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A review of Quinolones Pharmacological Activity

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Abstract

In this review article various pharmacological activities of quinolones are dealt with. Quinolones have a broad and potent spectrum of activity and are also used as first and second-line drugs to treat different types of diseases. Recently, quinolones have been reported to display various biological activities. There is a huge research potential in this moiety and with the help of different substituents various derivatives with different biological activity can be obtained. The present review focuses on the structural modifications responsible for the different biological activities.

Keywords: *Anticancer; FMS kinase inhibitors; Bactericidal; Anticonvulsant*

Introduction

Quinolones comprise a series of synthetic bactericidal agents with a broad spectrum of activity and good bioavailability, characteristics that make them suitable candidates for treating infectious diseases with various localizations: cutaneous, urinary, respiratory, bone, gastrointestinal, etc. The starting point in the development of quinolones was the synthesis of nalidixic acid by Lesher et al. [1], starting from 7-chloroquinoline (Figure 1A), a compound with antibacterial properties, a secondary product from the synthesis of chloroquine. Nalidixic acid (Figure 1B) was proven to be active against certain Gram-negative pathogens, which led to the start of its clinical use in the treatment of urinary tract infections. To date, numerous modifications have been brought to the nalidixic acid scaffold, which have resulted in a broader antibacterial spectrum, a different mode of binding to the plasmatic proteins and a longer half-time; significant changes have been obtained by the attachment of the fluorine atom in position 6 (fluoroquinolones) and a piperazine ring in position 7. Based on their chemical structures, these derivatives can be divided into four classes (Figure 1C): naphtyridine (nalidixic acid, enoxacin, gemifloxacin, tosufloxacin), cinnoline (cinoxacin), pyridopyrimidine (pipemidic acid, piromidic acid) and 4-quinolone (oxolinic acid, flumequine, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, etc.). Based on the antimicrobial spectrum and the pharmacological properties, four generations of quinolones are known. The improved properties of modern quinolones (4th generation) have rendered them suitable for treating more serious infections caused by pathogens (Gram-positive, resistant strains, anaerobe, etc.) with various localizations (respiratory, intra-abdominal, etc.) [1-6].

Biological activity of quinolones

Quinolone derivatives have been known to possess a variety of biological activities such as anticonvulsant, antibacterial, antitumor, antiplatelet, FMS kinase inhibitors and anti-HIV.

FMS kinase inhibitors activity

Wall et al. [7] synthesized some novel 3, 4, 6-substituted 2-quinolones and evaluated them as FMS kinase inhibitors. The macrophage colony-stimulating factor-1 receptor (FMS) is the cell surface receptor for colony-stimulating factor-1 (CSF-1), which controls

growth and differentiation of the monocyte's macrophage lineage. Macrophages are thought to play an important role in several diseases, including cancer and inflammation. In addition, expression of FMS in breast cancer has been linked to poor survivability and increased size, where presumably the receptor is involved in local invasion and metastasis. Consequently, there is significant interest in modulating the CSF-1 pathway and several structural classes of small-molecule inhibitors of FMS have been synthesized. The most active compound was the 1, 7-naphthyridine-2-one (26) [7] (Figure 2).

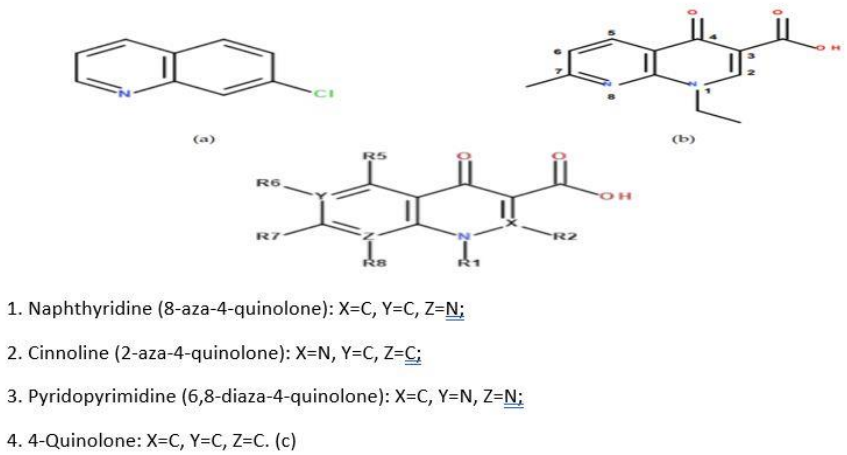


Figure 1. (A) 7-Chloroquinoline; (B) Nalidixic acid; (C) General structure and main classes of quinolones.

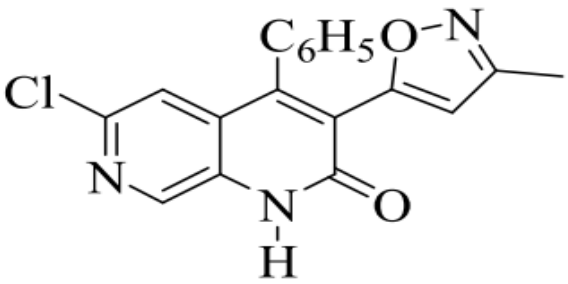


Figure 2: Structure of 1, 7- naphthyridine-2-one (26).

Anticonvulsant activity

Initially a series of derivatives of 6-alkoxy-3, 4-dihydro- 2(1H) quinoline were first found by Sun et al. among which 6-benzyloxy-3, 4-dihydro-2(1H)-quinoline (compound 4) showed the strongest activity with an ED50 value of 29.6 mg/kg in the MES test. Introduction of triazolo ring to the first and second positions of this compound I caused a remarkable increase in the anticonvulsant activity, as seen in 7-benzyloxyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline(compound 5),which showed ED50 values of 17.3 mg/kg and 24 mg/kg in the MES and the sc PTZ tests, respectively. Aim was exploring effective compounds with better anticonvulsant activity and lower neurotoxicity; compounds were designed and synthesized, by substituting triazone with triazolo as in compound II (Figure 3).

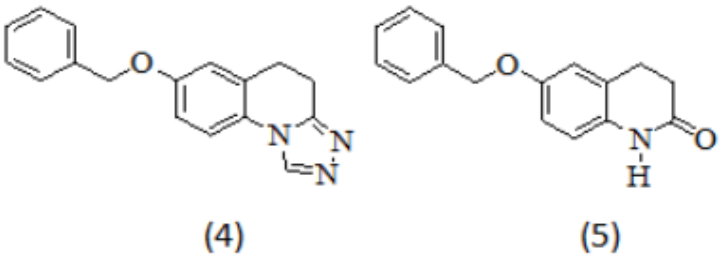
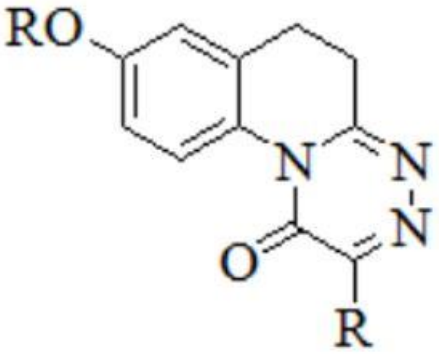


Figure 3: 6-benzyloxy-3, 4-dihydro-2(1H)-quinoline and 7-benzyloxyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline.

The hypothesis was that triazone compounds may have higher affinity to the receptor due to the carbonyl group, and thus may increase the anticonvulsant activity. The introduction of alkoxy group to the 7th position of 1, 2, 4-triazole quinoline remarkably increased their anticonvulsant activity. So, synthesis of a series of 8- alkoxy-5, 6-dihydro-[1, 2, 4] triazino [4, 3- a] quinolin-1- one derivatives was done to discuss the influence of the 8-alkoxy on anticonvulsant activity; and found (6) derivative as most active compound. Sun et al. synthesized series of 8-alkoxy-5, 6-dihydro-[1, 2, 4] triazino [4, 3-a] quinolin-1-one derivatives. Their anticonvulsant activities were evaluated by the maximal electroshock (MES) test and their neurotoxicity were evaluated by the rotarod neurotoxicity test. The results showed that 8-heptyloxy- 5, 6-dihydro-[1, 2, 4] triazino [4, 3-a] quinolin-1-one (6) was the most potent with median effective dose (ED50) value of 11.4 mg/kg, median toxicity dose (TD50) of 114.1 mg/kg. To explain the possible mechanism of anticonvulsant activity, the compound (6) was tested in chemically induced seizures [8] (Figure 4).



R	DERIVATIVES
n-C7H15	6

Figure 4: Derivate synthesised.

Anti-HIV activity

Souza et al; synthesized several 1-[(2-hydroxy-ethoxy) methyl]-3-carbethoxy- 4(1H) quinolones and l-[(2-hydroxy-ethoxy) methyl]-4(1H) quinolone-3-carboxylic acids and evaluated against herpes simplex virus type 1 (HSV-1). Compounds (24) and (25) were the most effective anti-HSV-1 derivatives and presented a 1.5- and 1.3-fold increase in their antiviral activity in relation to acyclovir.

Previous studies by using a structure-based approach, a series of novel quinazoline NNRTIs was designed and synthesized. SAR studies revealed the critical role of the cyclopropane moiety in positioning the substituents on the quinolone nucleus for optimal interactions with the enzyme. The ester moiety also plays an important role for the antiviral activity. Several of these quinolones exhibited potent inhibitory activity against the WT virus and showed promising activity against several NNRTI resistant mutants. These novel quinolones could serve as advanced leads for further optimizations, the goal of which will be focused on overcoming the NNRTI resistant (Figure 5).

Figure 5: Most active synthesised compounds.

Pasquini et al. aimed at rationalizing the influence on the anti-IN activity of the different decorating elements introduced on the 4-quinolone-3-carboxylic acid scaffold allowed us to highlight new aspects of structure-activity relationships for IN inhibiting quinolones. In particular, the substitution of the benzyl

group with aryl, stryl, aroylamino, and aniline groups results in inactive compounds that are not able to adopt the bioactive conformation; conversely, the phenylthio group is able to mimic quite efficiently the benzyl group. On the other hand, the substitution of the benzyl group with the electron-withdrawing benzoyl moiety gives compounds that can be accommodated in the same orientation as the active molecules within the binding site but show a reduced chelating ability. Finally, the replacement of the benzene ring of the quinolone with a quinone moiety gives compounds that, with the exception of (22), adopt a different orientation in the binding site and likely act through a pure ST inhibition mechanism [9-12].

Cholinesterase inhibitors

An enhanced acetylcholinesterase (AChE) activity is a hallmark in early stages of Alzhei- mer's ailment that results in decreased acetylcholine (ACh) levels, which in turn leads to cholinergic dysfunction and neurodegeneration. Consequently, inhibition of both AChE and butyryl- cholinesterase (BChE) is important to prolong ACh activity in synapses for the enhanced choliner- gic neurotransmission. In this study, a series of new fluoroquinolone derivatives (7a-m) have synthesized and evaluated for AChE and BChE inhibitory activities. The screening results suggested that 7g bearing ortho fluorophenyl was the most active inhibitor against both AChE and BChE, exhibiting IC50 values of 0.70 ± 0.10 mM and 2.20 ± 0.10 mM, respectively. The structure–activity relationship (SAR) revealed that compounds containing electronegative functions (F, Cl, OMe, N and O) at the ortho position of the phenyl group exhibited higher activities as compared to their meta- and/or para substituted counterparts.

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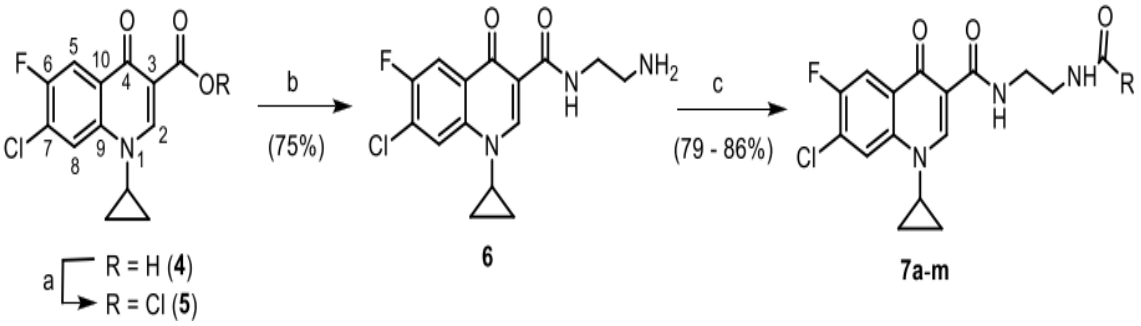

Figure 6: Synthesis of new fluoroquinolone derivatives.

Where R=All compound shown in figure 7. The AChE and BChE (source human: sigma 9000–81-1 and 9001–08-5, respectively) inhibitory studies were performed according to Ellman's method [13]. Donepezil was used as a positive control. Solutions of tested compounds 7a-m in DMSO with five different concentrations (0.01, 0.1, 0.5, 5.0, 10.0 mM) were prepared. For enzyme inhibition assay, 20 lL of the corresponding enzyme (0.2 units/mL in 1 M phosphate-pH 8.0 containing 25% v/v glycerol) was added to a 24- well plate containing 2000 lL of PBS, 30 lL solution of the tested compound and 60 lL of 5,50-dithiobis(2-nitroben zoic acid), DTNB, (0.5 mM). After 3 min of incubation, 20 lL of acetylthiocholine iodide/S-butyrylthiocholine chloride (10 mM) was added and then further incubated for at least 1 min at 25 °C. The reaction was initiated when enzyme was added and the blank reading were taken for all chemicals except the inhibitor [13,14].

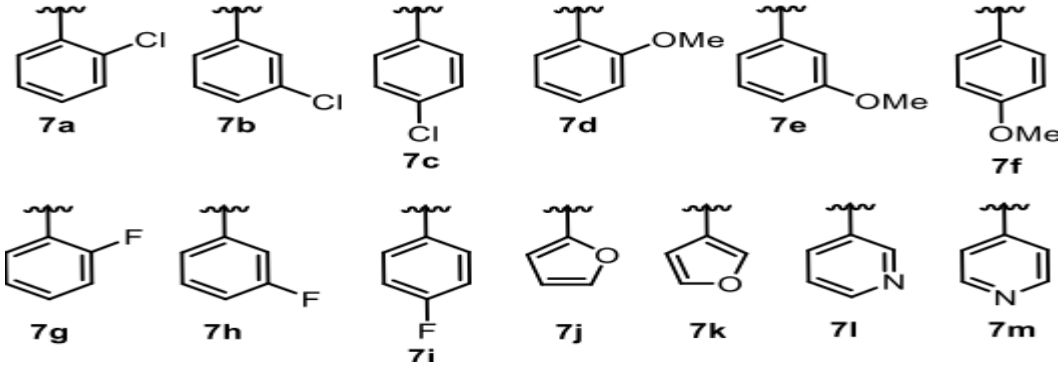

Figure 7: Different Substituents of derivatives.

Biological activity of metal complexes of quinolones with lanthanide ions

The biological activities of several metal complexes obtained in solid state have been assessed. Table 1 comprise data regarding the biological activities published for quinolone complexes with lanthanide ions, respectively.

Table 1: Biological activities of several metal complexes.

Ligand	Complex	Biological Activity Test	Results
Pipemidic acid (PPA)	[La(PPA)4Cl]Cl2	-antibacterial activity on *E. coli, S. aureus, P. aeruginosa* similar to PPA;	-antibacterial activity on S. pneumoniae much greater than PPA; -NO activity on S. aureus
	[M(PPA)4]Cl3 where M=Ce3+, Pr3+, Nd3+, Sm3+, Tb3+, Dy3+, Y3+.		-Pr, Sm, Y complexes have similar activity to PPA against *E. coli, S. aureus, B. subtilis, S. pneumoniae*; weaker activity on P. aeruginosa.
Ciprofloxacin (CPX)	[Er(CPX)2(H2O)8]Cl	-MIC determined by broth tube dilution method; *E. coli, P. aeruginosa, S. aureus*;	-for Ce, the activity is 2.5, 2.5,1.25 fold higher than CPX;
	[Ce(CPX)2(H2O)4]		-for Er, the activity is 2.5, 1.25 fold higher, resp. 3.0 fold lower than CPX.
	Cl·(H2O)3.25(C2H5OH)0.25		
	[La(H2O)4(CPX)2]Cl	-antibacterial activity against *E. coli* strains, through flat-filter paper method;	-the complex is less active than ciprofloxacin.
Enrofloxacin (EF)	[La2(EF)6(H2O)2]·14H2O	-antibacterial activity tested against *B. subtilis, S. aureus, E. coli* through the diffusimetric method;	-both complexes have bactericidal properties greater than the ligand; -the Sm3+ complex is more active than the La3+ complex.
	[Sm2(EF)6(H2O)2]·14H2O		
Gemifloxacin (GMFX)	[La(GMFX)2(H2O)2]Cl3·3H2O	-antibacterial activity tested against *S. aureus, B. subtilis, E. coli, P. aeruginosa*, by diffusimetric	-the activity of the La3+ complex is comparable to gemifloxacin, but the one of

		method; -antifungal activity tested against C. albicans, A. awamori, Altenaria sp. by diffusimetric method;	the Ce4+ complex is slightly higher;
	[Ce(GMFX)2(H2O)2]	-cytotoxic activity tested against human breast carcinoma cell line (MCF-7 cells), human colon carcinoma cell line (HCT-116 cells), through crystal violet colorimetric viability assay;	-only the Ce4+ complex is active and only against C. albicans;
	(SO4)2·2H2O		-results were compared to the activity of doxorubicin; both complexes were found to be active on both cell lines, but have IC50 higher than doxorubicin; Ce4+ complex more active than La3+ complex against the breast carcinoma cell line; La3+ complex more active than the Ce4+ complex against the colon carcinoma cell line.
	[La(GMFX)(phen)(H2O)2] Cl3·6H2O	-antibacterial activity against S. aureus, *B. subtilis*, *E. coli*, *P. aeruginosa*, by diffusimetric method;	-activity against S. aureus is comparable to GMFX; higher activities against the others;
	[Ce(GMFX)(phen)(H2O)2] (SO4)2·3H2O	-antifungal activity tested against C. albicans, A. awamori, Alternaria sp. by diffusimetric method;	-comparable activity against C. albicans to GFX; no activity against other fungi strains;
		-cytotoxic activity tested against human breast carcinoma cell line (MCF-7 cells) and human colon carcinoma cell line (HCT-116 cells) by crystal violet staining viability assay; doxorubicin used as positive control;	-complexes show cytotoxic activity, but lower than GMFX; phen also shows cytotoxic activity, but higher than GMFX.
	[Ce(GMFX)(Gly)(H2O)2]	-antibacterial activity tested against Xanthomonas campestris, Bacillus megeterium, *E. coli*, *Clavibacter michiganesis*;	-GMFX and complex proved to be active against all strains, the weakest activity being against *E. coli* and the highest against *C. michiganensis*; -complex shows lower activity than GMFX against all strains; -complex activity comparable to that of GMFX.
	Cl2·H2O	-antifungal activity tested against phytopathogenic fungi: Rhizoctonia solani, Sclerotinia sclerotium, Aspergillus niger, Botrytis cinerea, Penicillium digitatum;	

		-antioxidant activity tested through DPPH and ABTS methods;	
Levofloxacin (LEVO)	[Ce(LEVO)2(H2O)2]SO4·	-antibacterial activity tested against S. *aureus, B. subtilis, B. otitidis, E. coli*,	-the Ce4+ proves to be more active on B. subtilis and
	5H2O	P. *aeruginosa, K. oxytoca*, by cup-diffusion technique;	B. otitidis;
		-antifungal activity tested against A. flaurus, A. fumigatus, using the disc diffusion sensitivity method;	-no antifungal activity noted;
Moxifloxacin (MOXI)	[Ce(MOXI)2](SO4)2·2H2O	-antibacterial activity tested against *S. aureus, B. subtilis, B. otitidis, E. coli, P. aeruginosa, K. oxytoca* by cup-diffusion method;	-the complex shows similar activity against *E.coli*;
			-no activity against P. aeruginosa and K. oxytoca;
			-higher activity against B. subtilis, B. otitidis and S. aureus.
Norfloxacin (NOR)	[La(NOR)3]·3H2O	-antibacterial activities tested using modified Kirby-Bauer disk diffusion method, against S. aureus, *B. subtilis, E. coli, P. aeruginosa, C. albicans, A. flavus*; positive controls used: tetracycline and amphotericin;	-complexes in nanoparticle form displayed greater activities than those in normal- particle form, but lower than the positive controls; -La3+ nanocomplex is the most active.
	[Ce(NOR)3]·2H2O		
Ofloxacin (OFLO)	[Pr(L-OFLO)(NO3)2(CH3OH)] (NO3) [Nd(L-OFLO)(NO3)2(CH3OH)] (NO3), where L-OFLO=ofloxacin derivative.	-antioxidant activity tested through hydroxyl radical scavenging activity through the Fenton reaction;	-complexes show better activity than the ligand.
Sparfloxacin (SPAR)	[La(SPAR)2NO3·H2O]·2H2O (1)	-antibacterial activity tested against *S. aureus, E. coli* using modified Kirby-Bauer disc diffusion method; tetracycline used as control;	-the complexes show the same activity as the free ligand, which is higher than the control, against both bacteria;
	[La(SPAR)(HL)NO3·H2O]·	-antifungal activity tested against A. flavus, C. albicans using modified	-complexes and free ligand showed no antifungal activity.
	H2O (2), where L=DL-alanin.	Kirby-Bauer disc diffusion method; amphotericin B used as control;	

It was observed that the complexes have improved water solubility in comparison with the quinolone parent molecule. Thereby, the complexation may improve both the hydrophilic and lipophilic properties of quinolone and give better bioavailability and antibacterial activity [15]. Liposolubility is an important factor for the antimicrobial activity. Upon complexation, the polarity of the metal ion is reduced due to the overlap with ligand orbitals and partial sharing of the positive charge of the metal ion with the donor groups. The increased liposolubility of the ligand upon metal chelation may contribute to its facile transport into the bacterial cell; once it has entered the cell as a metal complex, the ligand blocks the metal binding sites of crucial bacterial enzymes [16].

When taking into account the chemical structures of the metal complexes, the following five principal factors greatly influence their antimicrobial activities: (1) the chelate effect-bidentate ligands show higher antimicrobial efficiency towards complexes with monodentate ligands; (2) the nature of the ligand/ligands; (3) the total charge of the complex; the antimicrobial activity varies in the following order—cationic > neutral > anionic complex; (4) the nature of the counter ion for ionic complexes; (5) the nuclearity of a metal center in complex with a dinuclear center is more active than that of a mononuclear one [16].

Briefly, lanthanide complexes of quinolones have been tested in regard to their antibacterial, antifungal, antitumoral and/or antioxidant properties; in addition, in some cases, their ability to bind to calf-thymus DNA (CT-DNA) and bovine serum albumin (BSA) has also been quantified. The antibacterial activity was tested against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae and Bacillus subtilis; meanwhile, the antifungal activity was tested against Candida albicans and Aspergillus awamori. As a general remark, the complexes showed no antifungal activity, except for the complex of Ce4+ with gemifloxacin . The antibacterial activity of the complexes varies greatly, from being lower than the ligand, to being the same for some strains and to being higher than the ligand . Regarding the CT-DNA and BSA binding experiments, the complexes proved to have higher affinity than the ligand both for the former and the latter [17].

Molecular docking for antiepileptic activity

Schiff bases of 1-amino-7-hydroxy-4-methylquinoline-2(1H)-one and 1-amino-7-hydroxy-2-methylquinoline-4(1H)- one with substituted aromatic carbonyl compounds were synthesized. The final test compounds were purified and characterized by IR, 1HNMR and Mass Spectral studies. M.P. of these compounds was confirmed by open capillary method instrument chemline cl 725. Docking study of quinolone derivatives was performed on the three high resolution crystal structures of hCA enzyme using Biopredicta module of VLife MDS 3.5 software to study the binding modes of quality and quantum interactions between synthesized compounds with the target enzymes (PDB pdb 3F8E). Synthesized compounds 14, 15, 31, 25 and 9 showed strong antiepileptic activity among all synthesized compound.

Docking study was performed on the three high resolution crystal structures of hCA enzyme using Biopredicta module of VLife MDS 3.5 software to study the binding modes of quality and quantum interactions between synthesized compounds with the target enzymes (PDB pdb 3F8E) .For each ligand, the best docked structure was chosen, and this receptor-based alignment was used for further studies. The docking of best molecule into the hcf II receptor confirmed that ILE91A, VAL121A, GLN92A, HIS94A, VAL121A, PHE131A, LEU198A, THR199A interacted with the receptor. The present study illustrates a new hypothesis about the binding interaction of these synthesized compounds inside the receptor, encouraging future investigations on new residues that might be fundamental for the ligand-receptor interactions, because, hCA enzyme are an interesting therapeutic target for antiepileptic activity. On the basis of results of docking studies, the synthesized compounds 14, 15, 31, 25 and 9 were initially screened for biological activity, which was promising and antiepileptic activity studies will be reported in detail using in vitro and in vivo assays [18] (Table 2) (Figure 8).

Table 2: Best 30 PLP Score of different conformations of synthesized compounds.

S. No	ligand	PLP Score
1	14_opt_P10	-35.2251
2	15_opt_P5	-34.3011
3	31_opt_P29	-34.0919
4	15_opt_P25	-33.6782
5	25_opt_P21	-33.5459
6	9_opt_P28	-33.0809
7	13_opt_P4	-32.9602
8	28_opt_P26	-32.1248

9	18_opt_P20	-31.9646
10	31_opt_P2	-31.6899
11	30_opt_P30	-31.5962
12	17_opt_P7	-31.5849
13	1_opt_P17	-31.3642
14	9_opt_P11	-31.1997
15	1_opt_P9	-30.9614
16	2_opt_P12	-30.8546
17	10_opt_P15	-30.844
18	29_opt_P22	-30.6811
19	26_opt_P1	-30.4479
20	18_opt_P27	-30.4034
21	18_opt_P14	-30.3815
22	16_opt_P18	-30.3406
23	25_opt_P19	-30.2321
24	31_opt_P3	-30.2083
25	1_opt_P8	-30.165
26	10_opt_P23	-30.0412
27	21_opt_P16	-29.981
28	15_opt_P24	-29.9639
29	7_opt_P6	-29.9573
30	16_opt_P13	-29.8683

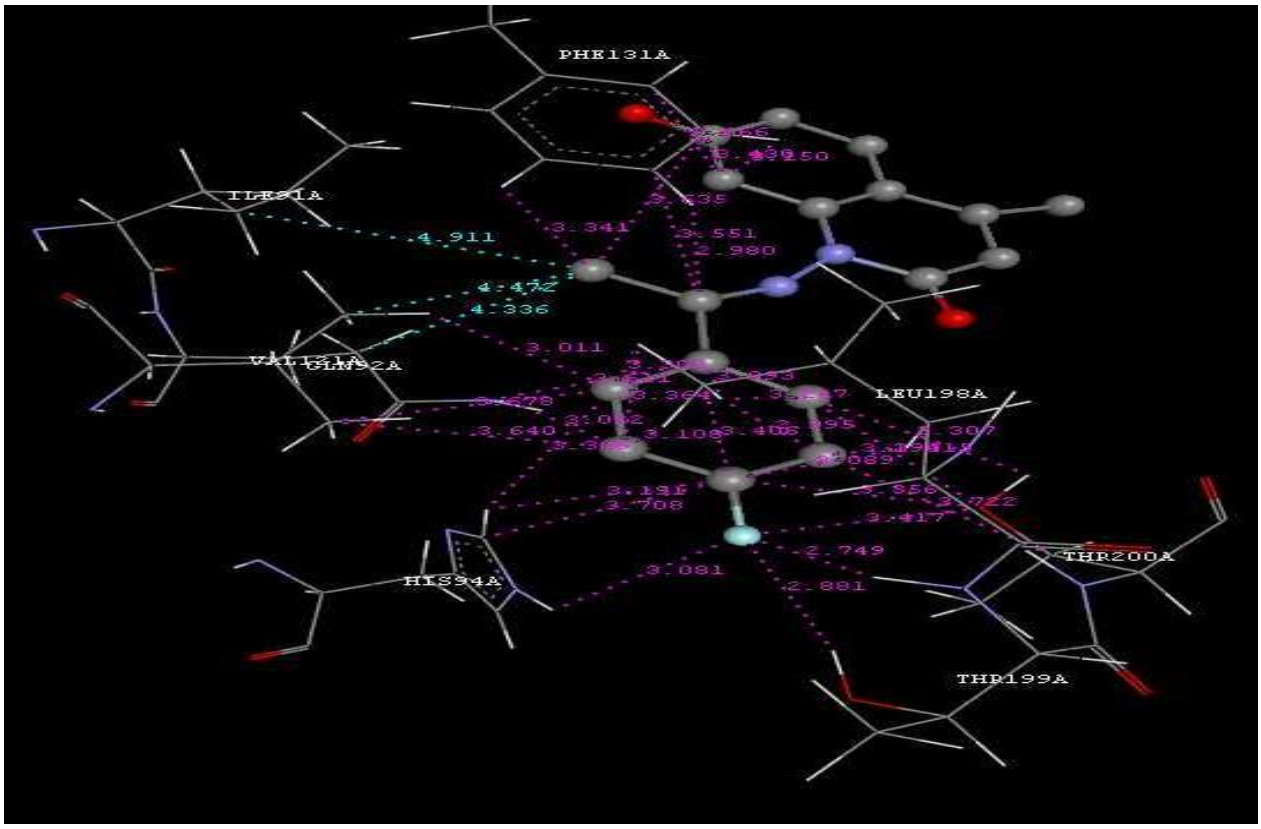

Figure 8: Complete interactions of best docked molecule 14 with active site of hCA II.

Antibacterial activity

A new series of copper(II) compounds, [Cu(pef)2(MeOH)] (1), [Cu(pef)(bipyam)Cl] (2), [Cu(pef)(phen)Cl] (3) and [Cu(pef)(bipy)Cl] (4), bearing the quinolone family member pefloxacin (Hpef) were self-assembled in the presence (optional) of N,N0-donor heterocyclic ligands such as 2,20-bipyridylamine (bipyam), 1,10-phenanthroline (phen), or 2,20-bipyridine (bipy). The products were fully characterized, including single-crystal X-ray diffraction analysis of 2–4. The structures are extended into 1D (2), 2D (3), or 3D (4) networks via multiple H-bonds between the monocopper(II) units and guest water and/or methanol molecules; the latter are arranged into different types of water and hybrid water–methanol clusters. The resulting H-bonded networks were classified from a topological viewpoint, revealing diverse topologies that also include an undocumented type. Compounds 2–4 also act as homogeneous catalysts in a model oxidation reaction, namely the mild oxidation of C6–C8 cycloalkanes by H2O2 at 50 1C to give cyclic alcohols and ketones. The effects of various reaction parameters (substrate scope, temperature, and loadings of catalyst, cycloalkane, and oxidant) and selectivity features were investigated. Besides, products 1–4 also show remarkable antibacterial activity against four different microorganisms (Escherichia coli, Xanthomonas campestris, Staphylococcus aureus and Bacillus subtilis), which is superior to that of free Hpef. The interaction of the Cu(II) compounds with calf-thymus DNA was studied suggesting inter- calation as the most possible binding mode. Furthermore, the interaction of the obtained copper(II)derivatives with human/bovine serum albumin was investigated by fluorescence emission spectroscopy and the corres-ponding albumin-binding constants were established. This study widens a limited family of transition metal pefloxacin derivatives [19] (Table 3).

Table 3: Antimicrobial activity of Hpef and complexes 1–4 expressed in MIC in mg mL1 or mM (the values in parentheses).

Compound	E. coli	X. campestris	S. aureus	B. subtilis
Pefloxacin (Hpef)	0.5 (1.50)	0.5 (1.50)	0.25 (0.75)	0.5 (1.50)
[Cu(pef)2(MeOH)], 1	0.5 (0.66)	0.5 (0.66)	0.25 (0.33)	1 (1.32)
[Cu(pef)(bipyam)Cl], 2	1 (1.66)	1 (1.66)	0.5 (0.83)	1 (1.66)
[Cu(pef)(phen)Cl], 3	1 (1.64)	1 (1.64)	0.5 (0.82)	1 (1.64)
[Cu(pef)(bipy)Cl], 4	1 (1.70)	1 (1.70)	0.5 (0.85)	2 (3.41)

Ciprofloxacin is a derivative of quinolone. Quinolones possesses antibacterial activity and they are structurally related to Nalidixic acid. Various modification has been done in quinolone moiety to enhance antibacterial activity and reduce resistance. On chelation, quinolones acts as unidentate, bidentate and bridging ligand. Metal ions play an important role in biological activity with quinolones. Various transition metals are used as chelating agent such as Ni2+, Co2+, Ca2+, Zn2+, Ag2+, Au2+, Mn2+, Mg2+, Fe2+ etc. [20].

Antiplasmodial activity

The compounds 2 and 3 and the synthetic compounds 1 and 5–8 were tested against the chloroquine-resistant Dd2 strain of P. falciparum. Compound 4 was not obtained completely pure, so accurate determination of its antiplasmodial activity was not possible. However, based on the activity of the fraction H4-6 which contained 4 as its major component, it almost certainly is active against the chloroquine-resistant Dd2 strain of P. falciparum. It has been previously shown to have activity against the chloroquine-sensitive 3D7 strain of P. falciparum [21] (Figure 9).

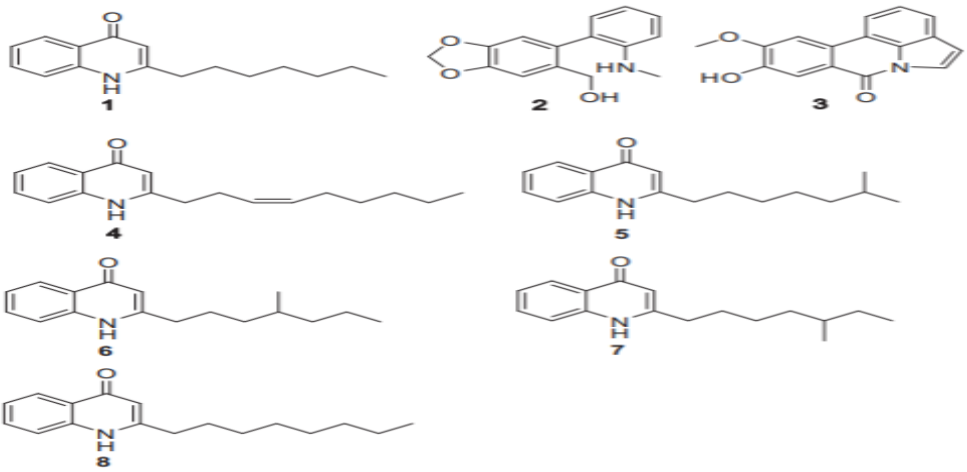

Figure 9: Structures 1 to 8. Compounds 1, 2, 3, 4, and 8 are known, and 5, 6, and 7 are new compounds.

Compound 1 was found to have a modest IC50 against the Dd2 strain of P. falciparum of 1.3 ± 0.3 mM; it has also been reported to have activity against the W2 and D6 strains of P. falciparum. Compounds 2 and 3 were found to be inactive against the Dd2 strain of P. falciparum at the highest concentrations tested of 39 mM and 38 mM respectively. The C17H23NO isomers 5, 6, 7, and 8 had IC50 values against the Dd2 strain of P. falciparum of 583 ± 330 nM, 330 ± 43 nM, 750 ± 93 nM, and 3.7 ± 0.5 mM respectively. The quinolones were also tested against the chloroquine-sensitive 3D7 strain of P. falciparum. Compounds 1, 5, 6, 7, and 8 had IC50 values of 1.3 ± 0.3 mM, 501 ± 82 nM, 385 ± 78 nM, 921 ± 206 nM, and 3.8 ± 0.6 mM respectively. The compounds were also tested against the A2780 drug-sensitive mammalian cancer cell line. Alkaloids 2 and 3 were found to be inactive at all concentrations tested, with IC50 values greater than 78 mM and 75 mM, respectively. The quinolones 1, 5, 6, 7, and 8 had IC50 values of 35 ± 5, 34 ± 5, 29 ± 1, 8.7 ± 2.1, and 12 ± 2 mM activities, respectively.

Anticancer activity

The methodology of the NCI for primary anticancer assay was performed at 60 human tumor cell lines panel derived from nine neoplastic diseases, according to the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda. The anticancer activity of thiazoloquinolones 7a-g was evaluated according to the protocol of the drug evaluation branch of the national cancer institute (NCI), Bethesda, USA, for in vitro anticancer activity (http://www.dtp.nci.nih.gov). Results for each tested compound were reported as the percentage of growth of the treated cells when compared to the untreated control cells. Thiazoloquinolone derivatives 7b,c,e,g exhibited weak to moderate anticancer activity. Moreover, the 6-methoxy analogue 7d showed remarkable activity against colon cancer HCT-15 and lung cancer NCIeH322 M. Also, compound 7a exhibited good anticancer activity against colon carcinoma HCT-15 [21] (Table 4).

Table 4: Sixty cell lines in vitro anticancer screening data of compounds 7a-e,g.

Subpanel tumor cell lines	**7a**	**7b**	**7c NSC 818871**	**7d**	**7e NSC 818872**	**7g**
Leukemia	NSC 818868	NSC 818869		NSC 818870		NSC 818873
CCRF-CEM	28.99	96.92	92.17	26.52	35.24	45.83
HL-60 (TB)	87.19	102.27	102.01	83.89	87.66	105.08
K-562	55.69	101.24	95.5	71.3	74.33	99.24
MOLT-4	39.41	108.09	103.06	35.23	42.19	80.24
RPMI-8226	67.41	104.37	106.59	70.58	75.67	83.8
SR	45.32	105.38	106.33	56.19	65.65	82.64

Non-Small Cell Lung Cancer	61.3	102.82	103.54	57.34	29.49	86.97
A549/ATCC						
EKVX	46.84	98.14	86.93	53.79	61.84	69.9
HOP-62	47.78	101.2	89.03	43.02	42.97	61.94
HOP-92	94.1	117.43	97.98	94.74	81.74	92.94
NCIeH226	70.61	99.39	103.28	66.6	81.68	83.61
NCIeH23	84.03	106.06	108.53	89.72	95.44	97
NCIeH322 M	71.58	101.47	100.53	18.22	79.78	85.24
NCIeH460	49.03	100.35	100.95	46.61	76.58	91.46
NCIeH522	74.33	94.94	92.07	80.13	72.69	90.47
Colon Cancer	97.5	107.01	108.78	106.03	95.4	105.04
COLO 205						
HCC-2998	74.15	115.1	111	77.59	100.57	110.37
HCT-116	43.28	93.93	101.19	50.83	62.75	75.39
HCT-15	19.41	102.95	93.56	20.51	28.05	40.82
HT29	60.88	103.51	105.7	70.25	44.07	81.79
KM12	69.3	100.76	100.06	69.34	87.24	97.25
SW-620	68.54	101.82	98.24	67.2	80.61	89.37
CNS Cancer	68.87	93.22	96.97	56.43	67.57	78.47
SF-268						
SF-295	68.56	101.8	98.14	69.33	82.85	90.24
SF-539	75.99	101.37	101.86	84.11	90.31	92.48
SNB-19	73.33	103.88	100.56	75.41	82.51	85.65
U251	45.05	99.64	97.29	44.28	33.82	68.51
Melanoma	58.94	96.7	91.44	59.95	74.44	83.15
LOX IMVI						
MALME-3M	80.85	107.17	105.78	84.48	96.52	98.79
M14	55.48	98.77	100.32	75.24	73.3	78.65
MDA-MB-435	83.17	99.12	99.9	79.32	91.06	96.55
SK-MEL-2	89.47	103.17	101.13	83.07	76.67	88.83
SK-MEL-28	76.93	105.69	104.02	75.99	88.26	92.92
SK-MEL-5	70.22	100.83	100.33	65.25	87.47	83.21
UACC-257	107.17	103.63	105	98.78	98.23	106.45
UACC-62	54.38	101.95	98.78	62.66	75.44	82.12
Ovarian Cancer	64.03	101.6	95.87	70.35	79.8	78.32
IGROV1						
OVCAR-3	43.35	107.16	105.74	24.16	68	84.66
OVCAR-4	52.22	103.3	91.89	47.88	56.84	65.72
OVCAR-5	82.56	105.35	102.09	85.58	94.9	98.88
OVCAR-8	66.51	107.67	103.16	55.1	61.26	82.53
NCI/ADR-RES	46.69	104.04	105.5	37.74	72.05	77.93
SK-OV-3	73.65	101.02	102.21	76.79	71.98	89.2

Renal Cancer	87.11	106.07	108.77	94.89	102.84	109.52
A498						
ACHN	30.92	107.61	101.76	48.64	68.35	73.49
CAKI-1	37.03	91.98	74.68	43.68	38.47	70.75
RXF 393	86.07	110.16	134.39	97.06	98.49	101.4
SN12C	77.05	100.11	97.83	73.78	80.5	83.87
TK-10	64.77	126.91	127.74	90.2	74.74	119.72
UO-31	35.85	91.46	71.14	42.53	51.11	49.44
Prostate Cancer	61.9	96.85	95.08	58.94	69.76	78.96
PC-3						
DU-145	73.05	106.59	110.11	63.71	84.47	95.05
Breast Cancer	74.73	107.09	93.89	67.16	89.24	93.72
MCF7						
MDA-MB-231/ATCC	60.93	99.79	91.09	57.53	70.58	63.58
HS 578T	115.62	109.49	116.46	111.71	108.82	114.14
BT-549	65.48	87.39	85.81	60.84	76.22	69.37
T-47D	70.97	95.82	98.87	72.59	68.46	85.17
MDA-MB-468	90.42	112.92	112.12	87.61	100.62	103.06

Conclusion

Quinolones are important class of drugs have various biological activities and because of importance of this moiety several new derivatives of this nucleus has been synthesised to explore the pharmacological actions. As a result, there is a huge research potential in it and novel biological activities can be explored.

References

1. Lesher GY, Froelich EJ, et al. 1,8-Naphthyridine derivatives. A new class of chemotherapeutic agents. J Med Pharma Chem 1962; 5:1063–1065.
2. Zhang GF, Zhang S, Pan B, et al. 4-Quinolone derivatives and their activities against gram positive pathogens. Eur J Med Chem 2018; 143:710-723.
3. Kocsis B, Domokos J, Szabo D. Chemical structure and pharmacokinetics of novel quinolone agents represented by avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and nemonoxacin. Annals Clin Microbiol Antimicrob 2016; 15:1-8.
4. Dhiman P, Arora N, Thanikachalam PV, et al. Recent advances in the synthetic and medicinal perspective of quinolones: A review. Bioorganic Chem 2019; 92:103291.
5. Ball P, Fernald A, Tillotson G. Therapeutic advances of new fluoroquinolones. In *Expert Opinion on Investigational Drugs* 1998; 7: 761–783.
6. Pham TD, Ziora ZM, Blaskovich MA. Quinolone antibiotics. Medchemcomm 2019; 10:1719-39.
7. Wall MJ, Chen J, Meegalla S, et al. Synthesis and evaluation of novel 3, 4, 6-substituted 2-quinolones as FMS kinase inhibitors. Bioorganic Med Chem Letters 2008; 18:2097-102.
8. Sun XY, Zhang L, Wei CX, et al. Design, synthesis of 8-alkoxy-5, 6-dihydro-[1, 2, 4] triazino [4, 3-a] quinolin-1-ones with anticonvulsant activity. Eur J Med Chem 2009; 44:1265-70.
9. Pasquini S, Mugnaini C, Tintori C, et al. Investigations on the 4-quinolone-3-carboxylic acid motif. 1. Synthesis and structure− activity relationship of a class of human immunodeficiency virus type 1 integrase inhibitors. J Med Chem 2008; 51:5125-9.
10. Ellis D, Kuhen KL, Anaclerio B, et al. Design, synthesis, and biological evaluations of novel quinolones as HIV-1 non-nucleoside reverse transcriptase inhibitors. Bioorganic Med Chem Letters 2006; 16:4246-51.
11. Lucero BD, Gomes CR, de PP Frugulhetti IC, et al. Synthesis and anti-HSV-1 activity of quinolonic acyclovir analogues. Bioorganic Med Chem Letters 2006; 16:1010-3.

12. Lucero BD, Gomes CR, de PP Frugulhetti IC, et al. Synthesis and anti-HSV-1 activity of quinolonic acyclovir analogues. Bioorganic Med Chem Letters 2006; 16:1010-3.
13. Ellman GL, Courtney KD, Andres Jr V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochemical pharmacology. 1961 Jul 1;7(2):88-95.
14. Mansha M, Taha M, Ullah N. The design of fluoroquinolone-based cholinesterase inhibitors: Synthesis, biological evaluation and in silico docking studies. Arabian J Chem 2021; 103211.
15. Li JB, Yang P, Gao F, et al. Novel lanthanide complexes of ciprofloxacin: Synthesis, characterization, crystal structure and in vitro antibacterial activity studies. Chinese J Chem 2001; 19:598-605.
16. Sadeek SA, El-Shwiniy WH. Preparation, structural characterization and biological studies of some new levofloxacin metal complexes. J Iranian Chem Society 2017; 14:1711-23.
17. Măciucă AM, Munteanu AC, Uivarosi V. Quinolone complexes with lanthanide ions: An insight into their analytical applications and biological activity. Molecules 2020; 25:1347.
18. Pradhan A, Vishwakarma S. Synthesis of quinolone derivatives and their molecular docking for antiepileptic activity. Chemistry International. 2020 Oct 1;6(4):224-31.
19. Xerras P, Bacharidou AM, Kalogiannis S, et al. Extending the family of quinolone antibacterials to new copper derivatives: Self-assembly, structural and topological features, catalytic and biological activity. New J Chem 2018; 42:19644-58.
20. Khan M, Ali M, Juyal D. Ciprofloxacin metal complexes and their biological activities: a review. The Pharma Innovation. 2017 May 1;6(5, Part B):73.
21. Presley CC, Du Y, Dalal S, et al. Isolation, structure elucidation, and synthesis of antiplasmodial quinolones from Crinum firmifolium. Bioorganic Med Chem 2017; 25:4203-11.
22. Mohamed AH, Ramadan M. Synthesis and colon anticancer activity of some novel thiazole/-2-quinolone derivatives. J Mol Structure 2020.
23. Jahangir MA, Taleuzzaman M, Alam MJ, et al. Analytical quality by design for capillary electrophoresis. InHandbook of Analytical Quality by Design 2021; 115-132: Academic Press.
24. Jahangir MA, Taleuzzaman M, Beg S, et al. A Review of Eugenol-based Nanomedicine: Recent Advancements. Current Bioactive Compounds 2021; 17: 214-219.
25. Muheem A, Shakeel F, Zafar S, et al. Development and validation of stability indicating liquid chromatographic (RP-HPLC) method for estimation of ubidecarenone in bulk drug and formulations using quality by design (QBD) approach. Brazilian J Pharmaceutical Sci 2018; 53.
26. Taleuzzamana M, Jahangir A, Gilania SJ. Quantification and Identification of Bioactive Eugenol in Myristica fragrans Seed Using Validated High Performance Thin Layer Chromatography Technique. Pharm Anal Acta 2017; 8: 2.