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Bioactive Score Testing of Newly Designed 5-Morpholineflouroquinolone Derivative from Counter Drug Ciprofloxacin

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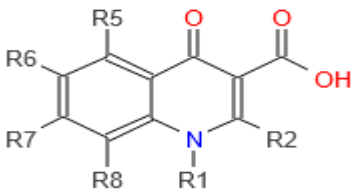
Abstract

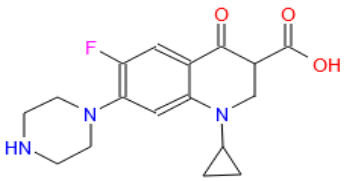
Over the last three decades discovery of fluoroquinolones attracted much attention because of their broad spectrum of activity against various bacteria.[1]Ciprofloxacin is a second-generation fluoroquinolone counter drug is taken for study SAR, QSAR and modifications to obtain more potential drug likeness with less side effects.[9,10] 5-Substituted morpholine derivative of ciprofloxacin has been designed with the help of SAR of fluoroquinolones and using multiple regression QSAR studiesusing toxicity, bioavailability and pharmacokinetic parameters.[2,4,5] Then newly modified C-5 morpholine ciprofloxacin has been tested online for bioactive score through Molinspiration.[8]

Keywords: Fluoroquinolones, Broad Spectrum, Ciprofloxacin, Fluoroquinolone, Counter Drug, SAR, QSAR Drug Likeness, Morpholine, Multiple Regression, Toxicity, Bioavailability, Pharmacokinetic Bioactive Score, Molinspiration.

Introduction

Ciprofloxacin (2) is belonging to fluoroquinolones (1) group. Its mode of action depends upon blocking bactericidal DNA replication by binding itself to an enzyme called DNA gyrase, thereby causing double stranded breaks in the bacterial chromosome.[9]

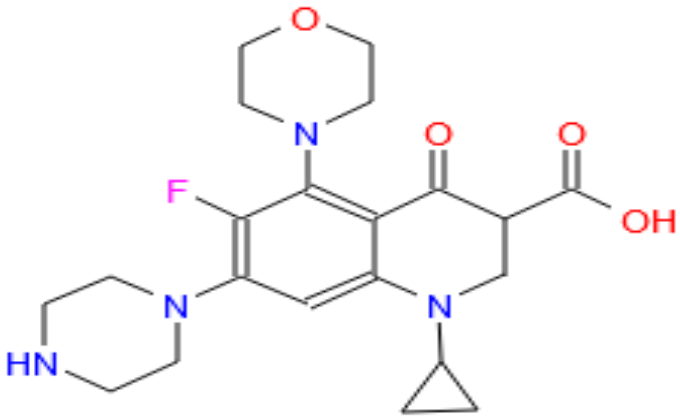




Fluoroquinolones Ciprofloxacin
(1) (2)

Ciprofloxacin (2) can cause photosensitivity reactions and can elevate plasma theophylline levels to toxic values. It can also cause swelling of joints and cartilage. Ciprofloxacin (2) can produce side effects like convulsion, dizziness, mentally stress, CNS restlessness, headache etc. Moreover because of its lower solubility in water leads to reduce drug absorptivity.[4]

To overcome from certain drawbacks of Ciprofloxacin (2) new 5-substituted morpholine ciprofloxacin (3) has been designed with the help of SAR and QSAR methods. Log P values and biological activity score have been finally tested online by Molinspiration.[6,7]



5-Substituted Morpholine derivative of ciprofloxacin (3)

Methodology

Ciprofloxacin **(2)**(1-cyclopropyl-6-flouro-1,4-dihydro-4-oxo-7-(1-N-piperazinyl-3-quinolone carboxylic acid) is afluoroquinolone counter drug which is available in market and it is found considerably less effective against bacterial pathogens at concentrations much higher as well as lower than their Minimum Inhibitory Concentrations (MICs).[9]

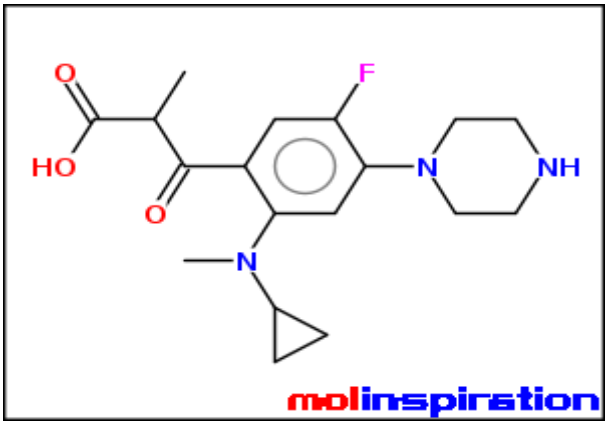
Structure Activity Relationship (SAR) reveals that ciprofloxacin (2) has oxogroup at C-4 position and it is essential for antibacterial activity and C-5 position has a hydrogen atom. If C-5 position proton is replaced by amine group then both properties like biological activityand absorptivity of ciprofloxacin (2) will increased.[9,10]

5-Substituted morpholine derivative of ciprofloxacin (3) has been designed and studied for Quantitative Structure Activity Relationship (QSAR). LogP is calculated based on the methodology published by Ertl *et al.*[7]as a sum of fragment contributions. O- and N- centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration.[8]

Rule of 5" Properties is set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5" [2]. The rule states, that most "drug-like" molecules have logP <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5", because the border values are 5, 500, 2*5, and 5.

It has concluded that newly designed drug 5-Substituted morpholine derivative ofciprofloxacin (3) following Lipinski's rule and more potent than parent ciprofloxacin (2). Further, 5-Substituted morpholine derivative ofciprofloxacin (3) has been tested for Biological Activity Score through Molinspiration online.[6,7,8]

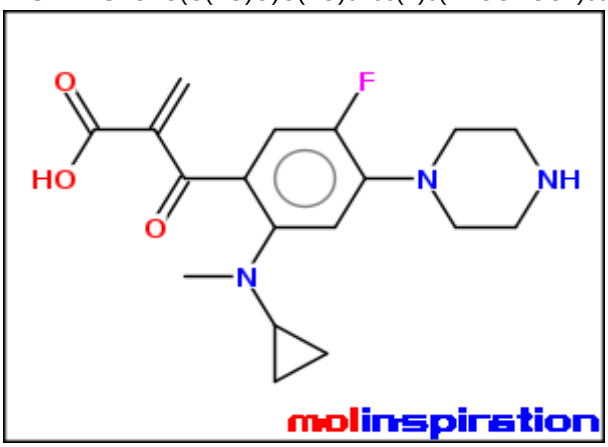
miSMILES: CC(C(=O)O)C(=O)c2cc(F)c(N1CCNCC1)cc2N(C)C3CC3



Molinspiration property engine v2018.10

miLogP	1.34
TPSA	72.87
natoms	25
MW	349.41
nON	6
nOHNH	2
nviolations	0
nrotb	6
volume	318.83

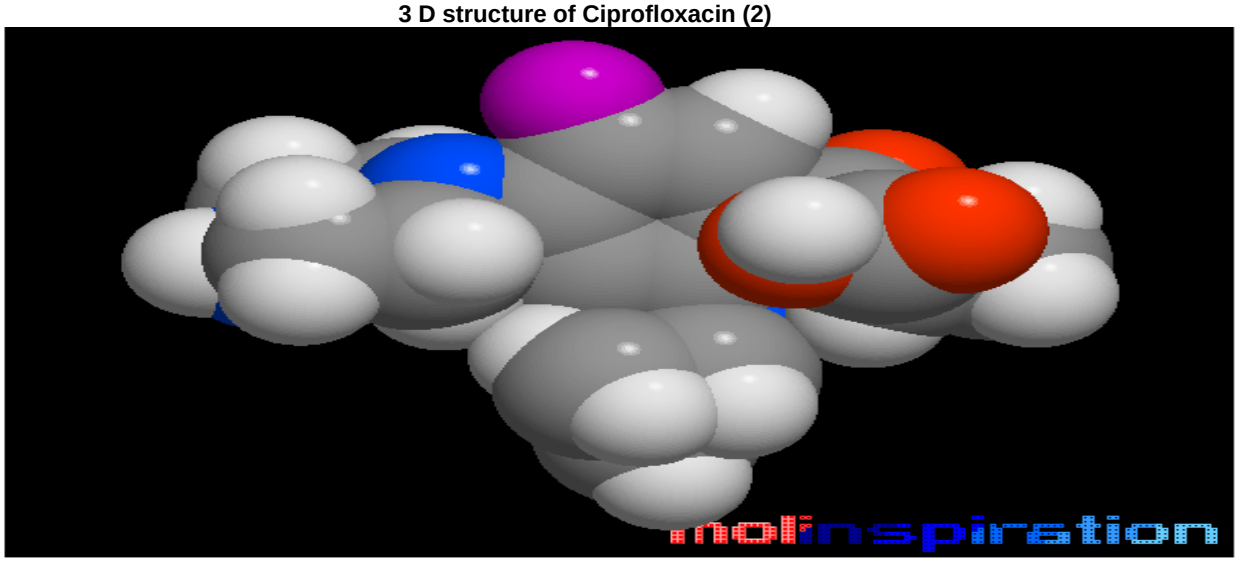
miSMILES: C=C(C(=O)O)C(=O)c2cc(F)c(N1CCNCC1)cc2N(C)C3CC3



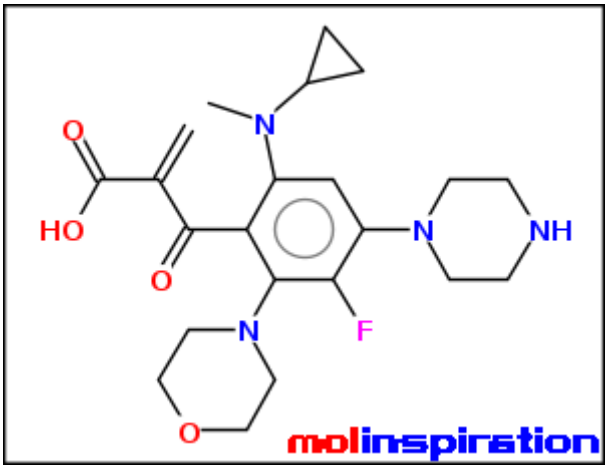
Molinspiration bioactivity score v2018.03

GPCR ligand	0.14
Ion channel modulator	-0.03
Kinase inhibitor	-0.11
Nuclear receptor ligand	-0.11
Protease inhibitor	-0.03
Enzyme inhibitor	0.06

3 D structure of Ciprofloxacin (2)



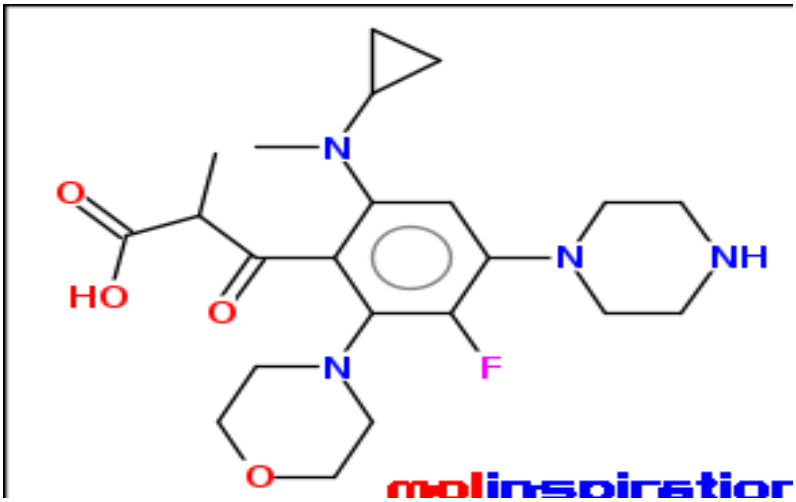
miSMILES: C=C(C(=O)O)C(=O)c3c(N(C)C1CC1)cc(N2CCNCC2)c(F)c3N4CCOCC4



Molinspiration property engine v2018.10

miLogP	1.05
TPSA	85.34
natoms	31
MW	432.50
nON	8
nOHNH	2
nviolations	0
nrotb	7
volume	391.31

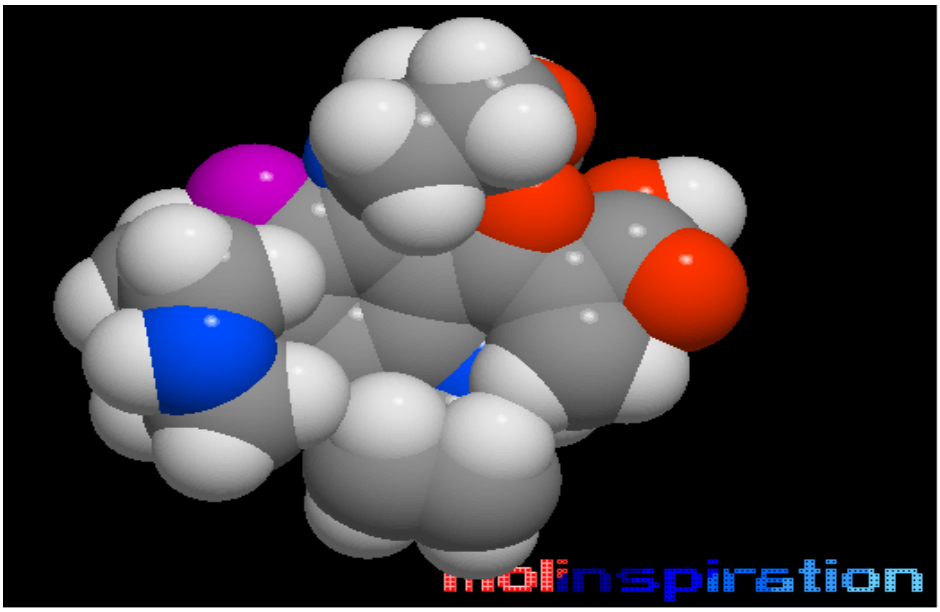
miSMILES: CC(C(=O)O)C(=O)c3c(N(C)C1CC1)cc(N2CCNCC2)c(F)c3N4CCOCC4



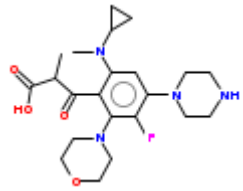
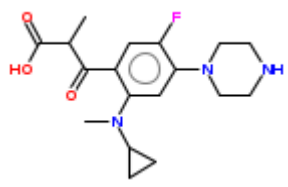
Molinspiration bioactivity score v2018.03

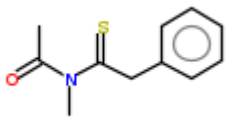
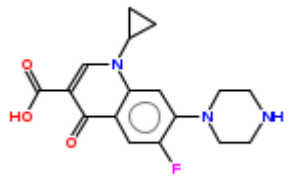
GPCR ligand	0.18
Ion channel modulator	-0.05
Kinase inhibitor	-0.02
Nuclear receptor ligand	-0.14
Protease inhibitor	0.08
Enzyme inhibitor	0.04

3 D Structure of 5-substituted morpholine ciprofloxacin derivative (3)



Comparative data obtain from Molinspiration online testing of biological activities of Ciprofloxacin (**2**) and newly designed 5-substituted morpholine ciprofloxacin (3) derivative (Table I)

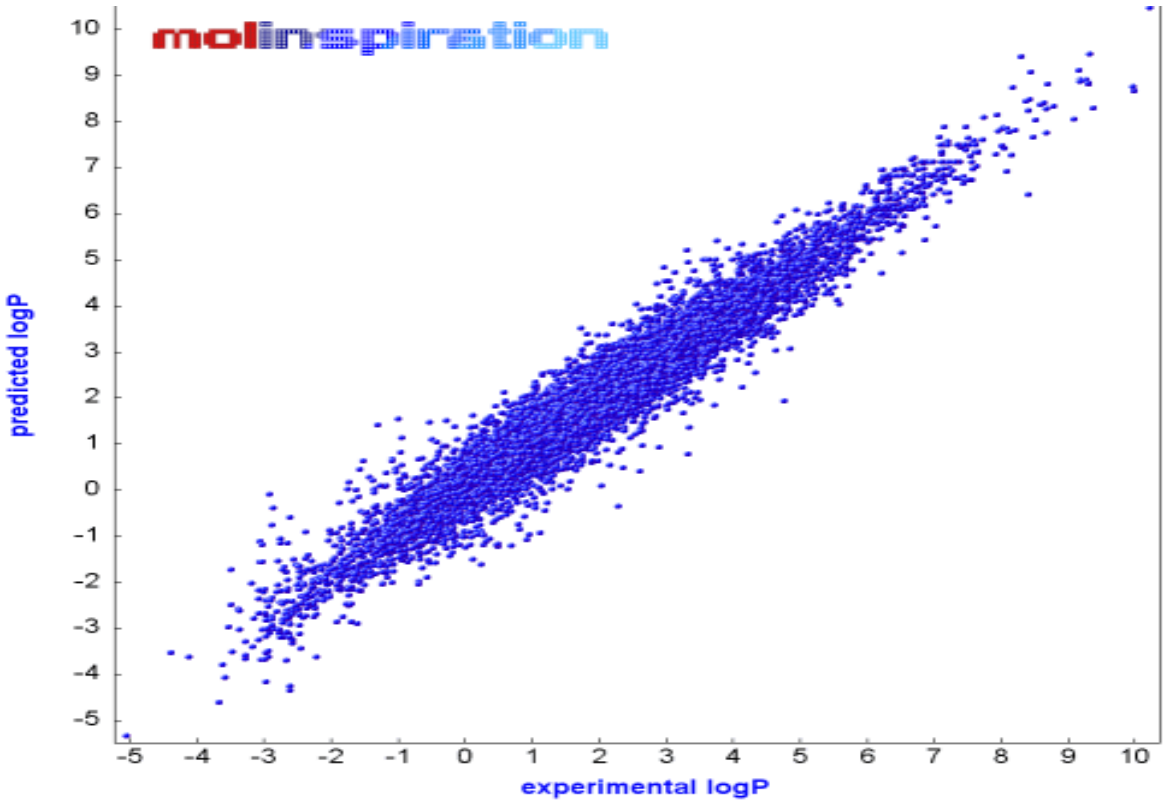
Structure	Name	miLogP	TPSA	MW	natoms	volume
	5-Substituted morpholine ciprofloxacin **3**	1.214	85.345	434.512	31	396.968
	Bioactive site of **3**	1.338	72.873	349.406	25	318.834

	Bioactive site of **2**	1.013	20.309	207.298	14	193.596
	Ciprofloxacin**2**	-0.701	74.569	331.347	24	285.46

Results & Discussion

Newly designed 5-Substituted morpholine derivative ofciprofloxacin**(3)** from ciprofloxacin (2) is showing increased biological activity as the results obtained are in accordance to Molinspiration methodology for observed Log P values and other activity scores e.g. GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptor ligands, protease inhibitors and other enzyme targets compared with scores for other drug like molecules.[11,12] The score allows efficient separation of active and inactive molecules, and hence the newly designed and synthesized 5-Substituted morpholine derivative of ciprofloxacin (3) is more potent (Figure 1).

Figure 1



$n = 12'202$, $r^2 = 0.944$, $r = 0.972$, $stdev = 0.428$, $mae = 0.328$

Review of Literature

1) B. Llorente and F. Leclerc reported in 1996 about the model of activity and structure of the quinolone DNA Complex using SAR and QSAR analysis.
2) G.Anquetin and M.Rouquayrol studied in 2004 about the synthesis of new fluoroquinolones and evaluation of their in Vitro activity.
3) Xiao-Hong et.al reported in 2006 structure activity relationships (SAR) study of fluoroquinolones with biological activity against Anti S. penmoniae.
4) XU Ju Li et.al had been reported QSAR Studies on 7- Substituted fluoroquinolones in 2007.
5) Zhuang, A.yu and W. Zhou worked on synthesis and structure activity relationships of 7-substituted

aminomethyl-4- quinolone-3- carboxylic acid derivatives in 2007.

Aim of the Study

Design of new molecule from counter drug with the help of Molinspiration online testing to reduce side its effect.

Conclusion

Structure-activity relationships (SAR) and Quantitative SAR studies have been extensively used to correlate molecular structure to their biological activities. Computer Assisted Drug Designing (CADD) and Molinspirationsoftware'sare widely used for QSAR Studies. Primary goal of QSAR/SAR methods is to find rules, which can lead to reliable classifications and predictions of the biological activity for tested, untested or hypothetical compounds. The obtained information can be used for the selection or design of better structure. The benefits of some of these compounds include oral and parenteral dosing, broader spectrum of activity, good tissue distribution, improved pharmacokinetic profiles, stability, and a comparatively low incidence of adverse effects.5,6,7,8

The results obtained from QSAR study consider not only a wide range of structures, but also various physic-chemical interactions involved in enzyme inhibitor complexes. QSAR studies evaluated that the biological activity of the newly designed drug is found more potent and hence concluded that this novel compound is following Lipinski's rules and were more active than the parent compound.9,10

The results obtained after designed agree with the observed QSAR result in more remarkable potential derivatives with fewer side effects. As this research was focussed on the designed and modify counter drug Ciprofloxacin (2) to potential 5-Substituted morpholine ciprofloxacin derivative (3).These provides an insight into the variety of approaches resulting in elegant manipulations of this basic skeleton and some break through in synthetic strategies of a widely used drugs and these have immensely helped in accelerating their market growth as well as continuing research for newer derivatives.

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