© 2018 IJSRSET | Volume 4 | Issue 4 | Print ISSN: 2395-1990 | Online ISSN : 2394-4099
Themed Section : Engineering and Technology

Synthetic Strategy, Characterization and Antimycobacterium Evaluation of 8-Hydroxy Quinoline Derivatives

Perumal Sarojini*[1], Malaichamy Jeyachandran[2], Vagolusivakrishna[3], Dharmarajan Sriram[3]

[1]Department of Chemistry, Sri S. Ramasamy Naidu Memorial College, Sattur, Virudhunagar, Tamil Nadu, India.

[2]Post Graduate and Research Department of Chemistry, Sri Paramakalyani College, Alwarkurichi, Tirunelveli, Tamil Nadu, India

[3]Department of Pharmacy,Birla Institute of Technology & Science-Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad, India

ABSTRACT

8-hydroxyquinoline derivatives are privileged structures for the design of new drug candidates. Due to its synthetic versatility, it holds many biological activities such as antibacterial, antifungal, immunosuppressive, analgesic, vasorelaxing, antiplasmodial, anticancer and antimycobacterium activity. In the present study, a series of 3-(substituted aryl)-1-(quinolin-8-yloxy) propan-2-ol were prepared and characterized. Primary *in vitro* screening of the synthesized compounds was performed against mycobacterium tuberculosis H37Ra. A significant decrease of mycobacterial cell metabolism (viability of M. *tuberculosis* H37Ra) was observed using MTB MABA assay. The structures of the compounds are elucidated with the aid of fourier transform infrared, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance spectral techniques.

Keywords: 8-hydroxyquinolines**,** Synthetic statergy, *In vitro* antimycobacterial activity**,** MTB MABA assay

I. INTRODUCTION

Tuberculosis is one of the world's deadliest communicable diseases and challenging worldwide health problem. Global plan to stop the tuberculosis "stop TB", WHO has estimated, 2006-2015, 1.3 million MDR-TB cases were treated in the 27 high MDR-TB burden countries between the years 2010-2015[1]. It is estimated that between the years 2005 to 2020, one billion people will be newly infected, over 125 million people will get sick and 30 million will die of tuberculosis if control is not further strengthened [2]. Mycobacterium tuberculosis is the pathogen responsible for TB [3]. Quinoline derivatives possess diverse pharmacological activities including antimicrobacterial, antitumour, caspase-3-inhibitors, anti-inflammatory activities[4-6], antileishmanial[7,8], antihypertensive, antirhythmics, schistomicidal activity, and cardiotonic activity [9-12] due to the broad range of biological activities. Quinoline compounds have been considered to be good starting materials for the search of novel pharmacological active compounds[13]. These compounds are interesting because they can perform as structurally related subunits in important biomolecules or biochemical process[14]. Among heterocyclic compounds, quinoline scaffold has become an important construction motif for the development of new drugs [15]. The interest in 8-hydroxyquinolines has grown exponentially in the last two decades as they are privileged structures for the design of new drug candidates that exert a host of biological effects on various targets [16]. The study of biological activities such as neuroprotection, anticancer, antibacterial, antifungal activity has been further promoted by the synthetic versatility of 8-hydroxyquinoline, which allows the generation of a large number of derivatives[17]. Quinoline is one of the most important N-based heterocyclic aromatic

compounds. It have been recently caught the attention of researchers because of their broad range of activities and of course for their wide applications too[18]. With the goal to discover novel antimycobacterium active compounds we have prepared seven 3-(substituted aryl)-1-(quinolin-8-yloxy)propan-2-ol.

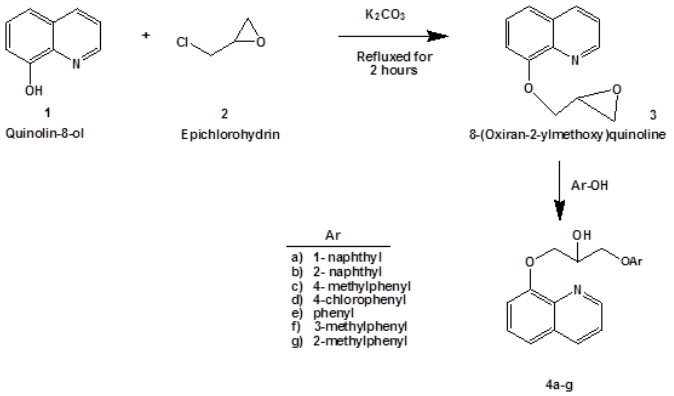
II. MATERIAL AND METHODS

The raw materials needed for the synthesis of 3-(substituted aryl)-1-(quinolin-8-yloxy)propan-2-ol such as 8-hydroxyquinoline, epichlorohydrin, potassium carbonate, phenols such as α-naphthol, β-naphthol, o-cresol, m-cresol, p-cresol, phenol, p-chlorophenol and other solvents were purchased from S.D Fine chemicals. All the solvents and chemicals were used directly without further purification. Fourier transform infrared (FT-IR) spectrometer using $CHCl_3$ and KBr. All ^1H and ^{13}C spectra were recorded on 500 MHz and 125 MHz (Brucker) spectrometers, respectively.

Typical procedure for the synthesis of 8-(oxiran-2ylmethoxy)quinoline (3) :

To the solution of 8-hydroxylquinoline (0.01mol), 1-chloro-2,3-epoxypropane(5ml) and K_2CO_3 (3g) were added and reaction mixture was refluxed for 1.30 hr. The reaction mixture was filtered and extracted with hot acetone (3*20ml) and the solvent was removed in vacuo. The residue was treated with cold water and the separated compound was extracted with ethylacetate. The solvent was removed in vacuo afforded the product. Colour : brown colour yield :90% . The confirmation of the product structure was done by H1NMR, ^{13}CNMR and IR spectroscopy.

Scheme 1



General procedure synthesis of 3-(substituted aryl)-1-(quinolin-8-yloxy) propan-2-ol.

To a solution of 8-(oxiran-2-ylmethoxy)quinoline (0.01 mol), appropriate phenol (0.01 mol) and K_2CO_3 (5 g) added and the solution was refluxed for 1.30 hr. The reaction mixture was filtered, the residue was extracted with acetone (3 x 20 mL) and the combined filtrate was concentrated and then treated with cold water. The residue obtained was extracted with ethyl acetate, and evaporate the solvent *in vacuo* to get desired product.

Characterization of synthesized compounds 4(a-g)

*1'-(naphthalen-1-yloxy)-3'-(quinolin-8-yloxy) propan-2'-ol, (**4a**)*

Viscous brown liquid: yield 80%; IR ($CHCl_3$): 3295, 1656, 1579, 1385, 1276, 1080, 773 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ/ppm 6.64 – 8.27 (m, 13H, Ar-H), 3.89 (s, 1H, 2'-OH), 3.67 (m, 1H, 2'-CH), 2.85 & 2.90 (m, 4H, 1'-CH_2 & 3'-CH_2); ^{13}CNMR ($CDCl_3$, 125 MHz) : δ = 155.4(C-O), 154.2(C-O), 148.4(C=N), 140.1(C-N), 135.5(Ar-C), 134.5 (Ar-C), 134.4(Ar-C), 129.2(Ar-C), 127.5(Ar-C), 126.8(Ar-C), 126.6(Ar-C), 126.1(Ar-C), 125.4(Ar-C), 123.4(Ar-C), 121.5(Ar-C), 120.4(Ar-C), 117.3(Ar-C), 107.2(Ar-C), 107.1(Ar-C), 70.5(C-C), 70.1(C-C), 69.1(C-OH).

*1'-(naphthalen-2-yloxy)-3'-(quinolin-8-yloxy) propan-2'-ol, (**4b**)*

Viscous brown liquid: yield 85%; IR ($CHCl_3$): 3339 , 1655, 1631, 1513, 1459, 1390, 1215, 847, 748 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$): δ 6.54 – 7.74 (m, 13H, Ar-H), 3.8 (s, 1H, 2'-OH) 3.56 (m, 1H, 2'-CH), 2.88 & 2.96 (m, 4H, 1'-CH_2 & 3'-CH_2) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ =155.6(C-O), 155.4(C-O), 149.12(C=N), 140.2(C-N),135.5(Ar-C), 129.6(Ar-C), 129.5(Ar-C), ,129.4(Ar-C), 127.7(Ar-C), 126.9(Ar-C), ,126.8(Ar-C), 126.7(Ar-C), 124(Ar-C), 121.8(Ar-C), 118.1(Ar-C), 117.3(Ar-C), 107.3(Ar-C), 107.1(Ar-C), 70.2(C-C),70.1(C-C), 69.01(C-OH).

1'-(quinolin-8-yloxy)-3'-(p-tolyloxy)propan-2'-ol, ***(4c)***

Brown solid : yield 85%; mp 158-160 °C ; IR ($CHCl_3$): 3437, 1650-1600, 1631, 1009, 847, 748 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$): δ 6.87-8.86 (m, 10H, Ar-H), 4.81 (s, 1H, 2'-OH) 3.8 (m, 1H, 2'-CH), 2.90 & 2.98 (m, 4H, 1'-CH_2 & 3'-CH_2), 2.34(s,3H,CH_3) ; ^{13}C NMR ($CDCl_3$, 125 MHz) : δ =156.4(C-O), 155.4(C-O), 149.0(C=N), 140.1(C-N), 135.7(Ar-C), 130.02(Ar-C), 129.6(Ar-C), 129.6(Ar-C), ,129.4(Ar-C), 126.8(Ar-C), 126.9(Ar-C), ,126.8(Ar-C), 121.7(Ar-C), 117.3(Ar-C), 114.2(Ar-C), 107.1(Ar-C), 70.2(C-C), 70.1(C-C), 69.01(C-OH), 21.3 (CH_3).

1'-(4-chlorophenoxy)-3'-(quinolin-8-yloxy) propan-2'-ol, ***(4d)***

Viscous brown liquid: yield 75%; IR ($CHCl_3$): 3341 (OH str.), 1591, 1492, 1435, 1360, 1240, 1093, 825,643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 – 7.37 (m, 10H, Ar-H) , 3.50 (s, 1H, 2'-OH) , 3.00 (m, 1H, 2'-CH), 2.20 & 2.90 (m, 4H, 1'-CH_2 & 3'-CH_2) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.4(C-O), 155.3(C-O), 149.2(C=N), 140.3(C-N), 135.7(Ar-C), 130.5(Ar-C), 129.4(Ar-C), 126.8(Ar-C), 126.9(Ar-C), 126.8(Ar-C),125.9(Ar-C), 121.8(Ar-C), 121.7(Ar-C), 117.5(Ar-C), 114.2(Ar-C), 107.2(Ar-C), 70.2(C-C), 70.1(C-C), 69.01(C-OH).

1-phenoxy -3-(quinolin-8-yloxy) propan-2-ol ***(4e)***

Viscous brown liquid: yield 80 %; IR ($CHCl_3$): 3340(OH str.), 1591, 1492, 1435, 1360, 1240, 1093, 825,643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 – 7.37 (m, 11H, Ar-H), 4.8 (s, 1H, 2'-OH) , 4.1 (m, 1H, 2'-CH), 3.8 & 3.96(m, 4H, 1'-CH_2 & 3'-CH_2) ; ^{13}C NMR ($CDCl_3$, 125 MHz) : δ = 159.4(C-O), 155.4(C-O), 149.1(C=N), 140.0(C-N), 135.6(Ar-C), 129.4(Ar-C), 129.3(Ar-C), 126.8(Ar-C), 126.8(Ar-C), 121.8(Ar-C), 120.4(Ar-C), 117.2(Ar-C), 114.4(Ar-C), 114.3(Ar-C), 107.1(Ar-C), 70.2(C-C), 70.1(C-C), 69.1(C-OH).

1-(quinolin-8-yloxy)-3-(o-tolyloxy) propan-2-ol ***(4f)***

Brown solid : yield 85%; mp 177-180 °C; IR ($CHCl_3$): 3340(OH str.), 1591, 1492, 1435, 1360, 1240, 1093, 825,643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 – 7.37 (m, 10H, Ar-H), 4.81 (s, 1H, 2'-OH), 4.1 (m, 1H, 2'-CH) , 3.8 & 3.96(m, 4H, 1'-CH_2 & 3'-CH_2) 2.1 (s, 3H, –CH_3) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.4(C-O), 155.2(C-O), 149.3(C=N), 140.2(C-N), 135.6(Ar-C), 131.3(Ar-C), 129.3(Ar-C), 126.8(Ar-C), 126.7(Ar-C), 126.3(Ar-C), 121.8(Ar-C), 120.3(Ar-C), 117.3(Ar-C), 112.4(Ar-C), 107.1(Ar-C), 70.4(C-C), 70.1(C-C), 69.0(C-OH), 15.4(CH_3).

1-(quinolin-8-yloxy)-3-(m-tolyloxy) propan-2-ol ***(4g)***

Viscous brown liquid: yield 85%; IR ($CHCl_3$): 3340, 1591, 1492, 1435, 1360, 1240, 1093, 825,643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 – 7.37 (m, 10H, Ar-H) , 4.81 (s, 1H, 2'-OH), 4.1 (m, 1H, 2'-CH), 3.8 & 3.96(m, 4H, 1'-CH_2 & 3'-CH_2), 2.34 (s, 3H, –CH_3) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.4(C-O), 155.2(C-O), 149.1(C=N), 140.2(C-N), 139.1(Ar-C), 135.7(Ar-C), 129.3(Ar-C), 129.2 (Ar-C), 126.7(Ar-C), 121.8(Ar-C), 120.6(Ar-C), 117.3(Ar-C), 113.4(Ar-C), 11.4(Ar-C), 107.1(Ar-C), 70.2(C-C), 70.1(C-C), 69.1(C-OH), 21.7(CH_3).

Antimycobacterium studies: The anti-mycobacterium activities [20-23] the synthesized compounds were determined by *in vitro* MTB MABA assay.

In-vitro MTB MABA assay

Briefly, the inoculum was prepared from fresh LJ medium re-suspended in 7H9-S medium (7H9 broth, 0.1% casitone, 0.5% glycerol, supplemented oleic acid, albumin, dextrose, and catalase [OADC]), adjusted to

a McFarland tube No. 1, and diluted 1:20; 100 µl was used as inoculum. Each drug stock solution was thawed and diluted in 7H9-S at four-fold the final highest concentration tested. Serial two-fold dilutions of each drug were prepared directly in a sterile 96-well microtiter plate using 100 µl 7H9-S. A growth control containing no antibiotic and a sterile control were also prepared on each plate. Sterile water was added to all perimetre wells to avoid evaporation during the incubation. The plate was covered, sealed in plastic bags and incubated at 37°C in normal atmosphere. After 7 days incubation, 30 ml of alamar blue solution was added to each, and the plate was re-incubated overnight. A change in colour from blue (oxidised state) to pink (reduced) indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in colour.

III. RESULTS AND DISCUSSION

To a solution of 8-(oxiran-2-ylmethoxy)quinoline (**3**) (0.01 mol), appropriate phenol (0.01 mol) and K_2CO_3 (5 g) added and the solution was refluxed for 1.30 hrs. During the reaction, an epoxide (**3**) readily undergo reactions in which epoxide ring was opened by nucleophiles. A reaction is a SN^2 reaction in which epoxides oxygen serves as a leaving group which doesnot depart as a separate entity, but rather remains in the same product. Epoxide is very reactive because they posses significant angle strain, thus broken easily. Opening of epoxide relieves the strain of the three membered rings. Nucleophile typically reacts with unsymmetrical epoxides at the carbon with fewer alkyl substituents and provides the desired product.

The presence of hydroxyl group in compound **4a** was established by IR band at 3295 cm^{-1}. In the NMR spectra of **4a**, the two multiplets appears at δ 2.85 and 2.90 is due to 1' and 3'- methylene (1'-C<u>H</u>$_2$ & 3'-C<u>H</u>$_2$) groups. The multiplet at δ 3.67 is due to 2'- methine (2'-C<u>H</u>) group and the singlet at δ 3.89 is attributed to the 2'- hydroxyl group. The aromatic hydrogens appears as a multiplet in the region δ 6.64 – 8.27. In C13 NMR , aliphatic carbon (-CH_3) 21.3, aliphatic methylene carbon(1'-C<u>H</u>$_2$ & 3'-C<u>H</u>$_2$) appears at 70 whereas aromatic carbon appears at 117-156.

Antimycobacterium studies:

The compounds were screened for their in vitro antimycobacterium activity against MTB H37Rv by MABA assay for the determination of MIC. The MIC is defined as the minimum concentration of compound required to inhibit 99% of bacterial growth and MIC values of the synthesised compounds along with standard drugs for the comparison as shown in the Table 1. All the compounds belonging the series showed less significant activity than standard drugs Rifamycin, Ethambutol and Ciprofloxacin.The table data show that the compounds with 4-chlorophenyl, phenyl rings displays maximum potency when compared to other compounds.

Table 1. MIC values of compounds **4(a-g)**

Compounds	**MIC (µg/mL)**
4a	12.5
4b	12.5
4c	>25
4d	3.25
4e	12.5
4f	>25
4g	7.21
Isoniazid	0.1
Rifampicin	0.2
Ethambutol	1.56
Ciprofloxacin	1.56

MTB: *Mycobacterium tuberculosis*

IV. CONCLUSION

In conclusion, we have synthesized 3-(substituted aryl)-1-(quinolin-8-yloxy) propan-2-ol from 8-(oxiran-2ylmethoxy) quinoline and were screened for antitubercular activity. *Invitro* antitubercular activity of the title compounds against MTB H37Rv strain has

been evaluated**. 4** compounds showed MIC in the range of 3.125-12.5 (µg/Ml), showing their potential activity.

V. REFERENCES

[1]. Patel.R.V, Kumari P, Rajani D P, & Chikhalia K H, Acta Chim. Slov. , 2011, 58, 802-810.

[2]. Jeyachandran M, Ramesh P, Sriram D, Senthilkumar P, Yogeeswari P, Bioorganic Med. Chem. Lett., 2012, 22, 4807-4809; DOI: 10.1016/j.bmcl.2012.05.054

[3]. Kos J, Zadrazilova I, Nevin E, Soral M., Gonec T, Kollar P, Oravec M., Coffey A., O'Mahony J, Liptaj T, Kralova K, Jampilek J, Bioorganic Med. Chem., 2015, 23, 4188-96; DOI: 10.1016/j.bmcl.2016.07.021

[4]. Cherdtrakulkiat R, Boonpangrak S, Sinthupoom N, Prachayasittikul S, Ruchirawat S, Prachayasittikul V,Biochem Biophys Rep, 2016,6, 6135-141; DOI: 10.1016/j.bbrep.2016.03.014

[5]. Chan S H, Chui C H, Chan S W, Kok S H L, Chan D, Tsoi M .Y T, Leung P H M, Lam A K Y, Chan A S C,Lam K H & Tang J C O, ACS Med Chem Lett., 2013 , 4(2), 170-174.

[6]. Deshmukh N, Das P, Karma K., Pharmaceutical And Biological Evaluations, 2016, 3, 135-139.

[7]. Ukrainets I V, Mospanova E V, Davidenko A A, Tkach and Gorokhova O V, Chem. Heterocycl.Compd., 2010, 46(8), 947-956; DOI:10.1007/s10593-010-0607

[8]. Y Song , H Xu , W Chen , P Zhan and Liu X , Med. Chem. Commun., 2015, 6, 61-74;DOI: 10.1039/C4MD00284A

[9]. Duarte M C, L M dos Reis Lage, Lage D P, Vet. Parasitol,2016, 217, 81-88; DOI:10.1371/journal.pone.0167638

[10]. Naik R N, Patil S C and Satyanarayan S B, Indo American Journal of Pharmaceutical research, 2014, 4(9) 3763-3772.

[11]. Vavsari V F, Ziarani G M, Balalaie S, Latifi A, Karimi M, Tetrahedron, 2016, 72, 5420-5426. DOI: 10.1016/j.tet.2016.07.034

[12]. Allam G, Ahmad F Eweas, Abdelaziz S A Abuelsaad, J Parasitol Res, 2013, 112(9), 3137-3149; DOI; 10.1007/s00436-013-3490-4.

[13]. Marella A, Tanwar O P, Saha R, Ali M R, Srivastava S, Akhter M, Shaquiquzzaman M, Alam M M, Saudi Pharm J., 2013, 21, 1-12. DOI: 10.1016/j.jsps.2012.03.002.

[14]. E M Kassem, Eslam R El-Sawy , Howaida I Abd-Alla, Adel H Mandour, Dina Abdel-Mogeed and Mounir M El-Safty Arch Pharm Res, 2012 ,35, 955-964, DOI :10.1007/s12272-012-0602-0.

[15]. Jahromia B T, Kharata A N, Foroutannejadb S, Res. J. Pharm., Biol. Chem. Sci. 2011 , 2(2), 61-71.

[16]. Jain S, ChandraV , Jain P K, Pathak K, Pathak D, Vaidya A, Arab. J. Chem, 2016, 1-27 DOI:10.1016/j.arabjc.2016.10.009.

[17]. Oliveri V.,& Vecchio G., Eur. J. Med. Chem, 2016 , 14;120:252-74. DOI: 10.1016/j.ejmech.2016.05.007.

[18]. Eweas A F, Allam G, Abuelsaad A S A., A Hamid AL Ghamdi , Ibrahim A Maghrabi, Bioorganic Med. Chem., 2013, 46, 17-25 DOI: 10.1016/j.bioorg.2012.

[19]. Prajapati S M, Patel K D, Vekariya R H, Panchaland S N, Patel H D RSC Adv., 2014, 4, 24463-24476, DOI: 10.1039/C4RA01814A.

[20]. Musiol R, Jampilek J, Nycz J E, Pesko M, Carroll J, Kralova K , Vejsova M, Mahony J O', Coffey A, Mrozek A and Polanski J, Molecules, 2010, 15, 288-304, DOI:10.3390/molecules15010288.

[21]. Dover L G and Coxon G D, J. Med. Chem.2011, 54, 6157- 6165, DOI: 10.1021/jm200305q

[22]. Bonde C G, Peepliwal A, Gaikwad N , J. Arch. Pharm. Chem. Life Sci. ,2010, 343, 228-236.10.1002/ardp.200900165.

[23]. Wube A A, Bucar F, Hochfellner C, Blunder M, Bauer R,Hüfner A, Eur. J. Med. Chem., 2011, 46, 2091-2101;DOI:10.1016/j.ejmech.2011.02.062