

Research Article

Fluoroquinolone Mannich bases as promising biologically beneficial molecules

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Abstract

Mannich bases, a structurally heterogeneous aminomethyl functionality, found numerous applications in medicinal chemistry field. Fluoroquinolones-Mannich bases here is discussed, with prominence on the correlation between structure and biological activity as it could be responsible for enhancing physicochemical properties of fluoroquinolones. The review covers broadly the literature works that correlated fluoroquinolones-Mannich bases cytotoxicity activity as anticancer agents rather than their antibacterial activity. The most applicable studies on the activity of fluoroquinolones-Mannich bases as potential antimycobacterial candidates and antiviral agents have been included as well. This contemporary review considers a first kernel for upcoming exertions in designing and synthesis of more Fluoroquinolone -Mannich bases.

Key words: Fluoroquinolones; Mannich bases; Antibacterial; Anticancer; Antimycobacterial.

Introduction

Mannich reaction is aminoalkylation reaction was named when chemist Carl Mannich carried out a three-component reaction that condensate structurally various substrates (**X-H**) having at least one active hydrogen atom, an aldehyde component (**HCHO**) and an amine reagent to afford a class of compounds generally known as Mannich bases, formaldehyde is considered to

be the most favorable aldehyde component, secondary aliphatic amines (**R₂NH**) represent the most widely used amine reagents, **Figure 1**. Structural diversity of Mannich bases were obtained by varying the substrates that can be aminomethylated and by introducing different amine reagents that can be possibly incorporated in the Mannich reaction⁽¹⁾.

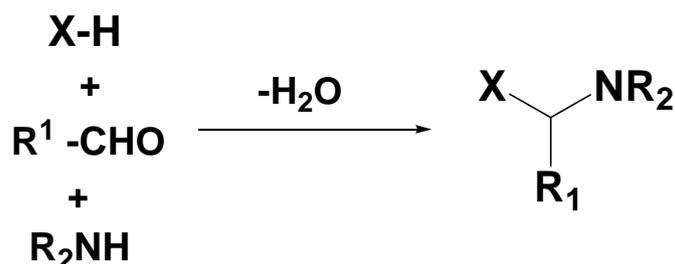


Figure 1: Main scheme of the Mannich reaction

Improving the distribution of drugs into the human body could utilize the aminomethylation that may be responsible of increasing the

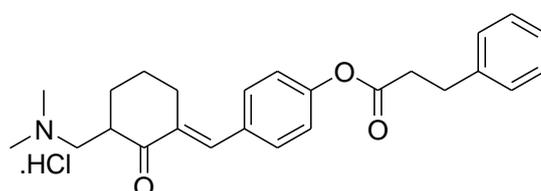
hydrophilic properties of drugs through the introduction of a functionality polar group into its chemical entity. A common example is

represented in the long-known antibiotic rolitetracycline⁽²⁾. Mannich bases could play a role as prodrugs which release the active form of the drug under controlled hydrolytic conditions *via* deamination process⁽³⁾. In addition, the Mannich base is assumed to enhance the lipophilicity of the corresponding amines at physiological pH by reducing their protonation, leading to increased absorption across biomembranes.⁽⁴⁾

Mannich bases are an imperative group of compounds in medicinal chemistry; that showed a wide range of biological activities, this is supported by the interest of research groups all over the world that reported their

cytotoxic⁽⁵⁾, antimicrobial⁽⁶⁾, anti-inflammatory⁽⁷⁾ and anticonvulsant⁽⁸⁾ activities.

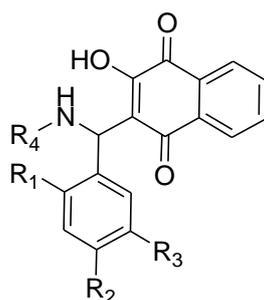
Anticancer properties and cytotoxicity of Mannich bases resulted from acetophenones as ketonic type of Mannich bases⁽⁹⁾ and of structurally related to α , β -unsaturated ketones⁽¹⁰⁾ were studied in the last decade. Mannich bases' cytotoxic action relies on the alkylation of thiols inside the cell, as glutathione or cysteine, which may sensitize tumor cells to anticancer agents, or even reverse resistance to drugs.⁽¹¹⁾ Therefore, compounds with both an activated unsaturated carbon-carbon double bond and a ketonic Mannich base moiety (for example, the Mannich base from chalcones such as 1) have been proposed as candidates for the validation of the consecutive cytotoxicity theory.⁽¹²⁾



1

Ketonic Mannich bases obtained from 4-aryloxyacetophenones have been shown to exhibit mild cytotoxic properties for murine L1210 cells as well as human Molt 4/C8 and CEM T-lymphocytes, and a number of these compounds have a distinct potential for different lines of human colon cancer cells⁽¹³⁾.

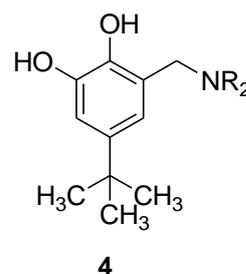
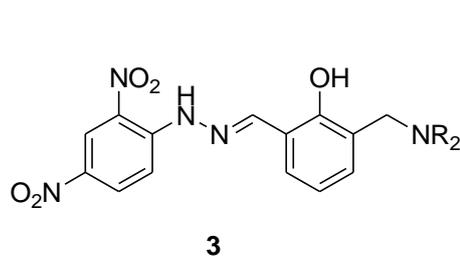
A number of new phenolic Mannich bases **2**, along with their complexes of copper (II), were synthesized from lawsone and examined for their antibacterial activity toward different types of bacteria, compound **2** showed higher potency regarding the corresponding complexes, this can be attributed to the enhancement of the solubility of the pro-ligands.⁽¹⁴⁾



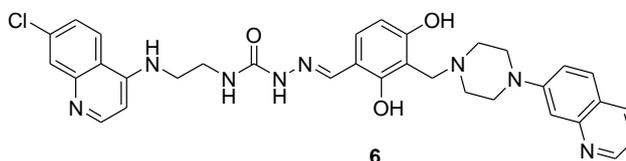
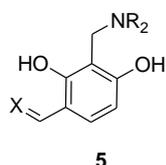
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Several studies reported the antifungal activity of phenolic Mannich bases **3**⁽¹⁵⁾. candidates **3** (NR₂ = diphenylamino, 4-morpholinyl, 1-piperazinyl) showed the greater anti-*Candida*

properties comparable with the reference drug clotrimazole. Nevertheless, most of the tested compounds inhibited the growth of *Aspergillus niger* with MIC of 1.56-3.12 $\mu\text{g}/\text{mL}$ ⁽¹⁵⁾.



Indeed, the aminomethylated 4-t-butylcatechol **4**, and their corresponding Cu (II) complexes have substantial antifungal activity with radial inhibition of mycelial growth $\geq 70\%$ against plant pathogenic fungi compared to nystatin and terbinafine⁽¹⁶⁾. In addition, Phenolic Mannich bases **5** of 2,4- dihydroxybenzaldehyde were



introduced and their corresponding semicarbazone and thiosemicarbazones were introduced⁽¹⁷⁾. The semicarbazone Mannich base **6** has promising potent antimalarial activity with $IC_{50} = 77$ nM) against chloroquine-resistant W2 *P. falciparum* strain⁽¹⁷⁾.

Fluoroquinolones

The fluoroquinolone scaffolds is considered as synthetic widespread antibiotics. The prototype, nalidixic acid has a prominent anti-Gram negative activity. On the other hand, newer derivatives having 6-fluoro and 7-piperazinyl showed excellent broad spectrum of activity. It is clear from SAR studies that 6-fluoro and 1-alkyl, 1,4-dihydro-4-oxoquinoline- 3-carboxylic acid moiety is responsible for enhanced potency as they bind with type-II topoisomerase enzymes, DNA gyrase, and topoisomerase IV⁽¹⁹⁾. Most fluoroquinolones are administered orally and thus need to proceed through a variety of membrane barriers before receptor interactions can occur. Lipophilicity of biologically active compounds typically correlates with the bacterial membranes' ability to penetrate, which is of great concern to the pharmaceutical industry.⁽²⁰⁾ It is believed that chemical modifications at C-7 are an appropriate target for controlling the pharmacokinetic properties and hence altering cell permeability of these compounds.⁽²¹⁾ The known released fluoroquinolone, levofloxacin, possesses a broad-spectrum antibacterial activity similar to lomefloxacin and sparfloxacin which is

considered members of the third generation of Fluoroquinolone, which have greater activity against Gram-positive and atypical organisms.⁽²²⁾

Despite these substantial achievements and enormous requirements in antibacterial therapy, These drugs have been found to experience various drawbacks, such as low hydrophilicity, less oral bioavailability, limited range of action, short half-life, poor systemic delivery, unpleasant taste, and less lipophilicity,⁽²³⁻²⁶⁾. Having a basic amino group in their 7-substituent, most of the fluoroquinolones exhibit low water solubility at physiological pH levels. for instance, this limits the intravenous dose of ciprofloxacin that can be given. Another drawback related to solubility issues is the Crystalluria adverse effect of fluoroquinolones.⁽²⁷⁾

Further modifications at *N*-terminal of piperazinyl moiety of Fluoroquinolone reported that it alters the physicochemical properties of Fluoroquinolone, hence consequently improve the antibacterial activity of them due to enhancement of their lipophilicity and avoiding

the formation of zwitterion formed between carboxylic group and the *N*-terminal of piperazinyl moiety, rather than overwhelming the main problems contributed with fluoroquinolones such as poor hydrophilicity, poor systemic distribution, short half-life, narrow spectrum of activity, less oral bioavailability, unpleasant taste and less lipophilicity.⁽²⁸⁾

The capability of fluoroquinolones to traverse bacterial membranes is greatly influenced with their lipophilicity. Subsequently, partition coefficient arose as a crucial parameter that affect their biological activity. Furthermore, it is clear that the neutral fluoroquinolone species are more lipophilic than the zwitterionic form.

Lipophilicity can also be affected by factors such as steric and electronic effects or charge density that can modulate *N*-4 protonation⁽²⁹⁾ Therefore, lipophilicity is considered a very important factor in the intestinal absorption of fluoroquinolones. Decreasing the zwitterionic nature of enhances lipophilicity that augments the weak correlation between *in vivo* and *in vitro* activity of fluoroquinolones.⁽³⁰⁾

Fluoroquinolone Mannich bases

Many structural hybrids as Fluoroquinolone Mannich bases have been synthesized in the last two decades with a variety of biologically active properties. Synthesis of various *N*-Mannich-based ciprofloxacin and norfloxacin prodrugs has already been reported and substantial antimicrobial potential has been identified for these synthesized prodrugs with enhanced lipophilicity^(31, 32). According to the aforementioned results, the synthesis of the *N*-Mannich base significantly reduces the PKa amines by around 3 points, resulting in an improvement in the lipophilicity of the parent drug and, subsequently, in diffusion potential. In addition, *N*-Mannich base hydrolyses release the bioactive compound at varying rates in buffers depending on its pH.⁽³³⁾ Hence, it may be anticipated that the synthesized prodrugs may undergo hydrolysis reaction to liberate the active drug molecule.

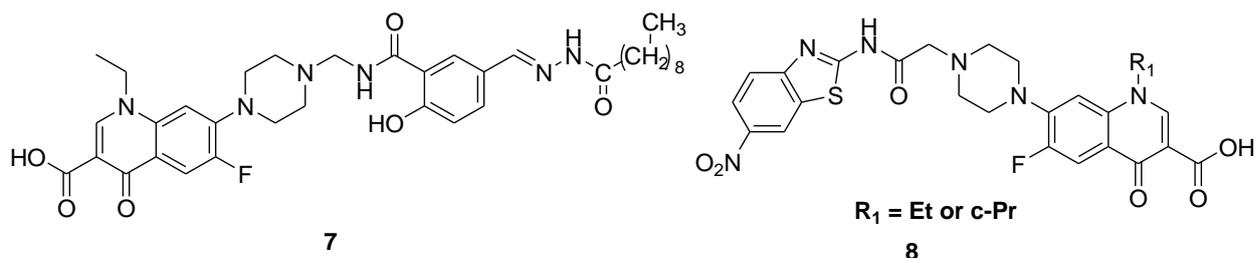
Despite the prodigious potential in medicinal chemistry of Fluoroquinolone Mannich bases, many recent literature reviews of consequences

do not appear to have been inspired, our present review fills this deficiency by providing comprehensive coverage of the most relevant developments of Fluoroquinolone Mannich bases generated exclusively through amino-methylation, this contemporary review considers the first kernel for upcoming exertions in designing and synthesis of more Fluoroquinolone Mannich bases. the information being ordered according to the reported biological activity.

Fluoroquinolone Mannich bases with Anticancer and cytotoxic activity

Among the reported mechanisms for the cytotoxic activity of Mannich bases, thiol alkylation⁽³⁴⁾ interfering with enzymes responsible for antioxidant mechanisms⁽³⁵⁾ and mitochondrial respiration inhibition⁽³⁶⁾ along with inhibition of topoisomerase enzyme⁽³⁷⁾, and tubulin polymerization⁽³⁸⁾, appeared to be the most operative.

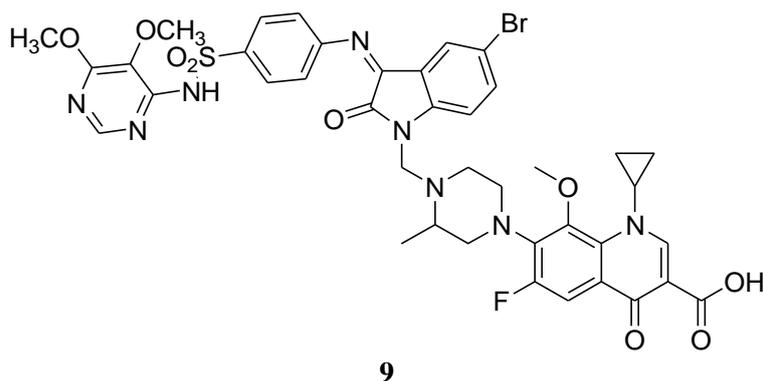
Piplani et al., synthesized lipid-based prodrugs of ciprofloxacin and norfloxacin by employing *N*-Mannich base reaction in two schemes one of them by refluxing norfloxacin or ciprofloxacin with 5-formyl salicylamide in presence of formalin. These *N*-Mannich bases were further reacted with fatty acid hydrazides to prepare the prodrugs/compounds. in the other scheme benzothiazole-clubbed analogs as of *N*-(benzo[*d*]thiazol-2-yl) acetamide was synthesized by reacting with norfloxacin or ciprofloxacin in the presence of formalin in alcohol. The cytotoxicity of the compounds was inspected in human lung cancer cell line **A549** using sulforhodamine (SRB) assay method. Among the tested prodrugs, fatty acid derivative **7** and 6-nitrobenzothiazole derivative of **8** showed greater potency against the human lung cancer cell line with GI₅₀ value of **67.38** µg/mL and **28.8** µg/mL, respectively. The amelioration of the synthesized prodrugs cytotoxic activity indicates their capability of penetration as a result of partition coefficient improvement when compared with the pure drug itself, obviously presence of electron-donating and electron-withdrawing groups had effected cytotoxic activity beneficially more than the parent drug⁽²⁸⁾.



Isatin derivatives are a promising scaffold for many biological activities including anticancer activity. towards the development of novel anticancer agents, a family of Mannich bases of Gatifloxacin containing isatin moiety at C-7 position was designed and synthesized by Yogeeswari et al., this was achieved simply by reacting the appropriate isatin derivatives in ethanol with gatifloxacin and 37% formaldehyde via irradiation in a microwave oven at an intensity of 80% with 30 s/cycle.⁽³⁹⁾

the synthesized compounds were subjected to an *In-vitro* cytotoxicity screen against a panel of 58 human tumor cell lines derived from nine neoplastic diseases using etoposide as the reference compound for comparison.

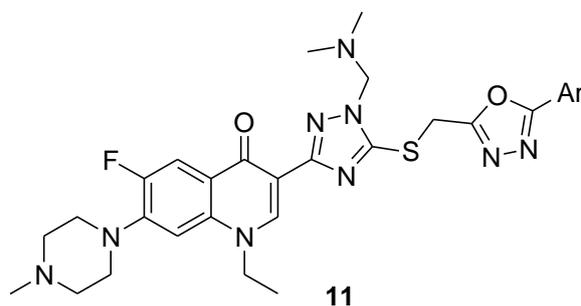
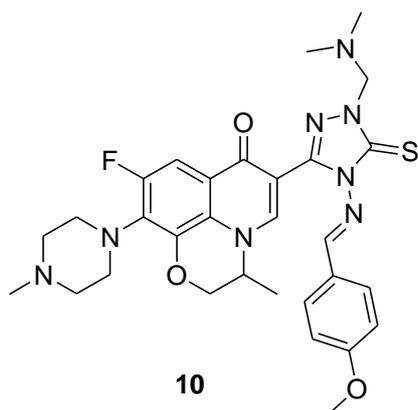
Compound **9** was more potent than the reference (etoposide) against five cell lines (A549/ATCC, EK VX, HOP-92, NCI-H23, and NCI-H322 M). Results revealed that it has **85** folds of activity more than etoposide against HOP-92 with GI₅₀ of 0.176 μ M.



Many literatures emphasized that presence triazole at the 3 position of fluoroquinolone moiety could be suitable for emerging lead compounds for designing and development of new anticancer agents. From this notion, Hu et al.,⁽⁴⁰⁾ have reported the synthesis of triazole-3-thione analogs **10** and evaluated their antitumor activity as ofloxacin derivatives. The target compounds were evaluated, using MTT assay, for their cytotoxic activity against leukemia cell

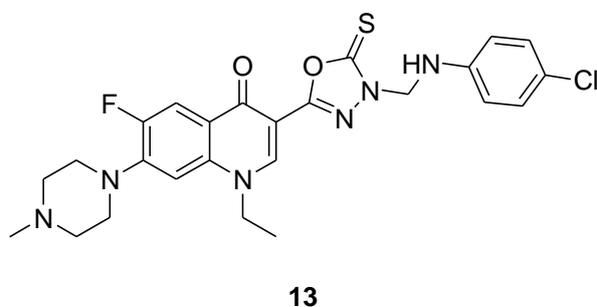
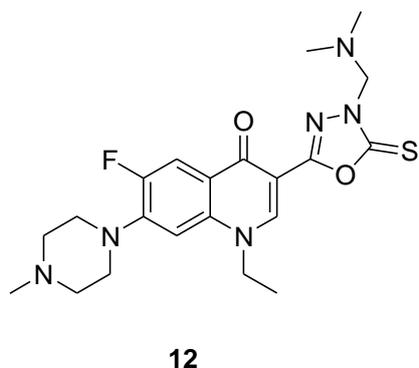
lines (L1210), (HL60), and Chinese hamster ovary cell line (CHO) using MTT assay.

The *in vitro* assay revealed a substantial increase of potency for the Schiff-Mannich bases **10** with IC₅₀ values of 0.14–17.6 μ M. compounds containing free phenolic group (R = 2-OH, 3-OH-4-MeO, and 4-OH-3-MeO) considered the most potent anti-proliferative agents⁽⁴⁰⁾.



Sun et al.,⁽⁴¹⁾ have synthesized a series of triazole – pefloxacin analogs **11** derived functionally as C-3 side chain. The effect of Mannich bases **11** on the *in vitro* growth of four human tumor cell lines namely SMMC-7721, L1210, HL60, Hep-3B, and Capan-1 was evaluated. The range of IC₅₀ values was 1.5-24.5 μ M, respectively. The presence of 2-MeO and 4-F on the aromatic pendant moiety **11** has been found to have a beneficial effect on the inhibitory profile.⁽⁴¹⁾

Oxadiazole is a distinguished structural motif found in numerous anticancer agents. Yinsheng et al., have reported the design and synthesis of C-3 modified pefloxacin derivatives possessing 1,3,4-oxadiazole thione Mannich base **12**⁽⁴²⁾. The cytotoxicity assay of the Mannich bases **12** against Hep-3B cancer cell line showed that all compounds displayed more potent activity than pefloxacin. Aliphatic amine-derived compounds (**12**, IC₅₀= 8.4 μ M) were more potent than the aniline-derived aromatic amine compounds (**13**, IC₅₀= 45.4 μ M).



Fluoroquinolone Mannich bases as Antibacterial agents

Most Fluoroquinolone, either on the market or in development, is generically distinguished by a broad spectrum of antibacterial activities, enhanced potency, and excellent oral bioavailability.⁽⁴³⁾ However, their activity is relatively moderate against certain clinically relevant gram-positive cocci including *Staphylococci*, *Streptococci* and *Enterococci*⁽⁴⁴⁾.

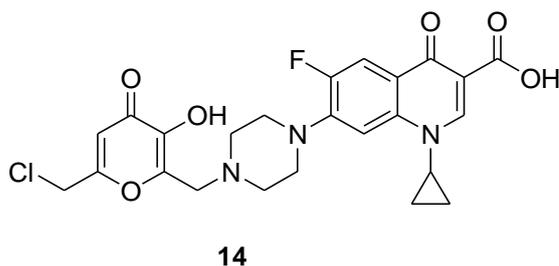
Furthermore, the prevalence of emerging virulence and the drug resistance of

fluoroquinolones pathogens has become a serious problem.⁽⁴⁵⁾ In the area of antimicrobial chemotherapy, therefore, the discovery and development of new agents or modified fluoroquinolone derivatives is crucial.

Emami et al., managed to synthesize Mannich bases of 7-piperazinyl quinolones with kojic acid and chlorokojic acid, relying on the fact that both of them possess antibacterial activity. The Mannich bases were prepared by the reaction of proper Fluoroquinolone with kojic

acid or chlorokojic acid and formalin in methanol at room temperature.⁽⁴⁶⁾

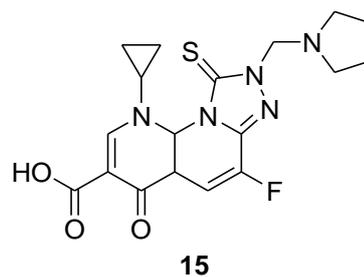
The antibacterial activities of the synthesized compounds were evaluated against a panel of Gram-positive (*Staph. aureus* ATCC 6538, *Staph. epidermidis* ATCC 12228, *B. subtilis* ATCC 6633) and Gram-negative (*E. coli* ATCC 8739, *P. aeruginosa* ATCC 9027, *K. pneumoniae* ATCC 10031), the MICs of the synthesized Mannich bases were determined using agar dilution method using norfloxacin as the reference drug. In general, Significant antibacterial activity was demonstrated for both Gram positively and Gram-negative bacteria, for all compounds. Compound **14** showed outstanding results against *S. aureus* and *P. aeruginosa*, with MIC value of 0.097 µg/mL and 0.19µg/mL with **4** folds and **8** folds more than norfloxacin, respectively. Furthermore, compound **14** showed the highest growth inhibitory activity against *S. epidermidis*, and *B. subtilis*, with equal potency as norfloxacin.



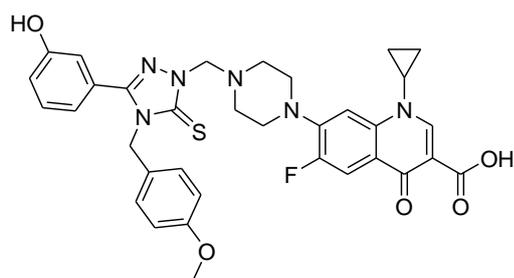
in an attempt to enhance the antibacterial effect of ciprofloxacin and seeking for potential antibacterial agents Plech, et al., used a molecular hybridization approach, to design Mannich bases of 1,2,4-triazole-3-thione derivatives with ciprofloxacin and formaldehyde as they clarified in their previous work^(49, 50). Results revealed that compound **16**

Additionally, Compound **14** exhibited a similar mode of binding compared to both co-crystallized and docked ciprofloxacin, the results revealed that in the most cases chlorokojic acid derivatives were more active than corresponding kojic acid analogs.

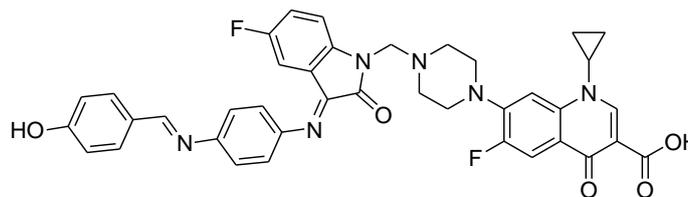
it is well established that chemical modifications at C-7 of Fluoroquinolone are suitable for controlling of the pharmacokinetic properties and enhancing the cell permeability⁽⁴⁷⁾. In an attempt to find new antibacterial agents with acceptable activity against resistant strains, Gao, et al., synthesized novel *s*-triazole-fused tricyclic fluoroquinolone carboxylic acid derivatives carrying a functional Mannich-base moiety at the C-8 position⁽⁴⁸⁾. among the synthesized Mannich bases, compound **15** with the pyrrolidine moiety showed MIC value of **0.25** µg/mL in antibacterial assay against multiple drug-resistant *Escherichia coli*, which represents about **30**-fold increase of potency compared to ciprofloxacin.



exhibited **16**-fold greater activity than ciprofloxacin with respect to *S. aureus*. Moreover, complete growth inhibition of *S. aureus* occurred with **8**-fold lower concentrations than ciprofloxacin, MICs of Mannich base **16** were about **15** times lower than in the case of vancomycin (i.e., 0.046µM vs. 0.68 µM)



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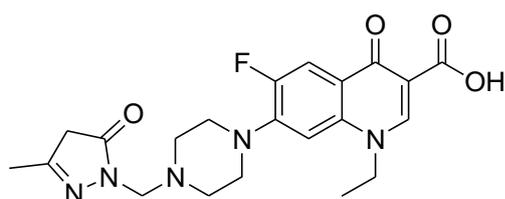
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SAR of the substituent in the position 4 of the 1,2,4-triazole-3-thione core revealed that the presence of a phenyl ring is essential for strong antibacterial effect. Electron-donating groups on a phenyl ring are more favorable than electron-withdrawing groups. An enzyme analysis performed on selected compounds indicates that a significant increase in ciprofloxacin-triazole hybrids' antibacterial activity does not result from an increase in their binding to the bacterial type of topoisomerase IV.

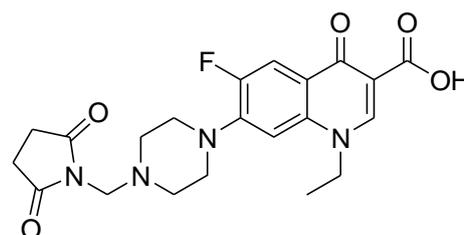
In another work regarding Isatin moiety, Prakash et al., opted a combination of Schiff and Mannich bases of isatin derivative to synthesis a novel derivative of ciprofloxacin. The presence of hydroxyl group in para position of Ciprofloxacin methylene isatin derivatives 17 enhanced the activity against *S. aureus* ATCC 9144 and *P.aeruginosa* ATCC 2853 with MIC = 7.81 µg/ml in both microorganisms than ciprofloxacin. On the other hand, nitro and chlorine substituted derivatives as electron-

withdrawing groups, displayed the lowest activity for the investigated strains.⁽⁵¹⁾

The N-Mannich base functional group is assumed to increase the lipophilicity of the parent amines at physiological pH values by reducing their protonation, leading to greater absorption through bio-membranes.⁽⁴⁾ In advance Abuo-Rahma et al., prepared Mannich bases by heating at the reflux of norfloxacin and different secondary amine, imide with excess formaldehyde in ethanol. The synthesized compounds were tested for their in vitro antibacterial activity against *P. aeruginosa*, *E. coli*, *K. pneumonia*, and *Staph. aureus* strains using norfloxacin as a reference drug, by agar diffusion method. Pyrazolone Mannich base 18 demonstrated strong inhibition activity against both Gram-positive and Gram-negative species, which is more than that exhibited by norfloxacin. Succinimide Mannich base 19 showed better activity than the reference in all the strains examined, excluding *K. Pneumonia*.⁽³⁰⁾



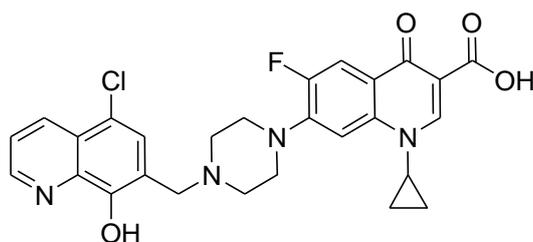
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19

Fu et al., managed to prepare a series of 5-chloroquinoline 8-ol derivatives via Mannich reaction, among the target compounds, a new derivative synthesized by linking ciprofloxacin as a privileged broad-spectrum scaffold at 7-position of quinolone core to generate a hybrid compound 20, aiming at exploring dual-target candidate against both Gram-positive and Gram-negative bacteria, all the novel target compounds were screened on both Gram-

positive and Gram-negative strains (*Staph. epidermidis*, *Staph. aureus*, *E. faecalis*, *E. faecium*) compound 20 showed the potential effect against most of the tested Gram-positive and Gram-negative strains with MIC values of 0.125–8 µg/mL. Molecular-docking assay revealed that compound 20 might target both bacterial lipopolysaccharide (LPS) transport LptA and Topoisomerase IV proteins.⁽⁵²⁾



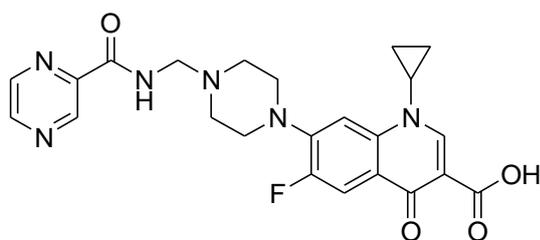
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Fluoroquinolone Mannich bases with antimycobacterial activity

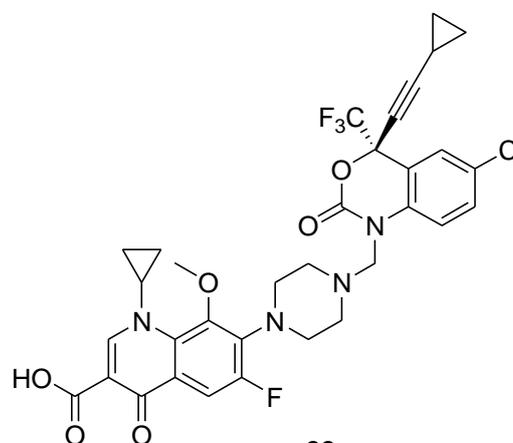
Tuberculosis is a communicable and even fatal disease caused by *Mycobacterium tuberculosis* and is responsible for up to 2 million deaths each year. Multidrug-regimen-resistant TB cases are also raging these days, creating a serious situation⁽⁵³⁾.

The research team of Sriram et al., introduced one of the frontline antimycobacterial agents, Pyrazinamide (PZA), into a Mannich base with various Fluoroquinolone compounds via Mannich reaction. The target compounds were screened for their antimycobacterial activity against MTB and MDR-TB by the agar dilution

method, among the synthesized compounds the ciprofloxacin Mannich hybrid **21** was the most potent (MIC = 0.20 µg/mL), and was >125 times more potent than that of the parent drug PAZ and >7 times more potent than isoniazid (MIC = 1.56 µg/mL) against MDR-TB. Subsequently, Compound **21** was subjected to an *in vivo* animal study for efficacy against MTB at a dose of 100 mg/kg in six-week-old female CD-1 mice, the tested Compound decreased the bacterial load in lung and spleen tissues with **1.86** and **1.66**-log₁₀ protections, respectively. Results proved that simply increasing lipophilicity expressed in log*P* (-1.04 to 01.95) of the new PAZ Mannich bases enhanced the biological activity⁽⁵⁴⁾.



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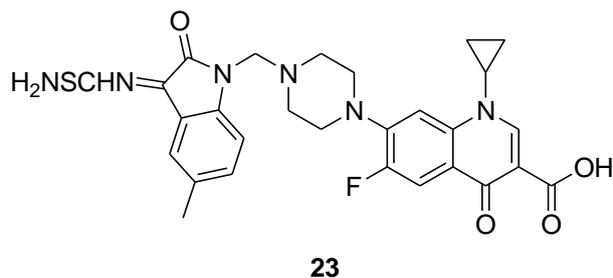


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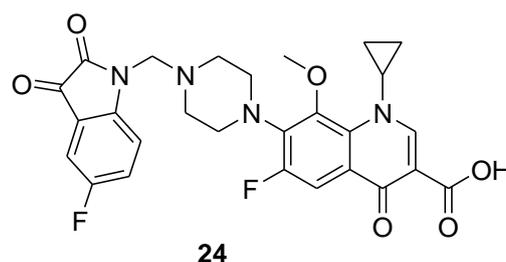
Continuing this research work by Sriram et al., on Mannich bases, a new efavirenz Mannich bases have been synthesized and investigated for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv by the agar dilution method. Compounds containing the fluoroquinolone moiety were found to be promising among the derivatives studied, and compound **22** was found to be the most active derivative with a MIC of 0.2 µg/mL⁽⁵⁵⁾.

Fluoroquinolone lipophilicity is well known to play a significant role in the penetration of these compounds into bacterial cells.⁽⁵⁶⁾ In another work, Sriram et al.,⁽⁵⁷⁾ reported the synthesis of novel isatin-ciprofloxacin Mannich bases. Using the microplate Alamar Blue assay, all compounds were tested for their antimycobacterial activity at 6.25 µg/mL against the MTB H37Rv strain.

In vitro studies showed that compound **23** exhibited a measurable potency with MIC of 1.21 nM as 5 folds more than ciprofloxacin. Preliminarily, antimycobacterial results asserted that the presence of bromine atom in the C-5 position of isatinimino derivatives had an eminent activity towards mycobacteria. Assuming that the issue of penetration is even more important for the action of Fluoroquinolone against mycobacteria, the results



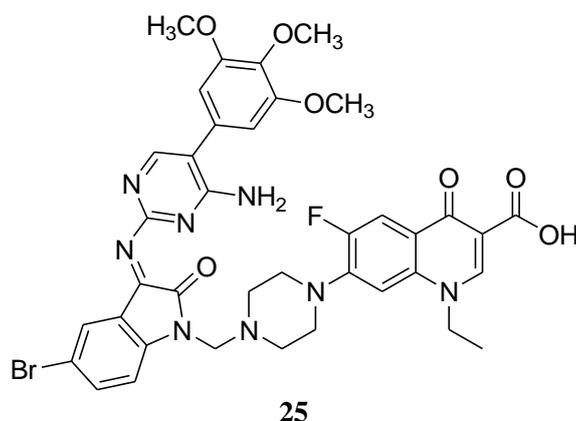
show that simply increasing the lipophilic character was sufficient to increase the activity of the synthesized compounds (0.89–2.04), which were much more than the parent compound (0.01). Additionally, toxicity (IC_{50}) in a mammalian cell line, Vero cells (specialized in assessing the cytotoxicity by the TAACF) revealed that the compounds that showed MIC of <2 nM, were nontoxic till 100 nM, and their selectivity indexes were more than 100.



In parallel work, a series of 8-OCH₃ ciprofloxacin methylene and ethylene isatin derivatives containing different oximes were designed and synthesized by Feng et al.,⁽⁵⁸⁾ For the sake of optimizing the potency of these compounds against mycobacteria, the targeted compounds were screened for their *in vitro* antimycobacterial activity against *M. smegmatis* CMCC 93202 using serial double dilution technique in duplicate along with 8-OCH₃ ciprofloxacin, ciprofloxacin, rifampicin and isoniazid for comparison⁽⁵⁹⁾. The results showed that compound **24** (MIC= 0.074 μ M) was 2-13-fold more potent than the reference compounds.

Fluoroquinolone Mannich bases with anti-viral activity

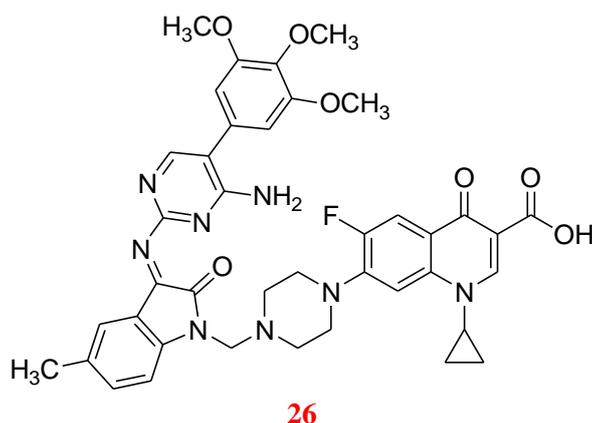
In Pandeya and Sriram's work, nine Mannich bases of norfloxacin were synthesized and investigated for their *in vitro* antimicrobial activity using the agar dilution method against 28 different bacteria strains and for anti-HIV activity against replication of HIV-1 (III B) in MT-4 cells. In the mouse protection test, compound **25** (ED_{50} : 1.62 mg/kg) was more active than norfloxacin (ED_{50} : 6mg/kg). meanwhile, Mannich base **25** had shown inhibition against HIV-1 (III B) with EC_{50} value of 13.9 μ g/mL and with selectivity index up to 5⁽⁶⁰⁾.



In their efforts towards the development of agents with broad-spectrum chemotherapeutic properties for effective treatment of HIV/AIDS, Sriram and Yogeewari supposed that an ideal drug for HIV/AIDS patients should suppress HIV replication thereby acting as an anti-HIV drug. Meanwhile treating opportunistic infections (OIs) like TB, hepatitis, and other bacterial infections.

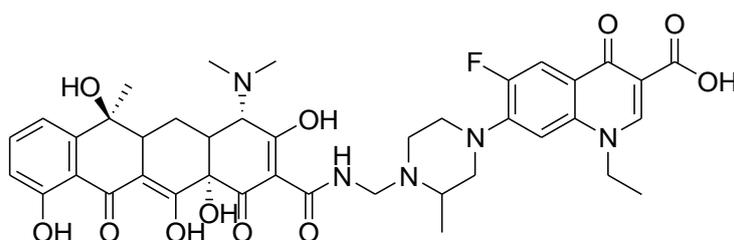
In Earlier work, they identified various isatinimino derivatives exhibiting broad-spectrum chemotherapeutic properties⁽⁶¹⁾. As a continuation to such effort in developing broad-spectrum chemotherapeutics agents, they designed and synthesized 12 new aminopyrimidinimino isatin analogs as a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) and evaluated them for anti-HIV activity against replication of HIV-1 (III B) in

MT-4 cells, inhibition of HCV viral RNA replication and screening against *M. tuberculosis* strain H37Rv besides *in vitro* antibacterial activity evaluation against 24 pathogenic bacteria by conventional agar dilution procedures. The results showed that four compounds of the 12 new derivatives produced in this study revealed inhibition against HIV-1 replication in MT-4 cells with EC₅₀ ranging from 11.6 to 28.4 μM . All compounds were active against HCV RNA replication, displaying inhibition of > 65% at 50 $\mu\text{g ml}^{-1}$. Three compounds inhibited *M. tuberculosis* H37Rv with MIC of 3.13 $\mu\text{g ml}^{-1}$. Three compounds showed very good activity against various pathogenic bacteria. The compound **26** containing ciprofloxacin moiety at N-1 position arose as more promising broad-spectrum chemotherapeutic agents among the synthesized compounds.⁽⁶²⁾



Tetracyclines represent one of the broad-spectrum bacteriostatic antibacterial agents, Sriram et al.,⁽⁶³⁾ clubbed a synthesis of a series of new fluoroquinolones tetracycline Mannich bases, the synthesized compounds were evaluated as a multi target agents against HIV and mycobacteria besides an evaluation for their HIV-1 integrase (IN) enzyme inhibition .

results revealed that compound **27** manage to inhibit the replication of HIV-1 with EC₅₀ of 5.2 μM and possess a safety range toward the CEM cells till 200 μM with a selective index (CC₅₀/EC₅₀) of >38, along with antimycobacterial activity with MIC of 0.2 $\mu\text{g/mL}$ against *M. tuberculosis*.



Conclusion

This review summarized distinct biological activities of Fluoroquinolone-Mannich base derivatives in the present scenario. As demonstrated in this review, Fluoroquinolone -Mannich bases are found to have potent multiple activities, it can be concluded that Fluoroquinolone -Mannich bases have remarkable biological potential which is remaining unrevealed. However, this review would hopefully shed light on ideas to raise the therapeutic value and specificity of Fluoroquinolone-Mannich bases.

Throughout the last decade, a large number of novel Fluoroquinolone -Mannich bases have been synthesized and evaluated as potential treatments for a multitude of diseases and medical conditions, as prodrugs, or as molecules provoking a response from biological targets. As such, the Mannich bases has earned its rightful place as a powerful moiety functionally, both for the synthesis of novel chemical entities and hybrids endowed with various and interesting biological properties and for the modification of physicochemical properties of Fluoroquinolone, that ultimately influence the candidate's biodisponibility, performance and pharmacological activity as a drug. The complete understanding of the structural requirements and molecular mechanisms of Fluoroquinolone -Mannich bases could open a new avenue in the drug discovery of valuable drugs that hold enormous potential to revolutionize the battle of humans against various diseases.

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