International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 5 Issue 2, January-February 2021 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Anti-Infective Fluoroquinolone Derivatives-An Update of Recent Patents

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ABSTRACT

Fluoroquinolones are well known and among most promising nitrogen containing heterocyclic compounds depicting broad spectrum and potent activities. This article is focussed on the recent patents of fluoroquinolone anti-infective agents including ciprofloxacin, norfloxacin and ofloxacin. Numerous fluoroquinolone derivatives have been found to possess considerable biological activities, which stimulate the research in this field. Fluoroquinolone show several favourable properties like excellent bioavailability, good tissue penetrability and low toxic effects thereby having major pharma- economical advantages over other antibiotics. The primary target for fluoroquinolones is DNA and cellular death is caused by irreversible formation of a ternary fluoroquinolone DNA-DNA gyrase complex. The present review illustrates an insight view on different aspects of fluoroquinolones including chemistry along with the compilation of recent patents of fluoroquinolones and their important derivatives.

KEYWORDS: *Anti-infective, ciprofloxacin, fluoroquinolones, norfloxacin, ofloxacin, patents*

How to cite this paper: Sugandha Sethi | P. K Sahoo "Anti-Infective Fluoroquinolone Derivatives-An Update of Recent Patents" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-5 | Issue-2, February 2021, pp.542-550, URL: www.ijtsrd.com/papers/ijtsrd38474.pdf

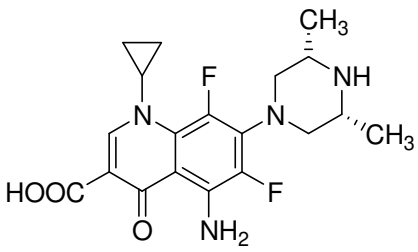
IJTSRD38474

INTRODUCTION

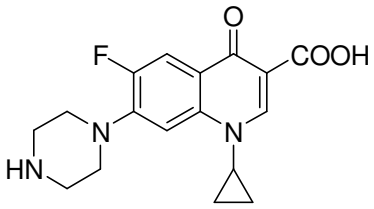
Despite a large number of antibiotics available for medical use, the emergence of resistance towards old and new antibiotics in the last decades has created a substantial medical need for new class of antibacterial agents [1]. In recent years, advanced research endeavours are being undertaken across the globe to synthesize novel derivatives of these drugs with improved properties [2]. As a result of intensive research endeavours, flouroquinolone class has emerged as a landmark discovery in the treatment of bacterial infections. Fluoroquinolones exhibit excellent activity against both pathogenic Gram-negative and Gram-positive bacteria in addition to having convenient pharmacokinetic profile and therapeutic-index and more importantly are capable to overcome the problems of growing bacterial resistance especially to *Staphylococci* and *Enterococci* [3]. This crucial group of orally active broad spectrum antibiotics is highly potent originating from nalidixic acid and is used against many clinically important pathogens responsible for variety of infections including urinary tract infections (UTI), gastrointestinal infections, respiratory tract infections (RTI), sexually transmitted diseases (STD) and skin infections [4].

ORIGIN AND DEVELOPMENT

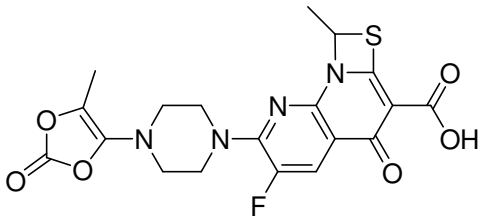
First clinically useful quinolone was naldixic acid, discovered by Lesher and co-workers in 1962 which was generated from chloroquine, an antimalarial agent. Flumequine was the first fluoroquinolone which was patented in 1973 and after flumequine, many fluoroquinolones have been patented and are still used today including norfloxacin (1978) a 6-fluorinated quinolone with a piperazinyl side chain at position 7 having a longer half life than the earlier compounds, pefloxacin (1979), enoxacin (1980), fleroxacin (1981), ciprofloxacin (1981) and ofloxacin (1982). The most successful and widely used fluoroquinolone, ciprofloxacin was marketed in 1986. In the 1990's further alterations of the quinolones resulted in the discovery of novel compounds which are not only active against Gram-negative but also to Gram-positive organisms like sparfloxacin, levofloxacin, gatifloxacin, lomefloxacin [5]. Chemical structure of some most common clinically employed fluoroquinolones are shown in Fig. (1).



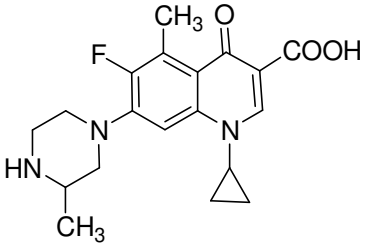
Sparfloxacin



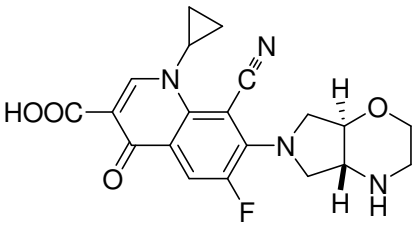
Ciprofloxacin



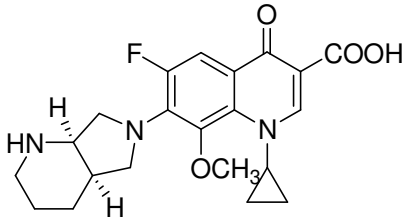
Prulifloxacin



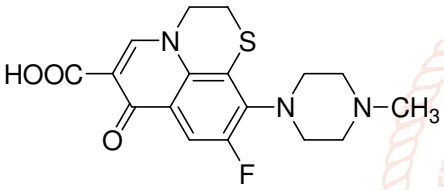
Grepafloxacin



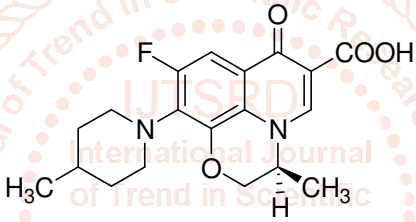
Finafloxacin



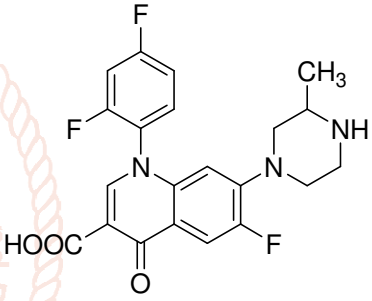
Moxifloxacin



Rufloxacin



Levofloxacin



Temafloxacin

Fig. (1). Some common clinically important fluoroquinolones

CLASSIFICATION OF QUINOLONES

Fluoroquinolones are classified as shown in Table (**1**) according to their pharmacokinetic profile and spectrum of activity [6].

Table 1 Classification of fluoroquinolones

Generation	Fluoroquinolones	Characteristic Feature
I	Flumequine, Oxolinic acid, Nalidixic acid	Poor oral bioavailability, active against some Gram negative bacteria and shorter half life.
II	Ciprofloxacin, Ofloxacin, Levofloxacin, Norfloxacin, Lomefloxacin, Marbofloxacin	Better oral bioavailability with Improved activity against Gram-negative and Gram-positive cocci also have longer half life
III	Timafloxacin, Grepafloxacin, Sparfloxacin, Tosufloxacin, Orbifloxacin	Excellent oral bioavailability with lower central nervous toxicities and fewer interactions with CYP 450.
IV	Gatifloxacin, Sitafloxacin, Prulifloxacin, Trovafloxacin, Moxifloxacin	Show extended activity against both strains of bacteria and also active against anaerobes.

CHEMISTRY

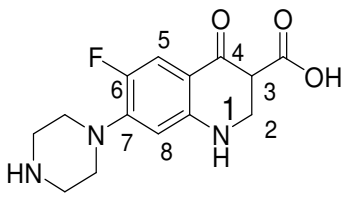


Fig. (2). Basic fluoroquinolone nucleus

The 6-fluoroquinolones are a series of synthetic antibacterial agents derived from, or related to nalidixic acid and oxolinic acid. Their basic nucleus is depicted in Fig. (**2**). Because of the presence of carboxylic acid and amine, these drugs are amphoteric in nature and considered zwitterionic. However, between the pKa of the acidic and basic functional groups (between pH 6-8), these compounds are sufficiently lipid-soluble to be able to penetrate tissues [7].

PHARMACOKINETICS AND PHARMACODYNAMICS

Fluoroquinolones exhibit rapid but not always complete absorption after oral administeration. Oral bioavailability is 30 to 50% for norfloxacin, 70 to 80% for ciprofloxacin and upto 100% for ofloxacin and fleroxacin [8]. Presence of food in the GIT has little influence on the absorption of quinolones [9]. Fluoroquinolones differ widely in the degree to which they are metabolised and eliminated in the liver or by renal excretion. The metabolism is inactivating, and is primarily by glucuronide conjugation at the 3-carboxylic group. The piperazine ring is readily metabolized and this results in decreased antimicrobial activity [10]. They are eliminated by both renal and non renal routes but the primary route of elimination of most fluoroquinolones is through the kidney. A number of quinolones are cleared almost exclusively by glomerular filteration and tubular secretion, they are poorly cleared by both peritoneal dialysis and hemodialysis [11].

STEREOCHEMISTRY

Fluoroquinolones having one or two chiral centers in their structures are available as racemates (ofloxacin, gemifloxacin, clinafloxacin), diastereoisomers (sparfloxacin) or pure enantiomers (levofloxacin, moxifloxacin). Stereochemistry significantly affects antibacterial activity. Grellet *et al* described that the S (-) ofloxacin isomer (levofloxacin) is 8–128 times more potent than R(+) ofloxacin [12]. Chu *et al* recognised the importance of proximity of chiral center in relation to its activity [13]. Chemical structures along with chiral centers of some chiral bicyclic fluoroquinolones (C*) are shown in Fig. (**2**)**.** Machida *et al* separated the enantiomers of fluoroquinolones having carboxylic acid at position three by normal or reversed phase HPLC columns. They also prepared the L-valinamide diastereoisomeric derivative of gatifloxacin [14].

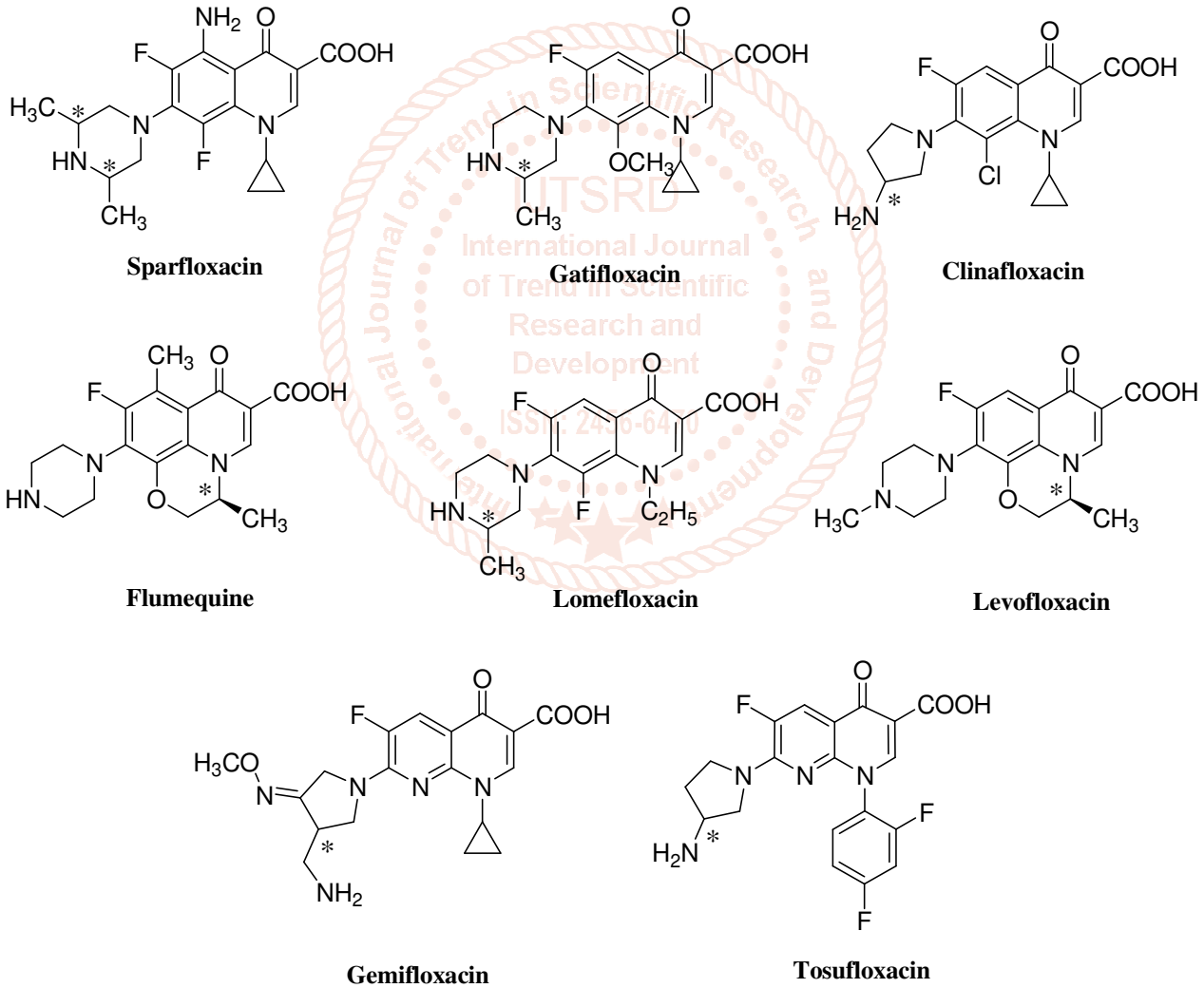


Fig. (3) Chemical Structure of some Chiral Fluoroquinolones

(* Chiral Center)

ADVERSE EFFECTS

Gastrointestinal side effects such as nausea, vomiting and diarrhoea and central nervous system related side effects such as headache dizziness and insomnia are common adverse effects associated with fluoroquinolones reported in 2 to 20% of patients [15]. Khaliq *et al* carried out retrospective surveillance studies on fluoroquinolone-induced tendon injury in 98 cases and found that male patients with a mean age of 59 years are more likely to experience tendon injuries when receiving fluoroquinolones [16]. *Torsade de pointes* is a rare occurring disease due to long QT interval but potentially fatal arrhythmia. Fluoroquinolones have been reported to prolong the QTc interval and precipitate Torsade de pointes. Moxifloxacin has the potential to prolong the QTc interval, but Torsade *de pointes* is very rare [17].

RECENT PATENTS

Over the past few decades there has been a large number of patent related activity in the field of anti-infective fluoroquinolones encompassing a range of various drugs including ciprofloxacin, norfloxacin, ofloxacin having various activities. The patents described here reveal the information regarding fluoroquinolones with novel approaches related to the area which provides potential for the development of therapeutic aspects.

CIPROFLOXACIN

Ciprofloxacin is the potent second generation fluoroquinolone active against a broad range of gram negative. Ciprofloxacin is marketed worldwide, with well over 300 different brand names. It is well absorbed orally and excreted mainly through the kidney. Ciprofloxacin is used in various infectious diseases mainly in urinary tract infections, osteomyelitis, gonorrhea, traveller's diarrhoea, tuberculosis, prostatitis, community-acquired pneumonia, anthrax [18]. There are numerous patents related to ciprofloxacin which include development of several types of dosage form like inhalable formulations, liposomal powders, infusion, and topical suspension. Moreover various method of manufacturing and optimising have also been patented. List of important patents on ciprofloxacin is summarized in Table (**2)** [39-55].

Table 2 List of patents related to ciprofloxacin

Sr. No	Date	Patent number	Invention disclosed	Reference
1	23/06/2011	US 0150983 A1	Concentrated inhalable ciprofloxacin formulation	39
2	12/03/2009	US 0069339 A1	Deuterium-enriched ciprofloxacin	40
3	04/12/2008	US 0300258 A1	Anhydrous ciprofloxacin hydrochloride	41
4	14/12/2006	US 0280691 A1	Spray freeze dried liposomal ciprofloxacin powder aerosol drug delivery	42
5	20/10/2005	US 0232985 A1	Ciprofloxacin HCL	43
6	14/10/2004	US 0202687 A1	Ciprofloxacin formulations and methods of making and using the same	44
7	29/04/2004	US 0082593 A1	Infusion of ciprofloxacin having reduced acid content and being stable in storage	45
8	11/12/2003	US 0229101 A1	Tablets comprising ciprofloxacin hydrochloride	46
9	24/04/2003	US 0078272 A1	Methods of fluoroquinolone compounds against ciprofloxacin-resistant and ciprofloxacin-sensitive pathogenic bacteria	47
10	07/01/2003	US 6503906 B1	Method for optimizing ciprofloxacin treatment of anthrax-exposed patients according to the patient's characteristics	48
11	14/11/2002	US 0169168 A1	Pharmaceutical formulations of ciprofloxacin	49
12	28/03/2002	US 0037883 A1	Process for manufacturing compositions containing ciprofloxacin and hydrocortisone	50
13	28/03/2002	US 0037884 A1	Topical composition comprising ciprofloxacin and hydrocortisone	51
14	19/03/2002	US 6359016 B2	Topical suspension formulations containing ciprofloxacin and dexamethasone	52
15	17/07/2001	US 6262072 B1	Orally administered antimicrobial pharmaceutical formulations of ciprofloxacin	53
16	12/10/1999	US 5965549	Ciprofloxacin-hydrocortisone suspension	54
17	20/09/1988	US 4772465	Method of treating polymicrobial burn wound sepsis with a combination therapy of ciprofloxacin and *Pseudomonas immune globulin*	55

NORFLOXACIN

Norfloxacin is an orally absorbed fluoroquinolone antibacterial with fluorine at position 6 and a piperazine ring at position 7. Specifically, the antibacterial spectrum of norfloxacin includes *Pseudomonas aeruginosa* as well as enteric pathogens. Norfloxacin is active against both penicillin-susceptible and penicillin-resistant strains of *Neisseria gonorrhoeae* [19]. The list of patents of norfloxacin is discussed in Table (**3)** [56-59].

Table 3 List of patents related to norfloxacin

Sr. No	Date	Patent Number	Invention Disclosed	Reference
1	07/02/1989	US 4803274	Norfloxacin intermediate	56
2	20/12/1988	US 4792552	Water-soluble adduct of norfloxacin	57
3	02/06/1987	US 4670440	Medicinal norfloxacin salts	58
4	05/11/1985	US 4551456	Ophthalmic use of norfloxacin and related antibiotics	59

OFLOXACIN

Ofloxacin is a broad spectrum second generation fluoroquinolone antibiotic which was first patented in 1982 [6]. Levofloxacin is the L-isomer of the racemate ofloxacin, a quinolone antimicrobial agent active against various bacteria including Gram-positive and Gram-negative microorganisms and has been widely used for the cure of various infectious diseases [20]. Number of inventions of ofloxacin are disclosed and patented for e.g. ophthalmic formulations, topical preparation etc has been granted. These inventions along with their patent number are discussed in Table (**4)** [60-66].

Table 4 List of patents related to ofloxacin

Sr. No	Date	Patent Number	Invention Disclosed	Reference
1	09/12/2010	US 0310597 A1	Anti-ofloxacin monoclonal antibody and immunoassay of ofloxacin using the same	60
2	12/08/2003	US 6605295 B1	Storage-stable opthalmic compositions comprising diclofenac and ofloxacin	61
3	08/07/2003	US 6589999 B2	Antibacterial aqueous opthalmic formulations containing ofloxacin and use of chitosan for solubilizing ofloxacin suspended in an aqueous media	62
4	28/03/1995	US 5401741	Topical preparation for treating otopathy	63
5	08/05/1990	US 4923862	Topical preparation containing ofloxacin	64
6	02/05/1989	US 4826985	Intermediates for preparation of racemate and optically active ofloxacin and related derivatives	65
7	11/10/1988	US 4777253	Process for preparation of racemate and optically active ofloxacin and related derivatives	66

MOXIFLOXACIN

Moxifloxacin is a fourth-generation fluoroquinolone having *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms, it binds both with bacterial DNA gyrase and topoisomerase IV enzymes which provide more effective bacterial killing and less bacterial mutation. Moxifloxacin was considerably more effective than ciprofloxacin against MRSA and MSSA. It was found highly active against *K. Pneumonia* isolates, which confirmed its uses in the treatment of respiratory tract infections [21].

Other patent of Fluoroquinolones

There are several patents summarized below in Table **(5)** regarding fluoroquinolones including patents related to method of synthesis, various dosage forms of fluoroquinolones and for treatment of particular diseases [67-108].

Table 5 List of other patents related to fluoroquinolones

Sr. No.	Date	Patent Number	Invention Disclosed	Reference
1	10/01/2012	US 8093381 B2	Method of synthesis of fluoroquinolones	67
2	06/09/2011	US 8012711 B2	Method of screening for compounds that reduce microbial resistance to fluoroquinolones	68
3	0 7/07/2011	US 0166126 A1	Compositions and methods for modulating endophthalmitis using fluoroquinolones	69
4	05/07/2011	US 7973022 B2	Fluoroquinolone carboxylic acid salt compositions	70
5	30/06/2011	US 0160172 A1	Fluoroquinolone derivatives for opthalmic applications	71
6	26/05/2011	US 0123626 A1	Pulmonary delivery of fluoroquinolone	72
7	03/02/2011	US 0028444 A1	Pharmaceutically acceptable salts of anti-infection quinolone compounds	73
8	09/12/2010	US 0311731 A1	Fluoroquinolone carboxylic acid molecular crystals	74
9	23/11/2010	US 7838532 B2	Aerosolized fluoroquinolones and uses thereof	75
10	16/09/2010	US 0234348 A1	Compositions and methods for potentiating antibiotic activity	76
11	01/07/2010	US 0166673 A1	Aerosolized fluoroquinolones and uses thereof	77
12	03/06/2010	US 0136523 A1	Molecular signature and assay for fluoroquinoline resistance in *Bacillus anthracis*	78
13	08/04/2010	US 0087386 A1	Topical use of levofloxacin for reducing lung inflammation	79
14	08/04/2010	US 0087416 A1	Aerosol fluoroquinolone formulations for improved pharmacokinetics	80
15	11/03/2010	US 0062974 A1	Combination therapy for the treatment of bacterial infections	81
16	18/02/2010	US 0037890 A1	Aerosolized fluoroquinolones and uses thereof	82
17	14/01/2010	US 0009979 A1	Pharmaceuticals containing fluoroquinolones	83
18	10/12/2009	US 0306128 A1	Pharmaceutical compositions containing a fluoroquinolone antibiotic drug	84
19	20/08/2009	US 0209574 A1	Fluoroquinolone derivatives for opthalmic applications	85
20	25/06/2009	US 0163484 A1	Pharmaceuticals containing fluoroquinolones	86
21	14/05/2009	US 0124632 A1	Methods and kits related to the topical administration of quinolone antibiotics	87
22	30/04/2009	US 0111991 A1	Coupling process for preparing quinolone intermediates	88
23	26/03/2009	US 0082337 A1	Composition comprising quinolone and methods for treating or controlling infections	89
24	26/02/2009	US 0054643 A1	Novel methods of synthesis of fluoroquinolones	90
25	08/01/2009	US 0012072 A1	Fluoroquinolone compositions	91

26	11/12/2008	US 0306038 A1	Compositions and methods for modulating inflammation using fluoroquinolones	92
27	20/11/2008	US 0287396 A1	Phosphonated fluoroquinolones, antibacterial analogs thereof, and methods for the prevention and treatment of bone and joint infections	93
28	12/06/2008	US 0138350 A1	Process for use of fluoroquinolones to reduce or modulate inflammation due to eye disease or opthalmic surgery	94
29	23/08/2007	US 0196398 A1	Fluoroquinolone fatty acid salt compositions	95
30	25/05/2006	US 0110787 A1	Use of fluorine-18-labelled fluoroquinolone antibiotics for diagnosing and monitering bacterial infection	96
31	25/11/2005	US 0261165 A1	Method of reducing resistance to drugs	97
32	22/06/2004	US 6753333 B2	Chiral fluoroquinolone arginine salt forms	98
33	05/02/2004	US 0023983 A1	Methods of use of fluoroquinolone compounds against pathogenic *helicobacter* bacteria	99
34	23/12/2003	US 6667042 B2	Flouroquinilone antibiotic product, use and formulation thereof	100
35	0 4/12/2003	US 0225119 A1	Crystalline fluoroquinolone arginine salt form	101
36	09/05/2000	US 6060474	Method for preventing scar tissue formation	102
37	25/01/2000	US 6017912	Topical fluoroquinolone antibiotics in an alcohol and acetone vehicle	103
38	15/06/1999	US 5912255	Topical fluoroquinolone antibiotics combined with benzoyl peroxide	104
39	30/09/1997	US 5672600	Antimicrobial dithiocarbamoyl quinolones	105
40	08/07/1997	US 5646163	Quinolone 5-(N-heterosubstituted amino) antimicrobials	106
41	07/02/1995	US 5387748	Antimicrobial dithiocarbamoyl quinolones	107
42	11/12/1990	US 4977154	5-amino and 5-hydroxy-6-fluoroquinoloes as antibacterial agents	108

CURRENT AND FUTURE DEVELOPMENTS

The future of the newer fluoroquinolones looks promising because of their unique mechanism of action. There is a great possibility of further developing novel and improved compounds in this class and the acceptance of these compounds as effective as well as therapeutic agents. In the current scenario of infections, new alternatives and progress are needed. As shown from the systematic literature survey, plenty of work has been done and patented by the number of investigators on fluoroquinolone moiety, yet further emphasis on examination of their impact is highly desirable. Therefore, it is clear that the development of newer therapeutics with a novel mechanism of action possessing superior efficacy and diminished potential for toxic effects appears to be a necessary requisite for treating the infections. Hence, across the globe, a ray of hope for new innovations and advancements are still rising. The patents described here reveal a wide range of novel approaches regarding several type of dosage forms, manufacturing, application and formulation etc that provide potential for the development of therapeutic effect of fluoroquinolones. Hopefully, newer and highly active anti-infective drugs would rapidly progress to various stages of development and enter the pharmaceutical market.

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