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DESIGN & SYNTHESIS OF FLUOROQUINOLONE THROUGH GREEN CHEMISTRY APPROACH

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ABSTRACT

The improvements for production of a direct chemical process to manufacture different upgraded chemicals from low-cost raw materials is a predominantly attractive concept and represents a significant challenge in sustainable organic synthesis. The green synthesis approach, following a oversimplified work-up procedures, produces diverse products in superior yields over the short period of time. The catalysts used are economical and readily accessible, constant and can be stored, recycled and reused with constant operation over numerous cycles. In broad terms, these green catalytic processes for the synthesis of fluoroquinolones provide rapid access to the products. Here in this review article various methods which signify a remarkable enhancement over the conventional methods that are presently accessible for design of fluoroquinolones were presented.

Keywords: Green chemistry, fluoroquinolones, harmful chemicals, Microwave assisted organic synthesis

INTRODUCTION:

Green chemistry/sustainable chemistry is a rapidly emerging branch of chemistry in modern era since of its environmentally benign synthesis, its growing significance is because of its least generation of pollution to the environment, less amount of waste product, starting materials are non-toxic, solvent used are eco-friendly, catalyst used are non-toxic and can be reused, all the reactants were consumed completely and

reaction should not generate toxic by product. There are various methods for the synthesis like microwave induced green synthesis, by the use of ultrasonic equipment, photochemical reactions, electrochemical synthesis, etc.

Gedye and Giguere in 1986 first discovered that the organic synthesis under microwave irradiation could be performed very quickly in which very much time is saving. Microwave irradiation technique, based on the capability to convert electromagnetic energy into heat. This method is useful for the rates of chemical reactions, obtained yields and safer product **[1]**.

Microwave assisted organic synthesis has revolutionized method for the synthesis of chemicals. Molecules can be design in a fraction of the time which is required in classical thermal methods. As a result, this technique accelerating drug discovery and development processes. Microwave synthesis is based on electromagnetic energy, which falls at the lower end of the electromagnetic spectrum and is defined in a measurement of frequency as 300 to 300,000 MHz, corresponding to wavelengths of 1 cm to 1. The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. Microwave energy is non-ionizing it does not change the molecular structure of any chemical compounds being heated – it provides only thermal activation. The organic compound transformations are mainly due to dielectric polarization. The ability of a material to convert electromagnetic energy into thermal energy is dependent on the dielectric constant. The larger the dielectric constant the greater is the coupling with microwaves. Thus, the solvents such as methanol, N, N-Dimethylformamide, ethyl acetate, acetone, acetic acid, water, etc. are all heated rapidly when irradiated with microwaves. On other hand, solvents which have low dielectric constants such as hexane, toluene, carbon tetrachloride, etc. do not couple and we Can't heat that rapidly by microwave irradiation methode. Scientist have analyzed the application of microwave oven to carry out chemical synthesis. It has been detected that many reactions progress much faster in microwave synthesis as compared to conventional chemical synthesis **[2]**.

The thought of a circular economy (CE) has been used since ten years for sustainable development and getting around the limitations of the current and linear dominant production and consumption patterns. The main aim of a circular economy is to promoted the adoption of closing-the-loop production methods to ameliorate resource use efficiency, alter chemical processes, and increase product self-life. 14 goals of EC have appropriate

application in green chemistry (GC) concepts and patterns **[18]**.

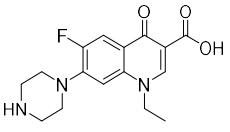
The chemist facing the question is, what will be the character, nature, and synthesis processes of synthetic chemicals needed for a sustainable civilization? Chemistry play an important role for invention of essential and beneficial products and processes with extraordinary performance. The chemical synthetic processes should be follow the principles of green chemistry which produced less hazardous and environmental benign chemicals with hundred percent atom economy and zero percent of waste **[19]**.

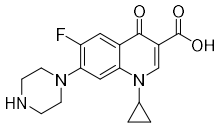
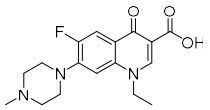
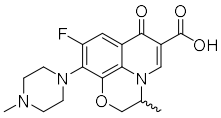
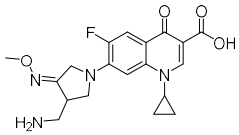
The fluoroquinolones are broad spectrum, antibacterial agents which are widely used in therapy of UTI and respiratory tract infections. Fluoroquinolones are inhibiting the wide range of bacteria. Gram-positive includes *Staphylococci, Streptococcus pneumoniae* and *viridians*, *Enterococcus faecalis*, *Listeria monocytogenes*, and *Nocardia* species **[3]**.

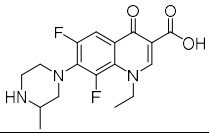
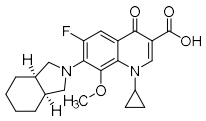
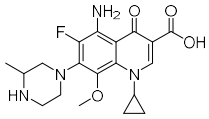
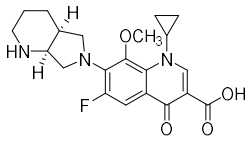
Fluoroquinolones and other anti-infective played a major role in saving of human lives. Fluoroquinolones is highly appreciated specially if there was big problem with microbial resistance against penicillin, macrolide and other antibiotics. Fluoroquinolone's pharmacophore is well known as antibacterial activity. The fluoroquinolones were found to be effective to treat urinary tract infection (UTI). It is use in treating Neisseria gonorrhea and highly effective to treat tuberculosis and other microbial infections. In addition, fluoroquinolones nucleus is widely active against biomolecules such as PDE4, PIM kinase.

The designing of hybridizing molecules from ciprofloxacin and norfloxacin by enhancing their pharmacodynamics activity with tetrazoles. The newer designed fluoroquinolones were tested in the interaction with the target enzyme DNA gyrase and COVID-19 main protease. A Quantitative structure-activity relationships (QSAR) study was carried out for the determination of antibacterial activity fluoroquinolones over S. aureus. The binding interaction of compounds with CoV-2-Mpro was done by docking and were compared with different inhibitors of this enzyme **[2]**.

Table 1: Fluoroquinolones with their structure and uses

First generation Fluoroquinolones	Structure	Uses
Norfloxacin		**Gynecological infection** **Urinary tract infection** **Chronic prostatitis**

		Gonorrhea
Ciprofloxacin		**Bone and joint infection** **Intra-abdominal infection** **Skin infection** **Typhoid fever**
Pefloxacin		**Urinary tract infection** **Ulcer**
Ofloxacin		**Skin infection** **Lung infection** **Prostate infection** **Gonorrhea**
Gemifloxacin		**Chronic bronchitis** **Pneumonia**

Second generation Fluoroquinolones	**Structure**	**Uses**
Lomefloxacin		**Bronchitis** **Urinary tract infection**
Moxifloxacin		**Urinary tract infection** **Pneumonia** **Gastroenteritis** **Prostatitis**
Gatifloxacin		**Bacterial conjunctivitis**
Levofloxacin		**Urinary tract infection** **Pneumonia** **Gastroenteritis** **Prostatitis**

Contemporaneous methods for green synthesis of fluoroquinolones

Mermer *et al* (2019), developed a new hybrid class of Piperazine azole-fluoroquinolones under the microwave irradiation technique and evaluated their microbial inhibition and DNA gyrase inhibition potentials. The results revealed that fluoroquinolone hybrids (1-12) exhibited good antimicrobial activity and effective inhibition of DNA gyrase with IC50 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 antimicrobial agent **[4]**.

Yahya Mirzaie *et al* (2017), published article on, fast and green method to synthesis of quinolone carboxylic acid derivatives by giant-ball Nano porous Isopolyoxomolybdate as highly efficient recyclable catalyst in refluxing water, giant-ball Nano porous isopolyoxomolybdate act as a catalyst in refluxing water, they show that catalyst act in effective way and give the highest percentage yield of drug in short reaction time. Completion of reaction was measured by TLC, purity of sample was measured by HPLC, and the FT-IR spectra of the products were obtained with KBr-disks, using a Tensor 27 Bruker spectrophotometer **[5]**.

G. Govinda Rajulu *et al* (2013), research on new azetidine-3-Carbonyl-N-methyl-hydrazino derivatives of fluoroquinolones synthesis and evaluate anticancer and anti-bacterial activity of obtained compound. Synthesized compounds were screened in vitro for antibacterial activity against representative Gram-positive and Gram-negative strains, by use of standard twofold serial dilution method using agar media. In obtained derivatives, compound **6i** showed good antibacterial activity by inhibiting the growth of Methicillin-sensitive *Staphylococcus aureus*, Methicillin-resistant *S. aureus* and ATCC 35218 Escherichia coli. And the minimum effective concentration was found to be (MIC: 0.25–16.00 μg/mL). Synthesized compound also evaluates for in vitro anticancer activity against human cancer cell lines (MCF-7 Breast carcinoma, HCT-116 Colon carcinoma and A549 Lung adenocarcinoma) obtained from American Type Culture Collection (ATCC). Compound **6h** against MCF-7 cell line is superior to the marketed drugs Ciprofloxacin and suberanilohydroxamic acid (SAHA) **[6]**.

Guruswamy *et al* (2012), synthesized some newer ciprofloxacin by the help of microwave irradiation and evaluated their antimicrobial activity towards several microorganisms. Ciprofloxacin was used as reference drug. The result demonstrated that some compounds exhibited excellent antibacterial activity and some compounds showed the potent antifungal activity **[1]**.

Lubna Swellmeen *et al* (2019), published an article on synthesis of fluoroquinolones derivatives as antimicrobial agents and says that fluoroquinolones are well known to have an anti-infective action and it work against microbial resistance which is big challenge for the scientist to over the bacterial resistance against antibiotics. Six bacterial strains were used for the antimicrobial assays, four Gram-positive (*Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus agalactiae, Streptococcus pyogenes*) and two Gram-negative (*Pseudomonas aeruginosa, Escherichia coli*). Antibacterial activities were evaluated by the agar well diffusion method. Experiments were carried using amoxicillin (20 mg), ciprofloxacin (5 mg) and gentamicin (10 mg), as positive controls. The sensitivities of the microorganisms to the synthetic compounds were determined by measuring the sizes of inhibitory zones, and values <8 mm **[8]**.

Ahmad Nakhaei *et al* (2018), research on application of ZrO2–SO3H as highly efficient recyclable nano catalyst for the green synthesis of fluoroquinolones having potent antibacterial activity. In this research, researchers developed fluoroquinolone derivatives in the presence of Zirconia Sulfuric Acid (ZrSA) as a highly effective catalyst for the direct amination of 7-halo-6-fluoroquinolone3-carboxylic acids. This method provided the high yields over short reaction time, following a facile procedure. The catalyst is easily recycled and reused for several cycles with consistent activity. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were determined by KBr disks, using a Tensor 27 Bruker spectrophotometer. The 1H NMR (300 MHZ) and 13C NMR (75 MHZ) spectra were recorded using Bruker spectrometers **[9]**.

Yıldız Uygun Cebeci *et al* (2018), research on microwave irradiated and conventional synthesis, antibacterial activity evaluation Studies of tryptamine-azole fluoroquinolones, tryptamine was converted to the corresponding 1,2,4-triazole, 1,3,4-oxadiazole, 5-oxo-1,3-thia(oxa) zolidine and 5-(4-chlorophenyl)-1,3-thia(oxa)role derivatives via several steps. 1,3,4-oxadiazole and 1,2,4-triazoles were then converted to the corresponding mannich bases containing fluoroquinolone core using a one-pot three-components procedure. Conventional and microwave-assisted methods were applied for all syntheses. All the newly synthesized compounds were screened for their antibacterial and most of them were found to have good–moderate antibacterial activity **[10]**.

Sabrina Noel *et al* (2011), research on Synthesis and biological properties of conjugates between fluoroquinolones and a N3``-functionalized pyochelin, Pyochelin is

a siderophore common to *Pseudomonas aeruginosa* and several other bacteria. The above work proved that this analog binds FptA, the pyochelin outer membrane receptor, and transports iron (III) efficiently into bacteria. This functionalized pyochelin seemed to be a good candidate for antibiotic. Evaluation of the activities was carried out in succinate medium by the two-fold serial dilution method. Data were reported as MIC50s, which reflects the lowest concentration of antibiotic that inhibit the more than 50% visible cell growth after incubation for 18 hours at 30 ◦C **[11]**.

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 compound 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]**.

Hairui Bai *et al* (2018), research on three-component one-pot approach to highly efficient and sustainable synthesis of the functionalized quinolones via linear/ branched domino protocols, key synthetic methods for the floxacin of quinolone drugs. The main advantages of these protocols are the simple experimental procedure, high bond-forming efficiency, inexpensive readily available starting materials, moderate to excellent yields with good functional group compatibility, and non-chromatographic purification, which render these methods particularly attractive for the sustainable preparation of biologically and medicinally interesting molecules. They have also characterized the synthesized compounds using NMR, IR, LC/MSD **[12]**.

M. Saeed Abaee *et al* (2005), research on one pot green synthesis method for fluoroquinolones which increase the up to 86 % yield of fluoroquinolones, one pot synthesis is a method to improve the efficiency of a chemical reaction. The present research focused on the efficient method of fluoroquinolones synthesis for further convenient industrial production of such compounds. The solvent was removed under reduced pressure, the residue was mixed with excessive amount of water, and the mixture was acidified by dilute HCl. The solid phase was separated by filtration and was added to a refluxing solution of piperazine in water in a flask. The mixture was refluxed for I h under atmospheric pressure. The solvent volume was reduced to 50 mL and refluxing continued for another 14 h at 115 °C. The course of the reaction was monitored by HPLC method **[13]**.

Navin B. Patel *et al* (2020), research on Lewis's acid promoted, one-pot synthesis of fluoroquinolone clubbed 1,3,4-thiadiazole

motifs under microwave irradiation and evaluated their microbial activity and proved that A Lewis acid promoted efficient procedure for one-pot green synthesis of newer class of fluoroquinolone clubbed with thiadiazols' motifs under microwave irradiation is described here. Fluoroquinolone, 1,3,4-Thiadiazole complex Motifs was prepared by Lewis acid promoted, one-pot synthesis, under microwave irradiation. All the synthesized molecules were determined by IR, 1 H NMR, 13C NMR, and Mass spectra. The antimicrobial activity of synthesized compounds was examined against two Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), two Gram-positive bacteria (*Staphylococcus aureus, Streptococcus pyogenes*), and three fungi (*Candida albicans*, *Aspergillus Niger*, *Aspergillus clavatus*) using the MIC (Minimal Inhibitory Concentration) method and anti-tubercular activity H37Rv using L. J. Slope Method **[14]**.

Nakhaei, Ahmad *et al* (2018), research on an efficient green approach for the synthesis of fluoroquinolones using nano zirconia sulfuric acid as highly efficient recyclable catalyst in two forms of water. The results showed that ZrSA showed high catalytic activity in the reaction of fluoroquinolone derivatives synthesis in two forms of water. Furthermore, the catalyst was recyclable and could be reuse without any loss in its catalytic activity. Overall, this catalytic method for the synthesis of fluoroquinolone derivatives provides rapid synthesis of desired compounds in refluxing water following a simple procedure and avoids the use of harmful organic solvents **[15]**.

Demirci *et al* (2018), proposed and synthesized a new class of 5-substituted-1,3,4- thiadiazole-based fluoroquinolone analogues and screened them for their antimicrobial potential. The results shown that compound 20 was found to be most potent, exemplify the antibacterial potential towards S. *aureus* (MIC value ¼ 2 μg/ml) and E. *coli* (MIC value ¼ 4 μg/ml). The compounds 19 and 20 exhibited the modest antitubercular activity (MIC value of 8 μg/ml for each) **[16]**.

Pandit *et al* (2016), synthesized some fluoroquinolone derivatives by with different thiadiazole derivatives by refluxing on an electrically heated water bath and screened them for their antimicrobial activity. Result presented shows that ciprofloxacin derivatives with thiadiazoles (21–23) exhibit superior antimicrobial activity. Also, sparfloxacin derivatives (24–26) shows both antibacterial and antifungal activity **[17]**.

CONCLUSION:

Our biggest challenges in future to save environment, therefore we need to design eco-friendly chemical reaction pathway to get chemical product. Green chemistry

resolved such type of challenges by inventing novel reaction scheme which is helped us to synthesized the chemicals with high percentage yield, Green chemistry helped us to reduced time, cost and simplify the reaction scheme involved in chemical synthesis. By using green chemistry, we can have synthesized the wide number of fluoroquinolones derivatives which are used to treat number of bacterial infection, as we know bacteria have tendency to cause resistance therefore we need to synthesized more antibiotics time to time, by using green chemistry method we can easily synthesized new generation of antibiotics.

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