well bioassay was employed for antifungal activity**.** The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO at different concentrations. After inoculation, wells were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each well different concentrations of test solutions were added. Controls were maintained. The treated and the controls were kept at 27 °C for 48 h. Inhibition zones were measured, the diameter calculated in millimetre.

Some of newly synthesized compounds shown excellent to good activity against *Candida albicans* (MTCC 227) only at 150 µg concentrations and inactive against 100 µg concentration, these compounds didn't shown any appreciable activity against other fungal strains. The results of the activity against *Candida albicans* are tabulated in Table 2.

3. Results and discussion

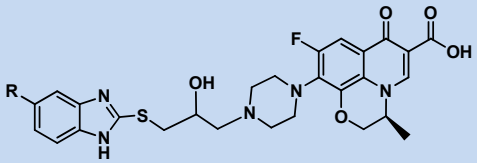
The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1, 2 and 3. Initially (3S)-9,10-difluoro-3-methyl-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid, **1**, on reaction with piperizine in presence of triethylamine in acetonitrile under reflux given the previously reported [21] (S)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-10-(piperazin-1-yl)-2*H*-[1,4]oxazino[2,3,4-ij] quinoline-6-carboxylic acid **2** on treatment with epichlrohydrine in presence of NaOH in acetone at 40-45 °C gave the corresponding 9-fluoro-3,7-dihydro-3-methyl-10-(4-((oxiran-2-yl)methyl)piperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-ij] quinoline-6-carboxylic acid, **3**, as shown in Scheme 1.

The structure of compound **3** was determined on the basis of its spectral data. The IR (KBr) spectrum of compound **3** has shown absorptions at 1708 and 1624 cm^{-1} assignable to two carbonyl groups as diagnostic absorptions. Typical aliphatic shift alignment in ^1H NMR spectrum at 1.42-1.44 ppm, 3 protons as doublet has shown the methyl protons adjacent to asymmetric carbon of oxazine ring. Chemical shifts at 3.51-3.53 ppm (d, 2H), 4.33-4.38 ppm (m, 1H) confirms the epoxide ring protons. However, the chemical shift at 7.52-7.56 (d, 1H) with coupling constant 12.0 Hz indicated proton coupled with adjacent fluorine atom and broad singlet at 15.17 ppm exchangeable with D_2O confirmed the presence of carboxylic acid. In ^{13}C NMR chemical shift at 18.34 ppm indicated the methyl group and signal at 146.51 ppm shown the carbon attached to fluorine. Enone carbon resonated downfield than all other carbons at 176.77 ppm, where as carboxylic acid carbon resonated at 166.45 ppm. Molecular mass of compound **3** has *m/z* 404.02 (M^+) indicates the molecular weight *m/z* 403.4. The results of elemental analysis for C, H and N were within ± 0.4 % of the theoretical values. The specific optical rotation -73.06 shown that the compound **3** is chiral.

Further, the nucleophilic opening of epoxide, **3**, was carried out with substituted 2-mercaptobenzimidazole in alcoholic NaOH solution at room temperature for 6 h, leads to formation of 7-(4-(3-(1*H*-benzo[d]imidazol-2-ylthio)-2-hydroxypropyl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro quinoline-3-carboxylic acid, **4a-e**, depicted in Scheme 2.

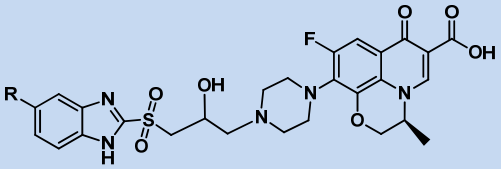
The synthesis of compounds **4a-e** was confirmed by IR, ^1H NMR, ^{13}C NMR, Mass spectrum and elemental analysis. The compound **4a** IR (KBr) spectrum shown absorption at 3401 cm^{-1} is indicated the presence of OH group and absorption at 1721 and 1619 cm^{-1} shown the presence of both carbonyl groups. Chemical shift in ^1H NMR spectrum at 1.39-1.41 ppm, 3 protons as doublet with coupling constant 6.0 Hz shown the presence of methyl group of oxazine ring. Proton shifts at 4.96 and 5.36 ppm as broad singlet and exchangeable with D_2O proved that the presence of OH and NH groups, further chemical shifts between 7.00 to 7.50 ppm in aromatic region indicated the presence of benzimidazolyl moity. In ^{13}C NMR chemical shift at 18.34 ppm indicated the chiral CH_3 group and chemical shift at 47.24 ppm indicated the methylene carbon attached to benzimidazolyl thiol moiety.

Table 3. Synthesis of various substituted mercaptobenzimdazole sulfides **4a-e.**



Sample no	R	Product	Yield (%)
1	H	4a	81.5
2	CH_3	4b	82.3
3	OCH_3	4c	76.6
4	OCH_2F_2	4d	74.8
5	Cl	4e	84.1

Table 4. Synthesis of various substituted mercaptobenzimdazolyl sulfones, **5a-e**, from corresponding sulfides using ammonium molybdate catalysed hydrogen peroxide.



Sample no	R	Reactant	Product	Yield (%)
1	H	4a	5a	83.4
2	CH_3	4b	5b	78.6
3	OCH_3	4c	5c	80.4
4	OCH_2F_2	4d	5d	79.5
5	Cl	4e	5e	86.8

Further, enone carbon resonated downfield than all the carbons at 176.83 ppm where as carboxylic acid carbon resonated at 166.39 ppm further proved the presence of both carbonyl carbons. Molecular mass of compound **4a** in the mass spectrum shown *m/z* 554.07 (M^+) indicated the molecular weight of compound i.e. *m/z* 553.60. The results of elemental analysis for C, H and N were within ±0.4 % of the theoretical values. The specific optical rotation $[\alpha]_D^{25}$: -91.68 proven that the compound **4a** is chiral. Similar reactions have been carried out with various substituted mercapto benzimdazoles dipicted in Table 3.

Initially, compounds **4a-e** was allowed to react with sodium hypochlorite in methylene chloride with different mole ratios and temperatures, observed the resulted product is mixture of sulfoxide and sulfone, the same oxidation reaction carried out using potassium peroxomonosulfate (oxone) but results are not encouraging. Further attempts made using hydrogen peroxide observed that reaction is taken longer hours and formation of other side products predominately corresponding sulfoxide, when the same reactions are carried out using ammonium molybdate catalysed H_2O_2 in presence of phase transfer catalyst like tetrabutyl ammonium bromide surprisingly reaction is completed within 4.0 h and resulted product is selectively desired sulfone. The chemical reaction depicted in Scheme 3.

The structure of compound **5a** was determined on the basis of its spectral data. Its IR (KBr) spectrum contains sharp absorption bands at 1718 and 1621 cm^{-1} indicated the presence of carbonyl groups. ^1H NMR spectra in DMSO-d_6 shown the absence of methylene protons at 2.64-2.66 ppm and shifted to little down field to 3.83-3.85 ppm proved the absence of starting sufide. Chemical shift at 15.12 ppm as broad singlet D_2O exchangeable proton indicated the presence of carboxylic acid which is essential to exhibit the antimicrobial activity. However absence the carbon chemical shift at 47.12 ppm and appeared at 64.51 ppm confirmed the formation of sulfone. The molecular mass of compound shown in the mass spectrum as *m/z* 586.07 (M^+) indicated its molecular weight *m/z* 585.60. The results of elemental analysis for C, H and N were within ±0.4 % of the theoretical values. The specific optical rotation $[\alpha]_D^{25}$: -84.24 proven that the compound **5a** is chiral.

The above reaction has been carried out with various *N*-substituted β-hydroxy benzimidazolyl sulfides to convert into corresponding sulfones using ammonium molybdate catalysed H_2O_2 as mentioned in Table 4.

All the newly synthesized compounds **2**, **3**, **4a-e** and **5a-e** were tested *invitro* against Gram-positive organisms *viz. Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Staphylococcus epidermidis* and Gram-negative organisms *viz. Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741), and *Klebsiella pneumoniae* (MTCC 618) and also synthesized compounds were screened *invitro* for antifungal activity aganist *Candida albicans* (MTCC 227), *Candida rugosa* (NCIM 3467), *Aspergillus flavus* (MTCC 277), and *Aspergillus niger* (MTCC 282). *Saccharomyces cervisiae* (MTCC 36) of yeasts. Most of the evaluated compounds exhibited remarkable antimicrobial activity.

4. Conclusion

In conclusion, synthesis of new β-hydroxy benzimidazolyl sulphides, **4a-e**, and corresponding sulfones, **5a-e**, containing 7-piperzine fluoroquinolones in presence of ammonium molybdate catalysed H_2O_2 has been described. The reaction was very simple, highly selective towards formation of sulfones and reproducible. All the newly synthesized compounds have been evaluated for their antimicrobial activity against bacteria and fungi and found potent against given bacteria and fungi strains. Compounds **5d**, **5c**, and **5b** are exhibited excellent anti bacterial activity against Gram-positive organisms *viz. Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Staphylococcus epidermidis* and Gram-negative organisms *viz Pseudomonas aeruginosa* (MTCC 741) and *Klebsiella pneumoniae* (MTCC 618). Compounds **4d** and **5c** have shown good activity and remaining compounds shown moderate to poor activity compared with levofloxacin (reference drug) but all the compounds shown equal or less activity against *Escherichia coli* (MTCC 443).

However, sulfones, **5a**-**e**, shown superior activity than corresponding sulfides. In the same way compounds **5d** and **5e** were shown excellent antifungal activity against *C. Albicans* and **4d** and **4e** also exhibited good antifungal activity comparatively other newly synthesized compounds in 150 µg/mL concentration comparisons with levofloxacin. Whereas no compound exhibited antifungal activity in 100 µg/mL concentration including reference drug.

Acknowledgements

The authors express their sincere thanks to Neuland Laboratories Limited, Hyderabad (A.P.), India for supporting this research work and Indian institute of chemical technology (IICT), Hyderabad for providing data of anti-microbial screening. Authors also thankful to authorities of Jawaharlal Nehru Technological University, Kukatpally, Hyderabad (A.P.), India.

References

[1]. Renau, T. E.; Sanchez, J. P.; Shapiro, M. A.; Dever, J. A.; Gracheck, S. J.; Domagala, J. M. *J. Med. Chem*. **1995**, *38*, 2974-2977.
[2]. Mascellino, M. T.; Ferinelli, S.; Iegri, F.; Iona, E.; DeSimone, C. *Drugs Expert. Clin. Res.* **1998**, *24*, 139-151.
[3]. Shen, L. L.; Mitscher, L. A.; Sharma, P. N.; Copper, C. S.; Rosen, T.; Pernet, A. G. *Biochemistry* **1989**, *28*, 3886-3894.
[4]. Kondo, H.; Sakamoto, F.; Koders, Y.; Tsukamoto, G. *J. Med. Chem*. 1986, *29*, 2020-2024.
[5]. Sheu, J. Y.; Chen, Y. L.; Tzeng, C. C. *Helv. Chim. Acta.* **2003**, *86*, 2481-2489.
[6]. Zhao, X.; Wang, J. Y.; Xu, C.; Dong, Y.; Zhou, J.; Domagala, J.; Drlica, K. *Antimicrob. Agents Chemother*. **1998**, *42*, 956-958.
[7]. Jafri, H. S.; McCracken, G. H. *Drugs* **1999**, *58*, 43-48.
[8]. Andriole, T. V. *Drugs* **1999**, *58*, 1-4.
[9]. Drlica, K.; Zhao, X. *Microbiol. Mol. Biol. Rev*. **1997**, *61*, 377-392.
[10]. Mitscher, L. A. Chem. Rev., **2005**, *105*, 559-592.
[11]. Garcia, G. F.; Cercenado, E.; Martin, P. J.; Cuevas, O.; Bouza, E. *J. Antimicrob. Chemother.* **2001**, *47*, 681-684.
[12]. Kim, J. H.; Kang, J. A.; Kim, Y. G.; Kim, J. W.; Lee, J. H.; Kim, B. K. *Antimicrob. Agents Chemother.* **1997**, *41*, 2209-2213.
[13]. Meena, C. *J. Pharm. Res.* **2012**, *25*, 324-326.
[14]. Huang, W.; Zhao, P. L.; Liu, C. L.; Chen, Q.; Liu, Z. M.; Yang, G. F. *J. Agr. Food Chem*. **2007**, *55*, 3004-3010.
[15]. John, R. P.; Maurizio, D. P.; Wiley, A.; Schell, R. R. *Antimicrob. Agents Chemother.* **1998**, *42*, 2503-2510.
[16]. Barbara, G; Tatiana, F.; Thomas, L. G. *Bioorg. Med. Chem.* , **2004**, *12*, 103-112.
[17]. Campbell, M. J. M.; Grzeskowiak, R.; Juneja, G. S. *J. Inorg. Nucl. Chem.* **1978**, *40*, 1507-1511.
[18]. Ono, K.; Yoshida, A.; Saito, N.; Fujishima, T.; Honzawa, S.; Suhara, Y.; Kishimoto, S.; Sugiura, T.; Waku, K.; Takayama, H.; Kittaka, A. *J. Org. Chem*. **2003**, *68*, 7407-7415.
[19]. Villanova, P. A. Performance Standards for Antimicrobial Disk Susceptibility Tests, 5th edition, Approved Standard M7-A5, NCCLS, 2000.
[20]. Linday, M. E. Practical Introduction to Microbiology, E and F. N. Spon Ltd., United Kingdom, 1962.
[21]. Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4907-4913.