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Green chemistry approaches towards the design and synthesis of anti-infective fluoroquinolone derivatives

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ABSTRACT

Fluoroquinolones are of pivotal interest for scientists because of their excellent pharmacological and pharmacokinetic profiles. They have a broad spectrum of antimicrobial activity and show several promising features such as, greater bioavailability, admirable tissue penetration and comparatively lower incidence of antagonistic and lethal effects. These have made the compounds highly desirable to combat several infectious diseases. Various synthetic conventions have been established to hasten the fluoroquinolone's amination rate and to improve yield. Such methods have significant disadvantages including, costly reagents, usage of vast quantities of harmful solvents, excessive heat and sideways reactions. These drawbacks aren't appropriate in current pharmaceutical market. Hence, it is highly desirable to develop a newer green and more efficient process for fluoroquinolones synthesis. Green chemistry methodology endeavours to achieve sustainability at the molecular level. The field of green chemistry has shown how chemists can design next-generation products and processes to make them more cost-effective while being virtuous for human health and the environment. This graphical review demonstrates the current developments in the synthesis of fluoroquinolones employing the principles of green chemistry by using the novel, recyclable and environmental-friendly catalysts and solvents.

1. Introduction

The growing prevalence of bacterial and fungal resistance to a wide number of anti-microbial mediators in both community and hospital-acquired infections has become a significant and global well-being issue with approximately 15 million deaths per annum, as currently, accessible medicines may no longer be successful for resistant infections as a consequence of pathogenic microbes implementing a range of strategies to solve these problems [1]. This unwanted occurrence encouraged the researchers to focused on the advancement of newer materials from bio renewable and sustainable sources because of great concerns about the environment, waste accumulation and destruction and the inevitable depletion of fossil resources [2]. Green chemistry is a modern area of chemistry that is rapidly emerging. Its growing significance is in making the use of maximum available resources in such a way that the production of chemical waste is negligible or minimal. This is one of the superlative possible replacements for conventional methods of chemical synthesis. Through using the green methodology, we can't only evade the usage of harmful and noxious chemicals, but also prevent the development of by-products. Therefore, they are flawlessly responsive to combinatorial synthesis automation. Gedye and Giguere, in 1986, first announced that the organic synthesis under microwave irradiation could be performed very quickly [3]. Microwave irradiation technique is another form of heating, based upon the capability of analogues to convert electromagnetic energy into heat. This approach will help to increase the rates of chemical reactions, yields and safer materials [4].

One area of great interest is the usage of environmental-friendly catalysts and solvents in the field of pharmaceutical chemistry. From both environmental and economical point of opinion, the use of green catalysts and non-volatile solvents support multiple organic transformations with added value [5]. The most significant area of study has become the usage of water as a green solvent in organic reactions, having

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unique physicochemical properties that lead to exclusive reactivity and discrimination in organic solvent assessment [6]. The role of chemistry is vital to make sure that our next generation of chemicals is more sustainable than existing generations. Increasing demand for environmental-friendly chemical procedures needs the production of innovative and economical methods. Green chemistry is the most compelling term for sustainability in chemistry. One of the crucial zones of green chemistry is the removal of solvents in chemical systems or replacing harmful solvents with environmentally benign solvents. The usage of other solvents such as water, fluorinated and ionic liquids, supercritical media and their different mixtures is quickly growing [7,8].

Various synthetic conventions have been established to accelerate the fluoroquinolone's amination rate and to improve yield. Such methods have significant disadvantages including, costly reagents, usage of vast quantities of harmful chemicals, excessive heating and sideways reactions. These drawbacks aren't appropriate in the modern pharmaceutical market. Hence, it is highly desirable to create a newer green and more efficient process for fluoroquinolones synthesis. To improve the disadvantages of these catalysts, replacing them with novel, non-toxic, eco-friendly, recyclable heterogeneous catalysts with improved efficiency have been the key topics of researchers over the past decades. They exhibited excellent properties such as greater reactivity, lower toxicity, simplicity of action, non-corrosiveness nature and prospective of recyclability [9]. Some fundamental principles of green chemistry are depicted in Fig. (1).

Pathogenic micro-organisms like bacteria, viruses, fungi or parasites cause infectious ailments which can spread (directly or indirectly) from one person to another. Millions of people die each year worldwide from infectious ailments. The prolonged usage of antibiotic drugs results in the antibacterial resistance; hence, their long-lasting effectiveness is inadequate [10]. The emerging antibiotic resistance problem, particularly among Gram-negative bacteria, has become a major threat to global public health. Different antibacterial classes used against antibiotic-resistant bacteria have lost their effectiveness and new antibiotic agents for this class of pathogens have been developed successfully [11]. The chain of infection and their prevalence and consequences is depicted in Fig. (2).

Fluoroquinolones are among the most auspicious and strongly tracked zones of modern anti-infective chemotherapy, portraying the wide-spectrum activity. They consist of a comparatively simple molecular core, which is responsive to several structural alterations. In recent

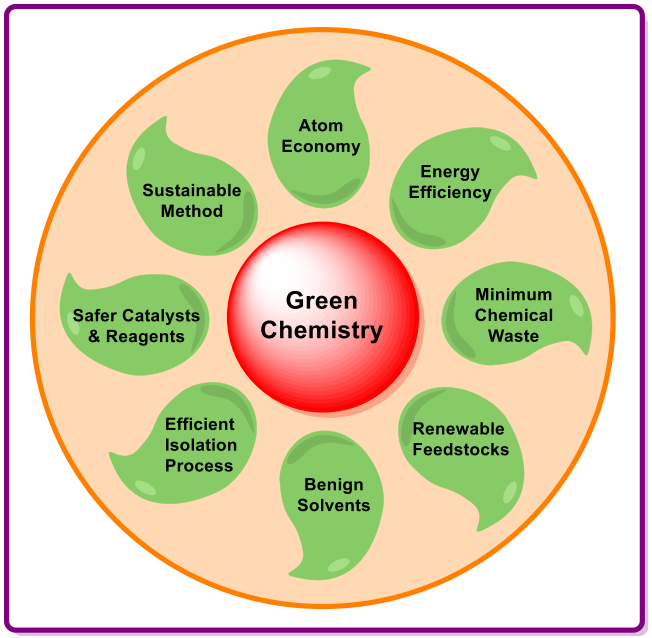


Fig. (1). Fundamental concepts of green chemistry.

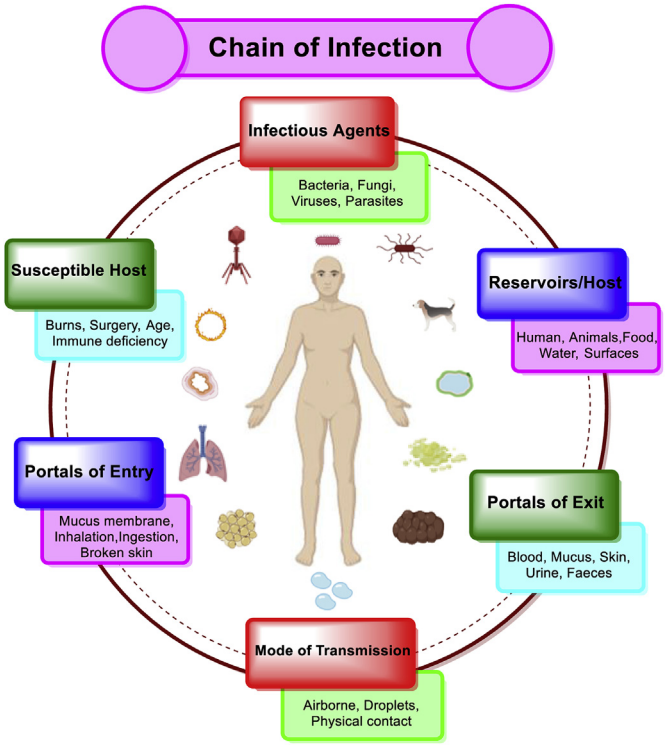


Fig. (2). Chain of infection and their prevalence and consequences.

years, they are one of the increasingly growing classes of antibiotic drugs in trade [12]. Quinolones were first found as an analogue of anti-malarial medication chloroquine. Nalidixic acid was the first antibacterial drug to enter into the market in 1962. The key mechanism of action and narrow range of activity restricted its use, but the analogues from this 1st generation of quinolones were further synthesized. The synthetic antibiotic medication was later altered in the late 1970s and early 1980s to include a fluorine atom in central carbon ring, thereby increasing the scale of activity and therapeutic uses in human medications [13]. Since of their broad-spectrum of antimicrobial activity and their *in-vivo* chemotherapeutic effectiveness, fluoroquinolones are the compounds of particular interest [14]. FQs bind to the enzyme-DNA complex via direct inhibition of DNA synthesis and by stabilizing DNA strand breakage formed by DNA gyrase and topoisomerase-IV. The ternary drug complexes of fluoroquinolone, DNA and enzyme block the development of fork replication. DNA gyrase inhibition and cell permeability of fluoroquinolones are heavily inclined by the nature of C-7 substituent in standard 4-quinolone-3-carboxylic acid structure [15]. The mechanism of action of fluoroquinolone agents is portrayed in Fig. (3).

Fluoroquinolone derivatives consist of some crucial structural constituents that are important for the effective pharmacological activity, described as (1) Nucleus of fluoroquinolone deploying the self-association of analogues, (2) Piperazinyl moiety that directs the molecular penetration into cells and, (3) N-substituent moiety that contributes in H-bond formation [16]. Fluoroquinolone agents exhibit higher bioavailability, strong tissue penetration, longer serum half-life and admirable safety. These have made the analogues highly desirable for the treatment of various infectious diseases. Sources from this class include ciprofloxacin, ofloxacin, norfloxacin, moxifloxacin, pefloxacin etc. [17]. The relationship between green chemistry and fluoroquinolones, and its different methods of synthesis by green approaches is depicted in Fig. (4).

2. Green synthesis of fluoroquinolone derivatives

Green chemistry (also termed as sustainable chemistry) is a field of chemistry and chemical engineering focused on developing products and

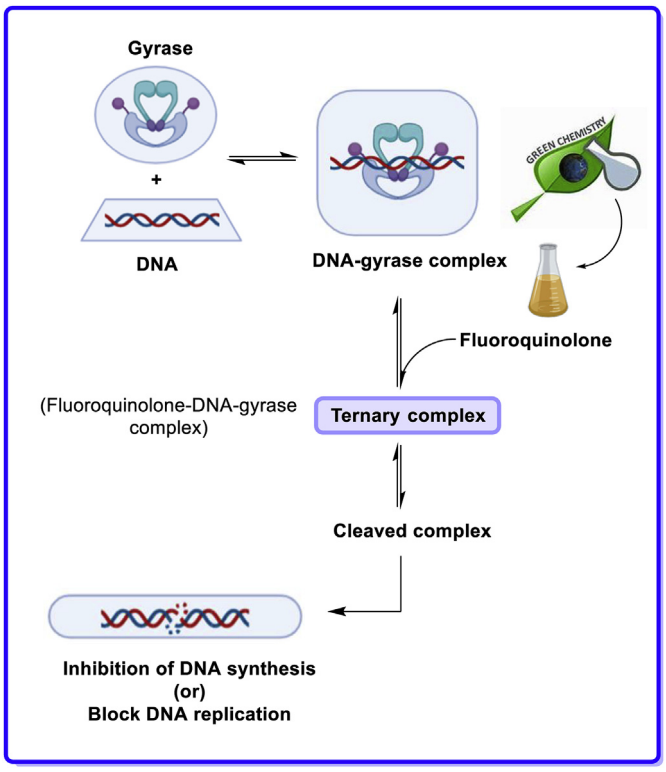


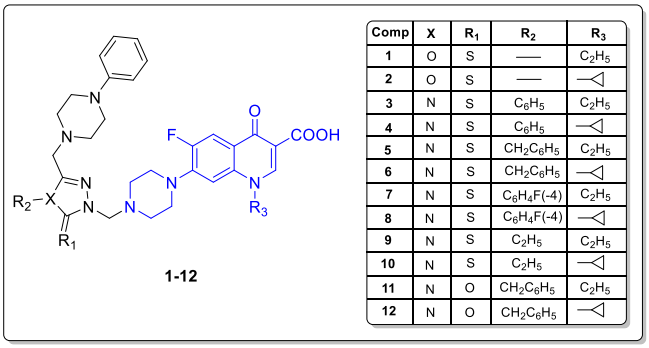
Fig. (3). Mechanism of action of fluoroquinolones.

processes which diminish or abolish the hazardous material usage and production. Because of the global curiosity in enduring research into the development of environmentally sustainable approaches for organic compound synthesis, we report herein the simple and efficient green synthesis of fluoroquinolone derivatives as potent anti-infective agents. Newer fluoroquinolone derivatives were prepared via green and environmentally benign approach with the aid of MW irradiation by using the novel, recyclable and environmental-friendly catalysts and solvents. Few examples of synthetic routes of fluoroquinolone derivatives by using green methodologies are depicted in Fig. (5).

3. Recent advances in green synthesis of fluoroquinolone derivatives and their role in anti-infective field

Numerous approaches were assessed for advancements of newer fluoroquinolone derivatives by using the green methodology. From last few years, FQs are the newer scaffolds, fascinated many researchers worldwide due to its virtuous anti-infective profile. Certain reports from the current scientific literature intricate the green synthesis of fluoroquinolones and their role in the treatment of severe infections have been discussed below.

Mermer *et al* (2019), designed a new hybrid class of Piperazine-azole-fluoroquinolones under the microwave irradiation technique and evaluated their antimicrobial and inhibition of DNA gyrase potentials. The results revealed that fluoroquinolone hybrids **(1-12)** exhibited good antimicrobial activity and effective inhibition of DNA gyrase with IC_{50} values in the range of 0.134–1.84 μg/ml. Therefore, by considering their bio-active potentials, these piperazine-azole functionalized fluoroquinolone hybrids would be the future antibiotics [20].



Comp	X	R_1	R_2	R_3
1	O	S	—	C_2H_5
2	O	S	—	◁
3	N	S	C_6H_5	C_2H_5
4	N	S	C_6H_5	◁
5	N	S	$CH_2C_6H_5$	C_2H_5
6	N	S	$CH_2C_6H_5$	◁
7	N	S	$C_6H_4F(-4)$	C_2H_5
8	N	S	$C_6H_4F(-4)$	◁
9	N	S	C_2H_5	C_2H_5
10	N	S	C_2H_5	◁
11	N	O	$CH_2C_6H_5$	C_2H_5
12	N	O	$CH_2C_6H_5$	◁

Ozdemir *et al* (2018), synthesized a novel sequence of 1,2,4-triazole based Piperazine-azole-fluoroquinolone analogues under microwave irradiation and evaluated their antimicrobial potential. The result displayed that compounds **(13–18)** containing a fluoroquinolone nucleus exhibited the potent antimicrobial and anti-mycobacterial activity (*Mycobacterium smegmatis*), having MIC values in the range from 0.24 to 3.9 μg/ml [1].

Demirci *et al* (2018), synthesized a new class of 5-substituted-1,3,4-thiadiazole-based fluoroquinolone analogues and screened them for their antimicrobial potential. The result revealed that compound **20** was found

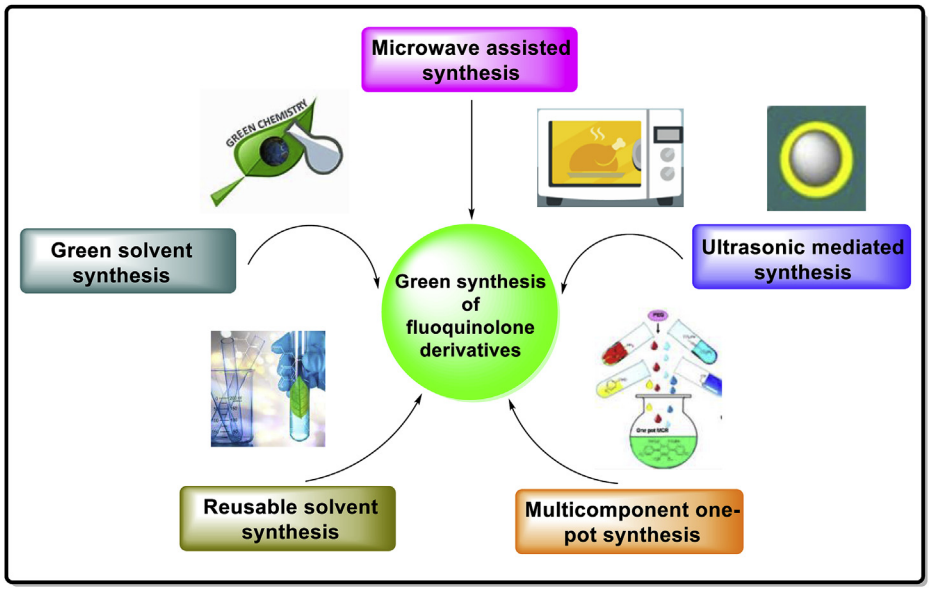


Fig. (4). Relationship between green chemistry and fluoroquinolones, and its different methods of synthesis by green approaches.

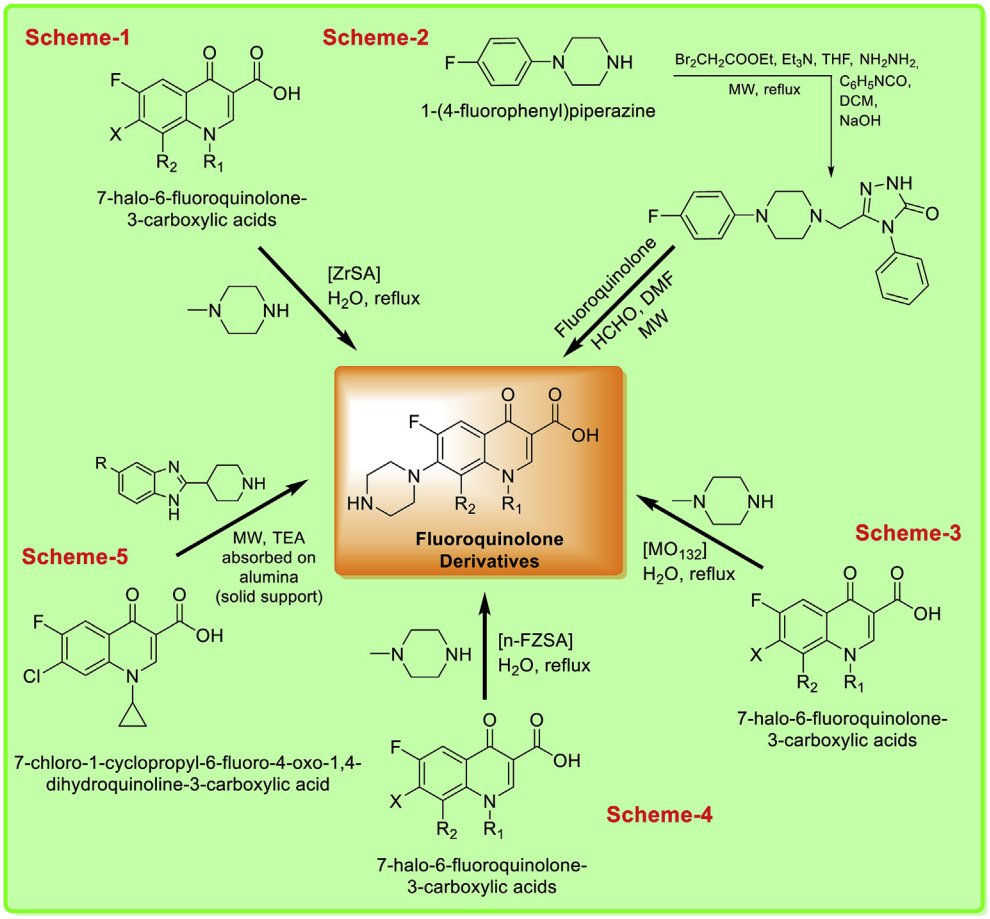
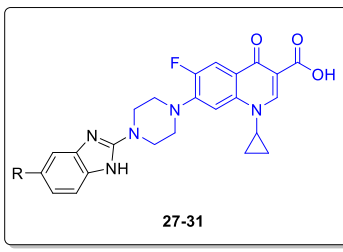


Fig. (5). Graphical representation of fluoroquinolone derivatives by using the principles of green chemistry. **In scheme-1**, Nakhaei et al. (2018), described several new antibacterial fluoroquinolone analogues by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with a variety of piperazine derivatives and (4aR, 7aR)-octahydro-1H-pyrrolo[3,4-b]pyridine using Zirconia Sulfuric Acid (ZrSA) nanoparticle, as a catalyst in the presence of ordinary or magnetized water upon reflux conditions. Result showed that ZrSA exhibited the high catalytic activity towards the synthesis of fluoroquinolone derivatives in two forms of water [6]. **In scheme-2**, Ozdemir et al. (2018), described the synthesis of Piperazine-Azole-Fluoroquinolone based 1,2,4-triazole analogues under the microwave irradiation by reaction starting from 1-(4-flouophenyl)piperazine and then undergoes the reaction via BrCH2COOEt, Et3N, THF, NH2NH2, C6H5NCO, DCM, NaOH, HCHO, DMF and suitable amines such as fluoroquinolone [1]. **In scheme-3**, Nakhaei et al. (2018), described the synthesis of noval fluoroquinolone compounds by using Nano-Fe3O4@ZrO2-SO3H (n-FZSA) as a magnetic catalyst. They were prepared by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with piperazine derivatives and (4aR,7aR)-octahydro-1H-pyrrolo[3,4-b] pyridine in water [9]. **In scheme-4**, Miraie et al. (2017), synthesized various potential antibacterial fluoroquinolone derivatives by direct amination of 7-halo-6- fluoroquinolone-3-carboxylic acids with piperazine derivatives and (4aR, 7aR)-octahydro-1H-pyrrolo[3,4-b]-pyridine using (NH4)42 [MoVI72Mo-V60O372(CH3COO)30 (H2O)72], a keplerate-type giant-ball nano-porous isopolyoxomolybdate, as a catalyst in refluxing water [18]. **In scheme-5**, Guruswamy et al. (2012), developed some noval ciprofloxacin derivatives by green and environmentally benign methodology with the help of a microwave irradiation technique in the presence of a catalytic amount of triethylamine adsorbed on alumina solid support. This microwave assisted method gave surprisingly excellent yields (72–90%) of products [19].

to be most potent, exemplify the antibacterial potential towards *S. aureus* (MIC value = 2 μg/ml) and *E. coli* (MIC value = 4 μg/ml). It was observed that the compounds **19** and **20** exhibited the modest antitubercular activity (MIC value of 8 μg/ml for each) [21].

Pandit *et al* (2016), synthesized some fluoroquinolone derivatives by combining it with different thiadiazole compounds by refluxing on an electrically heated water bath and screened them for their antimicrobial activity. Result revealed that ciprofloxacin derivatives with thiadiazoles **(21–23)** exhibited good antimicrobial activity. Also, sparfloxacin derivatives **(24–26)** displayed both antibacterial and antifungal activity [22].

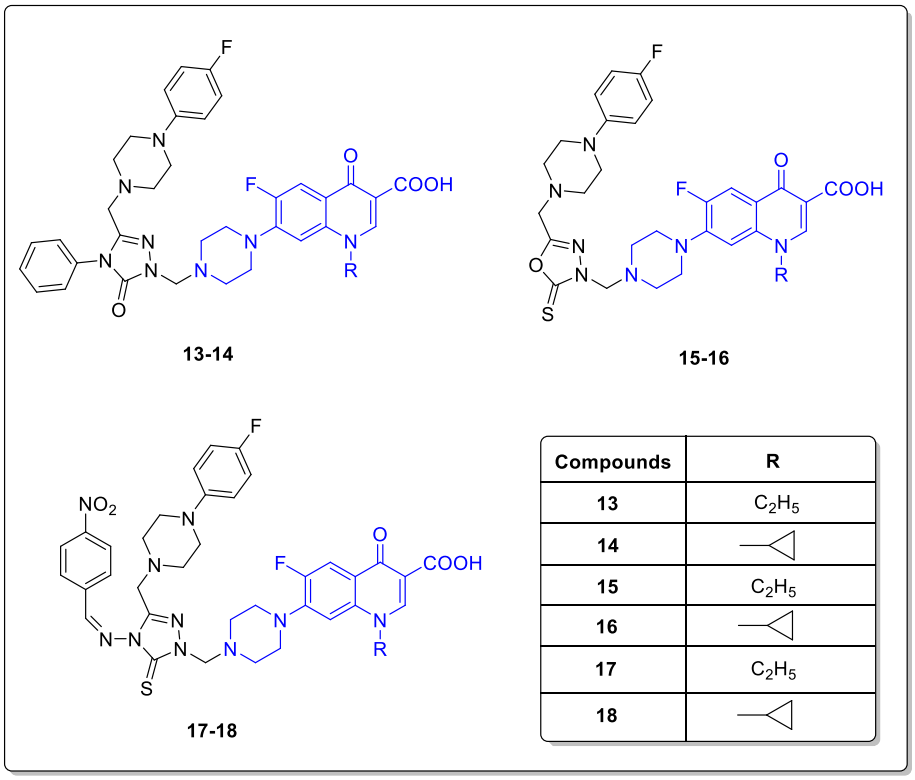
Guruswamy *et al* (2012), synthesized some newer ciprofloxacin analogues by using microwave irradiation and evaluated their antimicrobial potential towards several microorganisms. Ciprofloxacin was used as reference drug. The result demonstrated that compounds **(27–29)** exhibited excellent antibacterial activity and compounds **30** and **31** showed the potent antifungal activity [19].

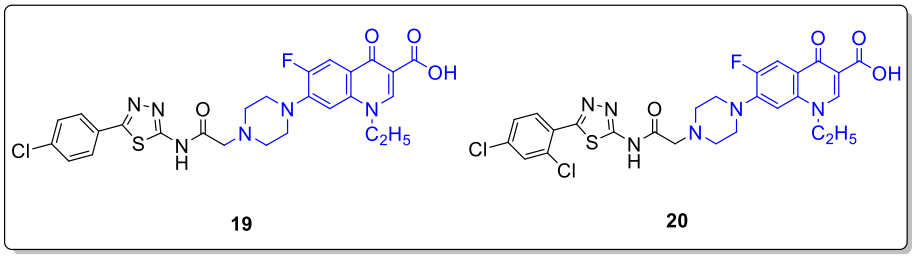


Compounds	R
27	H
28	CH_3
29	OCH_3
30	F
31	CF_3

4. Applications of fluoroquinolones

Fluoroquinolone is a sequence of synthetic antibacterial mediators that display a wide range of anti-microbial activity, comparatively low prevalence of antagonistic and lethal effects and admirable safety profile





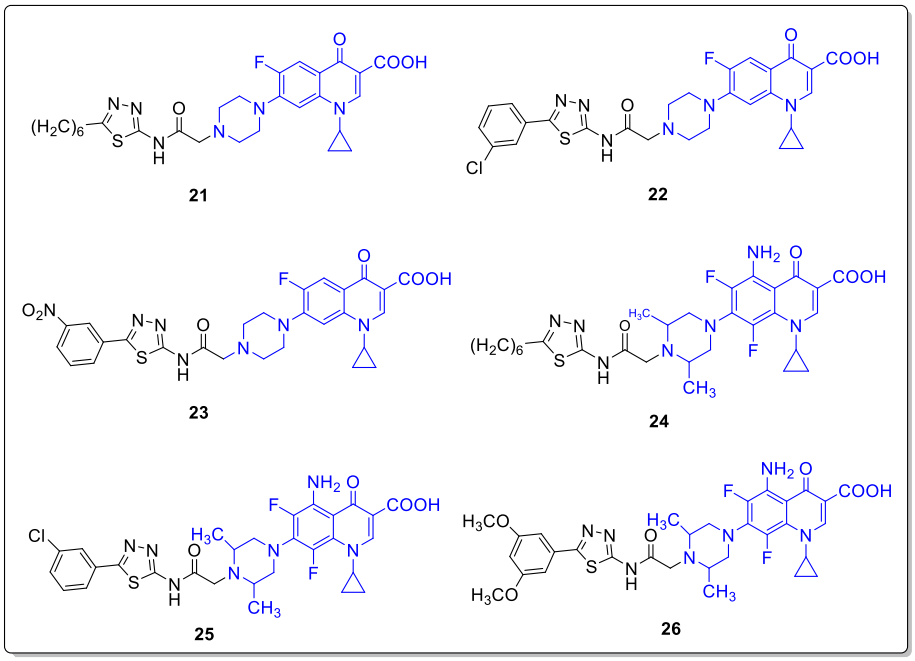
[23]. They have been used globally in management of bacterial origin infections and clinical applications fluctuating from urinary tract infections to the nearly entire body and are effective in treatment towards Gram-positive and Gram-negative species. Ciprofloxacin and ofloxacin are amongst the most commonly used fluoroquinolones. These are used for treating sexually transmitted diseases (STD), infections of bones and joints, typhoid fever and tuberculosis. The more recent fluoroquinolone agents such as gemifloxacin, moxifloxacin and gatilofloxacin are used to treat acute sinusitis, chronic bronchitis, cystitis, skin and soft tissue infections, pyelonephritis, gonorrhoea and complex urinary tract infections (UTI) [24]. They are also used in infections of the biliary tract, bacterial enteric infections and prophylaxis in the immunocompromised neutropenic host [25].

5. Conclusion

This graphical review is an endeavour to concentrate on numerous green synthetic features of anti-infective fluoroquinolones. Few examples of synthesis of newer fluoroquinolone derivatives via green methodologies by using microwave irradiation technique and novel, recyclable and environmental-friendly catalysts and solvents are described. The authors, in this review, also described the consequences and prevalence of infection, mechanism of action of fluoroquinolones along with their important structural features. Scientific information identified in this paper is estimated to be useful for aspiring researchers working on the relevance of green chemistry in anti-infective drugs and fluoroquinolone derivatives.

6. Future aspects

The green synthesis approach, following a simplistic work-up procedure, provides these products in higher yields over the short period. The catalysts used are cheap and readily available, constant and storable, recycled effortlessly and reused with continuous operation over several cycles. In general, these green catalytic processes for fluoroquinolones synthesis provides quick access to anticipated products in refluxing water after a facile work-up process and evades the harmful chemicals. Hence, this method signifies a noteworthy improvement over the conventional methods that are currently accessible for fluoroquinolones synthesis.



CRediT authorship contribution statement

Rajat Goyal: Writing - original draft. **Archana Sharma:** Writing - original draft. **Vijay Kumar Thakur:** Writing - original draft. **Monika Ola:** Writing - original draft. **Prabodh Chander Sharma:** Writing - original draft.

Declaration of competing interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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Abbreviations

MW	Microwave
FQs	Fluoroquinolones
DMF	Dimethyl formamide
TEA	Triethyl amine
ZrSA	Zirconia sulfuric acid
DNA	Deoxyribonucleic acid
MIC	Minimum inhibitory concentration
IC_{50}	Half maximal inhibitory concentration
μM	Micromolar
μg/ml	Microgram per milliliter
STD	Sexually transmitted disease
UTI	Urinary tract infections
MOA	Mechanism of Action

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