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Synthesis, Molecular Docking Analysis of New Hetercyclic Scaffolds-Based Quionoline Moiety as Possible Antimicrobial Agents.

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ABSTRACT

In the present work, a general approach for the synthesis of new heterocyclic scaffolds-based quinoline were synthesized. In addition, molecules docking studies were achieved which showed that all the newly synthesized compounds are interacting with active site region of the target enzyme Thymidylate kinase -4QGG, DNA gyrase (PDB ID: 2XCT) Topoisomerase, Dihydrofolate reductase-DHFR- 2w9s, Clumping factor A (ClfA)-1N67 hydrogen bonds and pi-stacked interactions.

Keywords: Scaffolds; Molecular Docking; Bioctivity; Targeted protein

INTRODUCTION

The categorization of antibiotics is depends on their mechanism of action, and the main groups comprise inhibitors of cell wall synthesis, inhibitors of protein synthesis, inhibitors of nucleic acids synthesis and antimetabolites [1]. In general antibiotics inhibit these routes by interacting with precise cell proteins, usually responsible for defined activity. Antimicrobials acting at the cell wall level are the most discerning being bactericidal and presenting a high therapeutic index, since inhibition of peptidoglycan synthesis leads to cell lysis [2]. There is a diversity of antibiotics that can act in different phases of peptidoglycan biosynthesis, namely in the cytoplasmic, membrane and parietal phases [3]. β-Lactams act entirely outside the cell membrane, in the final (parietal) phase of peptidoglycan biosynthesis[3,4]. Some antibiotics acting in protein synthesis affect bacteria ribosomes, namely 30S and/or 50S subunits, inhibiting the protein synthesis at the initial or elongation phases, or inducing the synthesis of abnormal proteins [5]. Chloramphenicol exhibits a broad bacteriostatic spectrum; it blocks the principal ribosome functions, including peptidyl transferase activity and aminoacyl-tRNA elongation, inhibiting peptidyl transferase by interfering in tRNA positioning [6]. Mupirocin is a Molecules 2014, 19 1674 bacteriostatic antibiotic with higher activity upon Gram-positive bacteria by inhibiting isoleucyl-tRNA synthetase (IARS), preventing the incorporation of amino acid isoleucine in peptides. Quinolones interfere in DNA replication by inhibiting the activity of bacteria type II topoisomerase (DNA gyrase) and type IV topoisomerase [7]. Rifampicin inhibits RNA polymerase activity by linking to β -subunit, preventing the synthesis of mRNA. Folic acid is essential for the synthesis of nitrogen base purines and pyrimidines and, consequently, for the synthesis of DNA. Antimetabolites act synergistically in two different points of folic acid formation, exhibiting bacteriostatic activity. Sulfonamides, dapsone and paminosalicylic acid are some examples [8]. Sulfonamides inhibit the action of dihydropteroate synthetase (with p-aminobenzoic acid (PABA) as substrate), preventing the synthesis of dihydrofolic acid. Trimetoprim blocks enzymatic activity of dihydrofolate reductase (DHFR), which is responsible for the formation of tetrahydrofolic acid. Considering bacterial evolution and the current increase of antibiotic resistance, the discovery of new natural compounds that can be used to treat infections with lower secondary effects than existing antibiotics is becoming crucial, in order to guarantee the health of future generations [9].

EXPERIMENTAL

Synthesis

Compound was synthesized using a literature procedure Semicarbazide hydrochloride (Scheme 1) (50 mg, 1 mmol) and sodium acetate (50 mg) are placed in a mortar and ground with a pestle. After this, an indole-3-carbaldehyde (1 mmol) is added. Mixing is continued for several minutes until to get smooth paste. The crude semicarbazone separates out when cold water is added to the paste and then it is recrystallized from ethanol.



Scheme 1: Synthesis of new heterocyclic scaffolds-based quinoline

RESULTS AND DISCUSSION

Molecular Docking

Molecules docking studies were achieved which showed that all the newly synthesized compounds are interacting with active site region of the target enzyme Thymidylate kinase -4QGG, DNA gyrase (PDB ID: 2XCT) Topoisomerase, Dihydrofolate reductase-DHFR- 2w9s, Clumping factor A (ClfA)-1N67 hydrogen bonds and pi-stacked interactions (Figure 1).



Figure 1: Thymidylate kinase -4QGG

The TMPK, an essential enzyme in bacterial DNA biosynthesis, is an attractive therapeutic target for the development of novel antibacterial agents (Figure 2) (Table 1).



Figure 2: 2-(3-chlorophenoxy)-3-fluoro-4-{(1R)-3-methyl-1-[(3S)-3-(5-methyl-2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl) piperidin-1-yl] butyl} benzoic acid $C_{28}H_{31}C_1FN_3O_5$

Table 1	: Schrö	dinger N	A aestro	software-	Thym	idvlate	kinase
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Name	Docking score	Binding energy (kcal/mol)
2-(3-chlorophenoxy)-3-fluoro-4-{(1R)-3-methyl-1-[(3S)-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)piperidin-1-yl]butyl}benzoic acid	-12.121	-136.741
C ₂₈ H ₃₁ ClFN ₃ O ₅		
Structure a	-4.978	-37.913
Structure b	-5.305	-40.389
Structure c	-4.199	-38.571
Structure d	-5.417	-40.939





Structure a

Structure b



Structure c



Structure a



Structure c



Structure d



Structure b



Structure d

DNA gyrase

DNA gyrase (PDB ID: 2XCT) Topoisomerase is an isomerase enzyme that provokes dramatic change in the topology of DNA structure. Topoisomerase is categorized as topoisomerase I and topoisomerase II, based on the number of strands cut in one phase of action. New topoisomerases, type III and IV have also been discovered recently. DNA gyrase subclass of type II topoisomerase is responsible primarily for DNA replication.



Table 2: Schrödinger Maestro software- topoisomerase II DNA gyrase- 2XCT

Name	Docking score	Binding energy (kcal/mol)
Ciprofloxacin (inbuilt ligand)	-4.62	-47.34
Structure a	-4.978	-37.913
Structure b	-5.305	-40.389
Structure c	-4.199	-38.579
Structure d	-5.417	-40.931
Chain A		



Structure a

Structure b



Structure d



Table 3: Schrödinger Maestro software- topoisomerase II DNA gyrase- 2XCT

Name	Docking score	Binding energy (kcal/mol)
Ciprofloxacin (inbuilt ligand)	-9.85	-102.312
Structure a	-7.03	-77.46
Structure b	-7.682	-76.282
Structure c	-6.161	-78.716
Structure d	-8.433	-87.316
Chain B		





Structure c

Structure d



Dihydrofolate reductase-DHFR- 2w9s

Dihydrofolate reductase (DHFR) is an enzyme that catalyses the formation of tetrahydrofolate (THF) by the reduction of Dihydrofolate (DHF) in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) [27, 28]. Also, it has a great role in the synthesis of thymidylate, purines, methionine, and some other important metabolites. These enzymes are required for cell proliferation. Thus, inhibition of dihydrofolate reductase will results in the destruction of the intracellular tetrahydrofolate pool thereby preventing biosynthesis of RNA, DNA, thymidine, and protein. Due to the wide range of cellular functions, they are targets for anticancer and antimicrobial agents.



Table 4: Schrödinger Maestro software- Dihydrofolate reductase-DHFR- 2w9s

Name	Docking score	Binding energy (kcal/mol)
NADPH DIHYDRO-NICOTINAMIDE- ADENINE-DINUCLEOTIDE PHOSPHATE (inbuilt ligand)	-9.43	-110.25
Structure a	-6.901	-63.925
Structure b	-7.461	-69.687
Structure c	-6.82	-56.68
Structure d	-7.69	-69.293
Chain A		



Table 5: Schrödinger Maestro software- Dihydrofolate reductase-DHFR- 2w9s

Name	Docking score	Binding energy (kcal/mol)
TRIMETHOPRIM(inbuilt	7 956	64.082
ligand)	-7.830	-04.082
Structure a	-6.663	-56.695
Structure b	-6.88	-59.804
Structure c	-6.472	-60.531
Structure d	-8.007	-67.744
Chain B		·



Clumping factor A (ClfA)-1N67

In blood plasma, there is a glycoprotein called fibrinogen (Fg) which is present at ~ 3 mg/ml concentration and has a significant role in coagulation and haemostasis. Six polypeptide chains are present in fibrinogen such as 2 Aa, 2 Bb, and 2 nd 2 Bb, which are dimeric and symmetrical. The γ chain has C-terminal residues which are biologically important. In the process of fibrinogen dependent platelet adherence and aggregation, they interact with platelet integrin aIIb3. This C-terminal residue of γ -chain is also targeted by the pathogenic bacterium Staphylococcus aureus, resulting in fibrinogendependent cell clumping and tissue adherence. Clumping factor A (ClfA) [29, 30] was the first Fg γ -chainbinding S. aureus adhesin identified.



 Table 6: Schrödinger Maestro software- Clumping factor A (ClfA)-1N67

Name	Docking score	Binding energy (kcal/mol)
(inbuilt ligand)		
Structure a	-4.757	-43.157
Structure b	-4.724	-43.443
Structure c	-4.442	-42.905
Structure d	-5.251	-44.525
Chain B	·	





Structure b



Structure c

Structure d



Structure c

Structure d

CONCLUSION

The synthesis of different Schiff Base Derivatives Constrained by Quinoline Carboxaldehyde And 1,3,4- Thiadiazoles Schiff Base Derivatives, which have been evaluated for Molecular docking study exhibits that among the synthesized compounds. At the molecular level, the docking experiments demonstrate 3d and 3b compounds had extremely low binding energies.

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