Review Article

An overview on antitubercular activity profile of fluoroquinolone derivatives and their molecular hybridization

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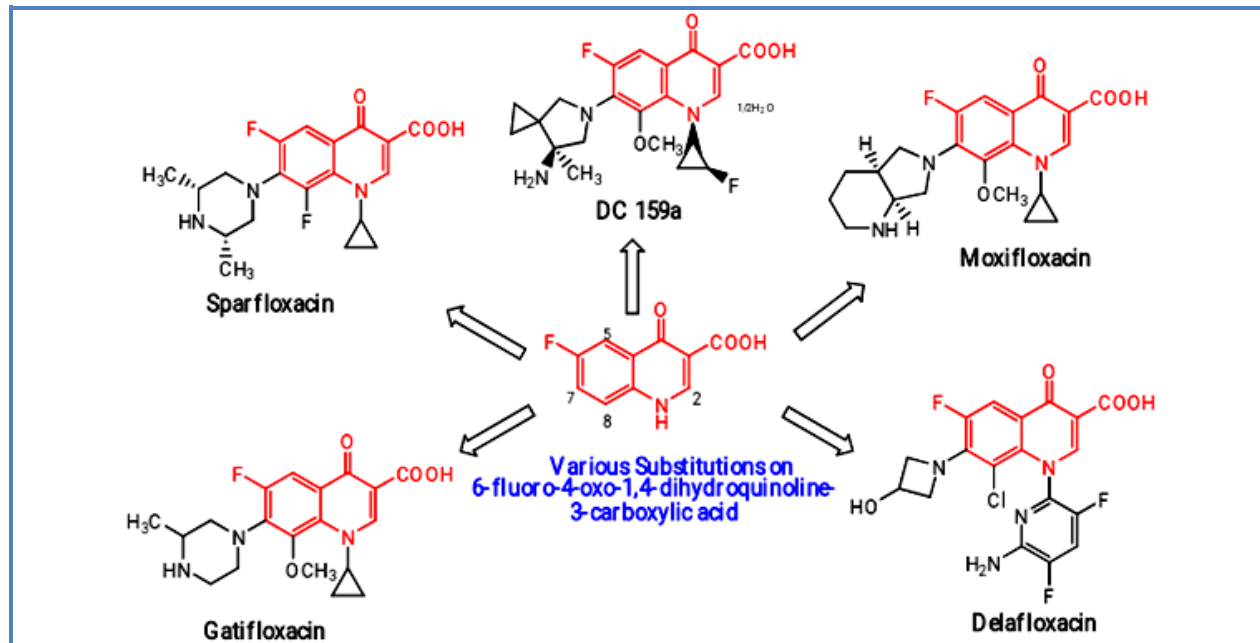
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ABSTRACT

Tuberculosis (TB) has been one of the main causes of morbidity, and the emergence of multi-drug resistant (MDR) *Mycobacterium tuberculosis* strains has become a major concern. The decrease in activity of the major anti-TB drugsincluding, isoniazid, and rifampicin is an important threat that requires an urgent therapy. Anti-TB activity of the fluoroquinolones (FQs) has been under investigation. Many FQs are active in vitro; however, only a few such as ofloxacin, ciprofloxacin, sparfloxacin, levofloxacin, Moxifloxacin, and gatifloxacin have been clinically tested. The FQs can be used in co-therapy with the available anti-TB drugs. Molecular hybridization is a concept of drug design and development based on combination of pharmacophoric moieties of various bioactive compounds to produce a new hybrid compound with improved affinity and efficacy compared with the present drugs.

Journal of Medicinal and Chemical Sciences: http://www.jmchemsci.com/

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Graphical Abstract

Sparfloxacin · DC 159a · Moxifloxacin · Gatifloxacin · Delafloxacin · Various Substitutions on 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Introduction

Currently the World Health Organization (WHO) only recommends fluoroquinolones (FQs) for people with presumed drug-sensitive tuberculosis (TB) who are not able to take standard first-line drugs. However, use of FQs could shorten the length of the treatment. This review summarizes the effects of FQs in first-line regimens in people with presumed drug-sensitive TB. Ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin have been tested for the standard first-line regimens based on the rifampicin and pyrazinamide for the treating drug-sensitive TB. There is insufficient evidence on whether addition or substitution of FQs for ethambutol or isoniazid in the first-line regimen reduces death or changes the culture conversion after eight weeks. Much larger trials with FQs in short course regimens of four months are currently in progress [1-5]. Among the new compounds that have been tested for their efficacy in TB treatment, the FQs are the first novel drugs since they show a significant activity against the *Mycobacterium tuberculosis*

(*Mt*b). Currently, FQs are used as anti-TB agents in MDR-TB. The FQs are not included at present in the first-line treatment of TB; however, that might change in the future to shorten the treatment duration. The newer FQs, MXF, and gatifloxacin have shown antitubercular activity associated with a lower probability of emergence of resistance [6-8].

The design of new drugs with better physiochemical properties, adequate absorption, distribution, metabolism, and excretion along with effective pharmacologic potency and lack of toxicity for the treatment of infectious diseases has suffered a continuous decrease. Development of such molecular frameworks with synthetic selectivity and economic accessibility still represents a big challenge for pharmaceutical sector, demanding continuous efforts. An emerging strategy within medicinal chemistry and drug discovery is a combination of two distinct pharmacophores into a single molecule, which is well documented as molecular hybridization [7, 8].
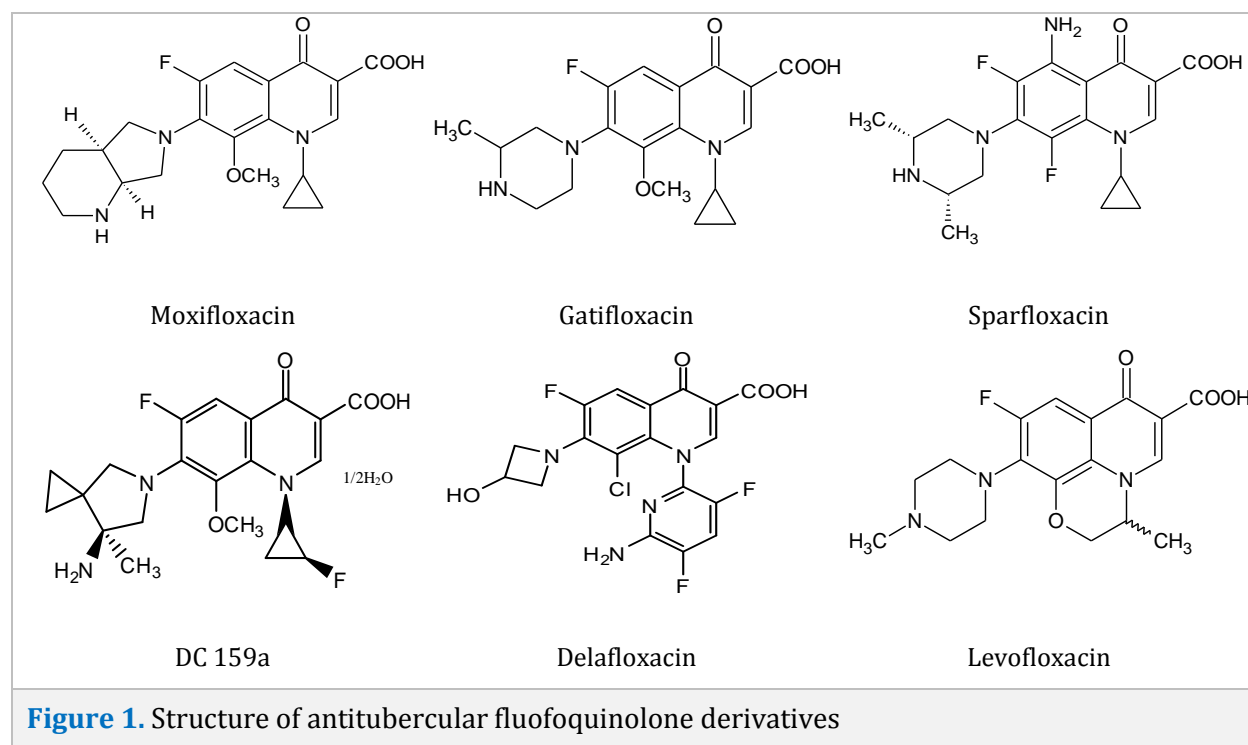
Figure 1. Structure of antitubercular fluofoquinolone derivatives

Moxifloxacin

Moxifloxacin (MFX) is fourth-generation synthetic FQs (initially called BAY 12-8039). The MFX is used eye drops for treatment of the conjunctivitis (pink eye). Its antibacterial spectrum includes enteric Gram-(−) rods (*Escherichia coli*, *Proteus* species, *Klebsiella* species), *Haemophilus influenzae*, atypical bacteria (*Mycoplasma*, *Chlamydia*, *Legionella*), and *Streptococcus pneumoniae*, and anaerobic bacteria. It differs from earlier antibacterials of the FQ class such as levofloxacin and ciprofloxacin in having greater activity against the Gram-positive bacteria and anaerobes. Due to the potent activity against the common respiratory pathogen *Streptococcus pneumoniae*, FQs is considered a respiratory quinolone. MFX is used for treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, complicated, and uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. MFX may cause muscle weakness and life-threatening breathing problems. MFX is used to treat many infections including, chronic bronchitis, acute bacterial sinusitis, community acquired pneumonia, respiratory tract infections, cellulitis, anthrax, intraabdominal infections, endocarditis, meningitis, and tuberculosis. In ophthalmology, MFX is approved for the treatment of conjunctival infections caused by susceptible bacteria [9-13].

The excellent in vitro activity of MXF translates into activity in the human host. Structure of Moxifloxacin is shown in Figure 1. Results of a comprehensive preclinical evaluation of the safety of MFX are consistent with those reported for other fluoroquinolones. Most of the findings (such as arthrotoxicity in juvenile animals and CNS toxicity) that have led to restrictions in the use of quinolones in general were also observed with MFX. In addition, MFX has a good EBA against MTB in patients with drug-susceptible TB. Its extended EBA activity from days 2 to 7, a putative

surrogate marker of sterilizing activity, may be slightly higher compared with that of the INH [88-90]. Substitution of MFX for INH in the standard regimen increased potency and reduced the course of TB therapy to 4 months or less. In contrast, substitution of MFX for EMB in the standard regimen did not have any effect on 2-month sputum culture status, which increased the frequency of negative cultures at earlier time points among patients with the smear-positive PTB. Therefore, MFX has sterilizing activity, instead insufficient activity when used in the manner evaluated in this trial (i.e., added to INH, RIF, and PZA) to support treatment shortening based on the surrogate marker of 2-month culture conversion [14-16].

Gatifloxacin

Gatifloxacin is an antibiotic of the fourth-generation fluoroquinolone family [1], inhibiting the bacterial enzymes DNA gyrase and topoisomerase IV. Gatifloxacin is used for treatment of the respiratory tract infections. Gatifloxacin is also available as tablets and in various aqueous solutions for intravenous therapy. Therefore, the systemic exposures resulting from the gatifloxacin ophthalmic solution are not likely to pose any risk for the systemic toxicities [17-19].

Gatifloxacin has also excellent EBA, only slightly less than that of the INH, and greater extended EBA. Gatifloxacin was evaluated alone and in combination with ethionamide, PZA, and EMB. Ethionamide appeared to be the most promising single agent used in combination with ratifloxacin. Gatifloxacin-ethionamide-PZA and EMB would likely be an effective regimen for treatment of MDR-TB. In the Randomized Clinical Trial that was conducted by substituting EMB for new drugs in the standard regimen, the response at the end of treatment was uniformly high in all regimens, with 95%-98% of the patients treated with a thrice-weekly 4-month

gatifloxacin and MFX regimens, respectively, which became culture negative at the end of treatment, compared to 97% in the standard regimen [20-22].

DC-159A

The DC-159a is a newly synthesized broad spectrum 8-methoxy fluoroquinolone (8-CH$_3$-FQ) with a potent activity against quinolone-resistant (QR) and the multidrug resistant (MDR-TB). This compound has potent activities against various respiratory pathogens such as QR strains.DC-159a exhibits high inhibitory activity against the altered DNA gyrases with substitutions Ala90Val andAsp94Gly in *GyrA* as well as wild-type enzyme of *M. tuberculosis* (*Mtb*), DNA replication. A G88C mutation in *GyrA* is one of the key alterations to acquire DC-159a resistance in *Mtb* mutants *in vitro*. DC-159a showed better *in* activities against QR-MDR-TB than some other FQs. DC-159a has MIC90 0.06 μg/mL against *Mtb*, which is 4 and 8 times lower than that of the MXF and levofloxacin (LVFX), respectively. The MIC$_{90}$ of DC-159a was 0.5 μg/mL against the clinical MDR-TB isolates which are resistant to other FQs (MXF and LVFX MIC$_{90}$ is 4 and 16 μg/mL, respectively) [23-26].

Delafloxacin

Delafloxacin (code name RX-3341), a FQ antibiotic, is more active (lower MIC$_{90}$) than other quinolones against Gram-positive bacteria such as MRSA. In contrast to the most approved FQs, which are zwitterionic, delafloxacin has an anionic character, resulting in a 10-fold increase in delafloxacin accumulation in both bacteria and cells at acidic pH. This property is believed to confer delafloxacin an advantage for the eradication of *Staphylococcus aureus* in acidic environments, including intracellular infections [27-29].

Sparfloxacin

Sparfloxacin is a FQ antibiotic used in the treatment of bacterial infections. It has a controversial safety profile. The compound is indicated for treating community-acquired lower respiratory tract infections (acute sinusitis, exacerbations of chronic bronchitis caused by susceptible bacteria, community-acquired pneumonia). Sparfloxacin, like other quinolones and FQs, are bactericidal drugs, actively killing bacteria. Quinolones inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, thereby inhibiting the DNA replication and transcription. Quinolones can enter cells easily and therefore are often used to treat intracellular pathogens such as *Legionella pneumophila* and *Mycoplasma pneumoniae*. For many gram-negative bacteria DNA gyrase is the target, whereas topoisomerase IV is the target for many gram-positive bacteria [30-35].

Levofloxacin

Levofloxacin (isomer of oflaxacin) is a second-generation FQ synthetic compound, which has a broader spectrum analog of norfloxacin. Ofloxacin treat bacterial sinusitus, bacterial exacerbations of bronchitis, community-acquired pneumonia, uncomplicated skin infections, complicated urinary tract infections, and acute pyelonephritis. Levofloxacin is the levo isomer of the racemate ofloxacin. In chemical terms, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (−)-(*S*)-enantiomer of the racemic of loxacin [36-38].

Fluoroquinolone (FQs), a broad-spectrum antibiotic, is active against both Gram-positive and Gram-negative bacteria. However, the choice of FQs should be based not only on the in vitro activity, but also on the long-term tolerance. The FQs are novel anti-TB drugs to be used when a patient is infected with a MDR-TB strain. Like all quinolones, FQs acts by inhibiting the two type-II topoisomerase enzymes, namely DNA gyrase and topoisomerase-IV. Topoisomerase-IV is necessary to separate DNA that has been replicated (doubled) prior to bacterial cell division. If the DNA is not separated, the process will be stopped, and the bacterium cannot divide. DNA gyrase, on the other hand, is responsible for supercoiling the DNA, so that it will fit in the newly formed cells. Both mechanisms amount to killing the bacterium. In this way, fluoroquinolone acts as a bactericide. Eukaryotic cells do not contain DNA gyrase or topoisomerase IV [39, 40].
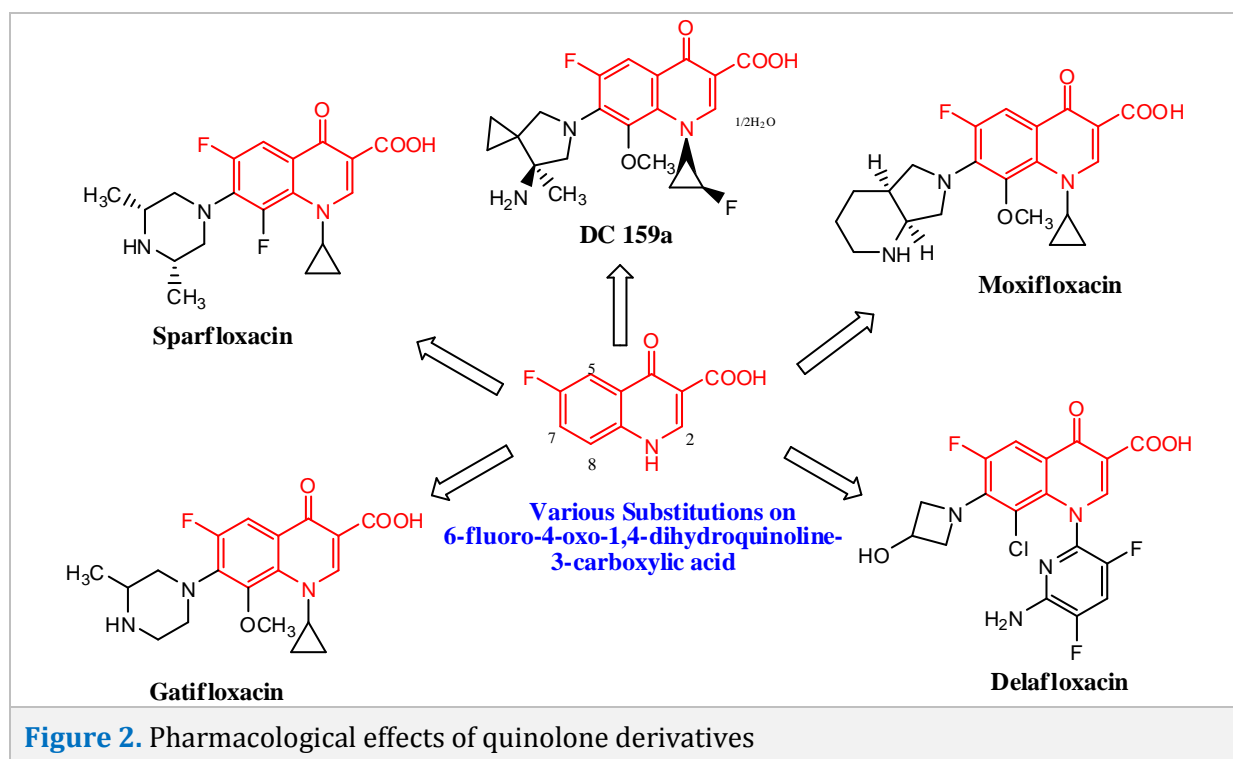
Molecular hybridization

Molecular hybridization is a molecular modification approach to obtain multiple-ligands compounds with pharmacokinetic advantages over concomitant administration of two different drugs [7, 8]. The advantages of the multiple ligands are their ability to activate different targets by a single molecule, thereby increasing therapeutic efficacy and to change the bioavailability profile in the cell and be effectively eliminated after exerting their effects [41]. Hybridization process is related to the strategy of obtaining a mutual prodrug, with the main difference being that the prodrug action is dependent on its *in vivo* cleavage while hybrid compounds can also act "*per se*" at their specific receptors or targets. Hybrid compounds can be constructed by linking pharmacophore subunits directly or with spacer agents. The simple association of two distinct active principles can also be considered as a hybrid compound [42]. Molecular hybridization is a drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Additionally, this strategy can result in

compounds presenting the modified selectivity profile with different and dual modes of action and hence reduced the undesired side effects. The molecular hybridization of more than one biolabile moiety is an organized and chief technique to expand the vicinity of medicinal chemistry research. It involves the combination of separate pharmacophoric groups of analogous activity into one compound, causes substantial changes in the biological activity. Molecular hybridization is a structural modification strategy useful in the design of new optimized ligands and prototypes with new molecular architectures composed of two or more known bioactive derivatives, through the adequate fusion of these sub-unities [43-48].

In recent years, medicinal chemists have modified the quinolone scaffold to develop novel heterocycles with fascinating anti-tubercular and anti-microbial activities. A number of modifications have been made on the benzenoid ring (C-5, C-6, C-7 and C-8 positions) of quinolone to optimize its pharmacology; however, modifications on the pyridinone ring (C-2, C-3 and C-4) are still less common (Figure 2) [49-52]. On the other hand, new chemical entities are also in progress based on optimization of Isonicotin-ylhydrazine (INH) with various chemical scaffolds to get better anti-tubercular activity. In spite of the immense pharmacological effects of quinolone derivatives and INH, not many research studies have been conducted on synthesis of a heterocycles incorporating and evaluating their anti-microbial and anti-tubercular activities [53-59].

Figure 2. Pharmacological effects of quinolone derivatives

Biquinolone-isoniazid hybrids were designed (Figure 3) based on molecular hybridization technique and synthesized *via* multicomponent cyclocondensation (MCC) approach [58, 59].

Figure 3. Design of biquinolone-INH hybrids
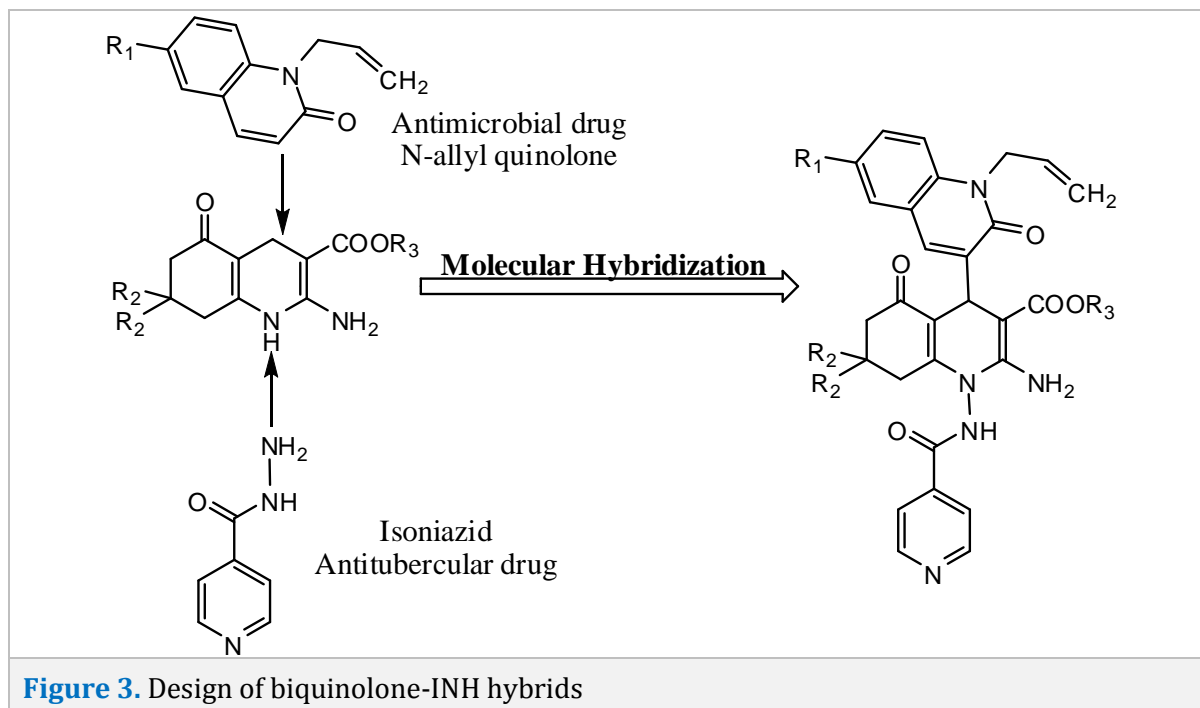
The synthesized compounds were screened for their anti-microbial and anti-tubercular activities. Certain hybrid molecules exhibited excellent anti-microbial activity compared with that of the standard drugs; whereas few molecules displayed 99% inhibition against *Mycobacterium tuberculosis* bacteria.

Conclusion

Fluoroquinolone derivatives are known as the promising anti-infective agents. Various substituted fluoroquinolone derivatives have been effective against the gram negative, gram positive and resistance bacteria strains as well as *Mycobacterium tuberculosis*. These drugs have DNA gyrase, inhibiting the bacterial growth. Fluoroquionlones have attracted a great deal of attention due to their good bioavailability, tissue penetrability, and relatively low incidence of adverse and toxic effects. They are effective in treatment of various infectious diseases. This review presented some significant information regarding the therapeutic prospects of fluoroquinolones as atitubercular agents.

Conflict of interest

We have no conflicts of interest to disclose.

References

[1]. Ziganshina L.E., Titarenko A.F., Davies G.R. *Cochrane Database Syst Rev.* 2013, 6:CD004795

[2]. Asif M., Siddiqui A.A., Husain A. *Med. Chem. Res.*, 2013, **22**:1029

[3]. Asif M. *Orient. Pharm Exp. Med.*, 2012, **12**:15

[4]. Asif M. *Indian drugs.*, 2012, **49**: 5

[5]. Asif M. *Mini Rev. Med. Chem.,* 2012, **12**: 1404

[6]. Bryskier A., Lowther J. Expert Opin. Inv. Drug., 2002, **11**:233

[7]. Iseman M.D. *Eur. Respir. J.,* 2002, **36**:S87

[8]. Manika K., Kioumis I. *Pneumon.*, 2008, **21**:395

[9]. Karande S.C., Kshirsagar N.A. *Indian. Pediatr.*, 1992, **29**: 181

[10]. Dolui S.K., Das M., Hazra A. *J. Postgrad Med.*, 2007, **53**: 144

[11]. Drlica K., Zhao X. *Microbiol Mol. Biol. Rev.*, 1997, **61**: 377

[12]. Alffenaar J. W. C, van Altena R., Bökkerink H. *Clin. Infec. Dis.*, 2009, **49**: 1080

[13]. Peterson U. *Quinolone Antibiotics: The Development of Moxifloxacin. In IUPAC. Analogue-based Drug Discovery.* John Wiley & Sons. pp. 2006, 338–342

[14]. Gosling R.D., Uiso L.O., Sam N.E., et al. *Am. J. Respir. Crit. Care. Med.*, 2003, **168**:1342

[15]. Von Keutz E., Schluter G. *J. Antimicrob Chemother.*, 1999, **43**:91

[16]. Johnson J.L., Hadad D.J., Boom W.H., et al. *Int. J. Tuberc Lung. Dis.*, 2006, **10**:605

[17]. Burka J.M., Bower K.S., Vanroekel R.C., Stutzman R.D., Kuzmowych C.P., Howard R.S. *Am. J. Ophthalmol.,* 2005, **140**: 83

[18]. Park-Wyllie L.Y., Laura Y., Juurlink D.N., Kopp A., Shah B.R., Stukel T.A., Stumpo C., Dresser L,. Low D.E., Mamdani M.M. *The New Eng. J. Med.,* 2006, **354**: 1352

[19]. Jerry H. G. *The New Eng. J. Med.,* 2006, **354**: 1413

[20]. Nuermberger E.L., Yoshimatsu T., Tyagi S., et al. *Am. J. Respir. Crit. Care Med.*, 2004, **169**:421

[21]. Burman W.J., Goldberg S., Johnson J.L. *Am. J. Respir. Crit. Care. Med.*, 2006, **174**: 331

[22]. Alvirez-Freites E.J., Carter J.L., Cynamon M.H. *Antimicrob. Agents Chemother*, 2002, **46**:1022

[23]. Okumura R., Hirata T., Onodera Y., Hoshino K., Otani T., Yamamoto T. *J. Antimicrob. Chemother.*, 2008, **62**: 98

[24]. Hoshino K., Inoue K., Murakami Y., Kurosaka Y., Namba K., Kashimoto Y., Uoyama S., Okumura R., Higuchi S., Otani T. *Antimicrob. Agents Chemother.,* 2008, **52**: 65

[25]. Disratthakit A., Doi N. *Antimicrob. Agents Chemother.,* 2010, **54**: 2684

[26]. Ahmad Z., Minkowski A., Peloquin Williams K.N., Mdluli K.E., Grosset J.H., Nuermberger E.L. *Antimicrob. Agents Chemother.*, 2011, 1781

[27]. Kocsis B., Domokos J., Szabo D. *Ann. Clin. Microbiol. Antimicrob.,* 2016, **15**:34

[28]. Hoover R., Hunt T., Benedict M., Paulson S.K., Lawrence L., Cammarata S., Sun E. *Clin. Ther.*, 2016, **38**: 53

[29]. Van Bambeke F. *Future. Microbiol.*, 2015, **10**:1111

[30]. Psaty B.M. *Clin. Infect. Dis.*, 2008, **47 Suppl 3**: S176

[31]. Shimada J., Nogita T., Ishibashi Y. *Clin. Pharmacokinetics.*, 1993, **25**: 358

[32]. Rubinstein E. *J. Antimicrob. Chemother.*, 1996, **37 Suppl A**: 145

[33]. Stein G.E., Havlichek D.H. *Pharmacother*, 1997, **17**: 1139

[34]. Zhanel G.G., Ennis K., Vercaigne L., Walkty A., Gin A.S., Embil J., Smith H., Hoban D.J. *Drugs,* 2002, **62**: 13

[35]. Rubinstein E. *The J. antimicrobchemother*, 1996, **37 Suppl A**: 145

[36]. Noel G.J., Bradley J.S., Kauffman R.E. *Pediatr. Infect. Dis. J.*, 2007, **26**: 879

[37]. Carbon C. *Chemother.*, 2001, **47**:9

[38]. Liu H.H. *Drug. Saf.*, 2010, **33**: 353

[39]. Stahlmann R., Lode H.M., *Expert. Opin. Drug. Saf.*, 2013, **12**: 497

[40]. Bosso J.A. *J. Infec. Dis. Pharmacother.*, 1998, **2**: 61

[41]. Morphy R., Kay C., Rankovic Z. *Drug. Discov. Today.,* 2004, **9**: 641

[42]. Bosquesi P.L., Melo T.R.F, Vizioli E.O., Santos J.L., Chung M.C. *Pharmaceuticals.,* 2011, **4**: 1450

[43]. Viegas-Jr C., Danuello A., Bolzani S.V., Barreiro E.J., Fraga C.A.M. *Curr. Med. Chem.,* 2007, **14**: 1829

[44]. Borges L.G., Froehlich P.E. *Rev. Assoc. Med. Bras.*, 2003, **49**: 96

[45]. Ugale V.G., Patel H.M., Wadodkar S.G., Bari S.B., Shirkhedkar A.A., Surana S.J. *Eur. J. Med. Chem.,* 2012, **53**: 107

[46]. Shi L., Hu R., Wei Y., Liang Y., Yang Z., Ke S. *Eur. J. Med. Chem.,* 2012, **53**: 107

[47]. Du L., Li M., Yang Q., Tang Y., You Q., Xia L. *Bioorg. Med. Chem. Lett.,* 2009, **19**:1477

[48]. Ranjeet B., Manoj K., Nilesh R.T., Jaya L., Ray M.K., Rajan M.G.R., Degani M.S. *Bioorg. Med. Chem. Lett.,* 2010, **20**: 1623

[49]. Reck F., Alm R.A., Brassil P., Newman J.V., Ciaccio P., Mc Nulty J., Barthlow H., Goteti K., Breen J., Comita-Prevoir J., Cronin M., Ehmann D.E., Geng B., Godfrey A.A., Fisher S.L. *J. Med. Chem.,* 2012, **55**: 6916

[50]. Chai Y., Liu M.-L., Lv K., Feng L.-S., Li S.-J., Sun L.-Y., Wang S., Guo H.-Y. *Eur. J. Med. Chem.,* 2011, **46**: 4267

[51]. Plech T., Wujec M., Kosikowska U., Malm A., Rajtar B., Polz-Dacewicz M. *Eur. J. Med. Chem.,* 2013, **60**: 128

[52]. Qi Q.R., Pan J., Guo X.-, Weng L.-, Liang Y.-F. *Bioorg. Med. Chem. Lett.,* 2012, **22**: 7688.

[53]. Manjashetty T.H., Yogeeswari P., Sriram D. *Bioorg. Med. Chem. Lett.,* 2011, **21**: 2125.

[54]. Torres E., Moreno E., Ancizu S., Barea C., Galiano S., Aldana I., Monge A., Pérez-Silanes S. *Bioorg. Med. Chem. Lett*., 2011, **21**: 3699

[55]. Ramani A.V., Monika A., Indira V.L., Karyavardhi G., Venkatesh J., Jeankumar V.U., Manjashetty T.H., Yogeeswari P., Sriram D. *Bioorg. Med. Chem. Lett.,* 2012, **22**: 2764

[56]. Almeida da Silva P.E., Ramos D.F., Bonacorso H.G., de la Iglesia A.I., Oliveira M.R., Coelho T., Navarini J., Morbidoni H.R., Zanatta N., Martins M.A.P. *Int. J. Antimicrob. Agents.,* 2008, **32**: 139

[57]. Myangar K.N., Raval J.P. *Med. Chem. Res.,* 2012, **21**: 2762

[58]. Hardik H.J., Patel M.P. *Eur. J. Med. Chem*., 2013, **65**: 348

[59]. Romeo R., Baraldi P.G, Salvador M.K., Camacho M.E., Balzarini J., Bermejo J., Francisco E. *Eur. J. Med. Chem.,* 2013, **63**: 544