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RESEARCH ARTICLE

Exploiting the Potential of Transforming Anti-Bacterial Xacins into Anti-Tumor Hit Compounds

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Abstract

Objectives: Exploit the possibility of turning anti-bacterial drugs, xacins, into anti-tumor hit compounds.

Materials and methods: Data of xacins were collected. The energy minimization and molecular overlay were conducted to evaluate the consistency in conformation. Docking simulation into topoisomerases was performed to develop possible inhibitors from the usual anti-bacterial drugs.

Results: The energy minimization and molecular overlay showed good consistency. The binding situations were available for developing prodrugs for Topo II and Topo III from the xacins. Alatrofloxacin was the top hit into both Topo II and Topo III.

Conclusions: The traditional anti-bacterial xacins were potential hit compounds for developing Human Topo II and Topo III inhibitors.

Introduction

Along with the development of the modern society, the risk of suffering from cancer has become a worldwide and urgent problem with increasing occurrence [1]. Though researchers have achieved tremendous progress on novel agents and therapeutic methods, more and more drugs and techniques in medicinal chemistry are still in emergency [2].

One feasible approach is exploiting novel anti-cancer hit compounds from traditional drugs for other diseases [3-5]. It can be realized if the targets (unique proteins or nucleic acid sequences) exist similarities or homology [6]. In this work, we chose anti-bacterial drugs because of several significant reasons. 1) Universality: The antibiotics have been studied for more than four generations, and the modification on each site has been refined to the preferable situation [7]. Consulting the previous experience in using these traditional drugs, medical practitioners can be more skilled in controlling the treating projects and detailed dosages [8]. Meanwhile, the delivery and toxicity will be easier to investigate compared with the properties of all-new designed molecules [9]. 2) Homology: The selected antibiotics are quinolone derivatives with known medicinal mechanism [10,11]. The major target of this species is the bacterial DNA gyrase or Topoisomerase IV [12]. This enzyme belongs to topoisomerase, among which there exist anti-cancer targets [13-15]. Known anti-tumor agents against topoisomerase include Adriamycin, Actinomycin D, Daunomycin and Epipodophyllotoxin [16-19]. Since the xacins are usually smaller in size than these drugs, the modification of surrounding substitutes seemed available to introduce anti-tumor activity. 3) Co-promotion: Drug resistance is a common problem for many targets [20]. Recruiting traditional molecules into other targets will further generate modified molecules, which can raise alternative choices to solve the drug resistance problem for both studied targets.

Modification of antibiotics and treatment of carcinoma are both hot spots. Though the xacins are commonly used drugs, they are merely connected with the treatment of cancer. Aiming at raising more information and then building certain

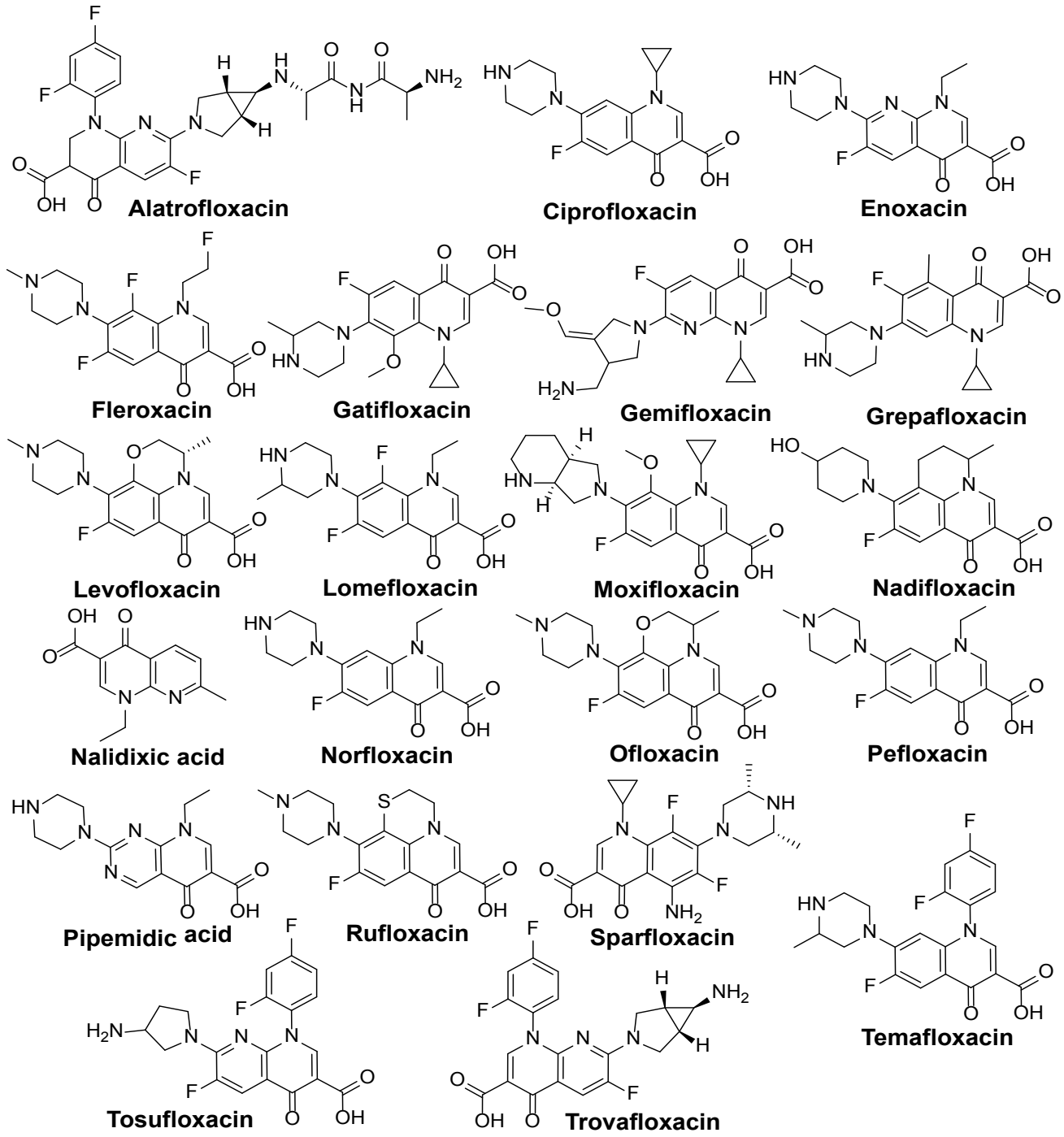

Figure 1: The structures of the studied xacins. The structures involved all four generations of xacins. They are all typical antibiotics with the quinolone core. The various surrounding moieties affect their biological activities.

connections between the structures of xacins and the anti-tumor activities, we performed this preliminary investigation to pick the unrecognized talent. Here we collected the data of xacins, refined the steric conformations and performed the molecular docking simulation with different types of topoisomerases. Revealing one corner of the iceberg, we hope the information provided in this work can lead to deeper and further achievements in developing anti-tumor agents and therapies.

Materials and Methods

The energy minimization

The information of the xacins were collected from SciFinder (Database, ACS). The involved structures were listed in Figure 1. Then energy minimization of these molecules was conducted by using CHARMm as the force field. The optimizing steps

were set as 5000 to ensure that the final status was the energy minimized. The steric conformations were checked to avoid false isomerism by external force.

The molecular overlay

The molecular overlay was conducted according to the backbone of Ciprofloxacin because it is the most typical quinolone antibiotic. The affection of electronic potential and *Van Der Waals* field was set as 50% each. The result was checked to guarantee that the quinolone cores were basically overlapped.

The molecular docking

Molecular docking simulation was conducted via the software Discovery Studio (Accelrys, USA). The crystal structures of human topoisomerase I (PDB Code: 1A35), topoisomerase II (PDB Code: 4R1F) and topoisomerase III (PDB Code: 4CGY) were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org). The preparation of the protein obeyed the standard protocol. The original ligands and water molecules were deleted from the crystal structures of the proteins. The polar hydrogen was added to the cleaned proteins. The binding sites were defined from the cavities and numbered according to the size. Then all the binding sites were checked to keep the radius of the spheres in a suitable range (0.5-10 nm) therefore the models could be relatively reliable. Again, CHARMm force field was recruited to complete the docking using the CDOCKER program with the random generated ligand conformations and a half-flexible receptor. First, the ligands conformations in series were generated by high temperature molecular dynamics with various random seeds. Second, random orientations of the conformations were subsequently created by translating the center of the ligand to a specified position within the receptor active site and making a series of random rotations. A softened energy was calculated. Then the orientation was kept when it was less than a specified limit. The process repeats until either the desired number of low-energy orientations was obtained, or the test times of bad orientations reached the maximum number. Third, each orientation was subjected to simulated annealing molecular dynamics. The temperature was heated up to a high temperature then cooled to the target temperature. A final energy minimization of the ligand in the rigid receptor using non-softened potential was performed. Finally, the CHARMm energy (interaction energy plus ligand strain) and the interaction energy alone were figured out for each of the final pose. The poses were sorted according to CHARMm energy and the top scoring (most negative, thus favorable to binding) poses were retained. The whole kinase domain defined as a receptor and the site sphere was selected based on the original ligand binding location, then the original ligand was removed, and the ligands prepared by us were placed during the molecular docking procedure. In the simulated annealing method, the heating steps were 2000 with 700 of heating target temperature and the cooling steps were 5000 with 300 cooling target temperature. For each ligand, ten final poses were saved according to their dock score rank. The pose with the lowest energy was chosen as the most suitable one. The pattern analysis was conducted accordingly.

Results and Discussion

As seen in Figure 2A, after energy minimization in CHARMm force field for adequate steps, the 3D structures of the selected xacins converged into a steric range with similar volumes. This result ensured the accuracy of the following procedures including molecular overlay and docking. Seen in Figure 2B, after molecular overlay, all the investigated molecules showed good consistency as the quinolone cores were basically overlapped. This will reduce the major concern of insufficient confidence level of docking simulation.

The binding energy of the studied xacins into Human Topo I, II and III was presented in Table 1. The larger the value was, the lower the energy was, thus the easier the binding would occur. According to the data, several hints could be organized. First, the xacins showed the preference in binding situations with the order Topo II >

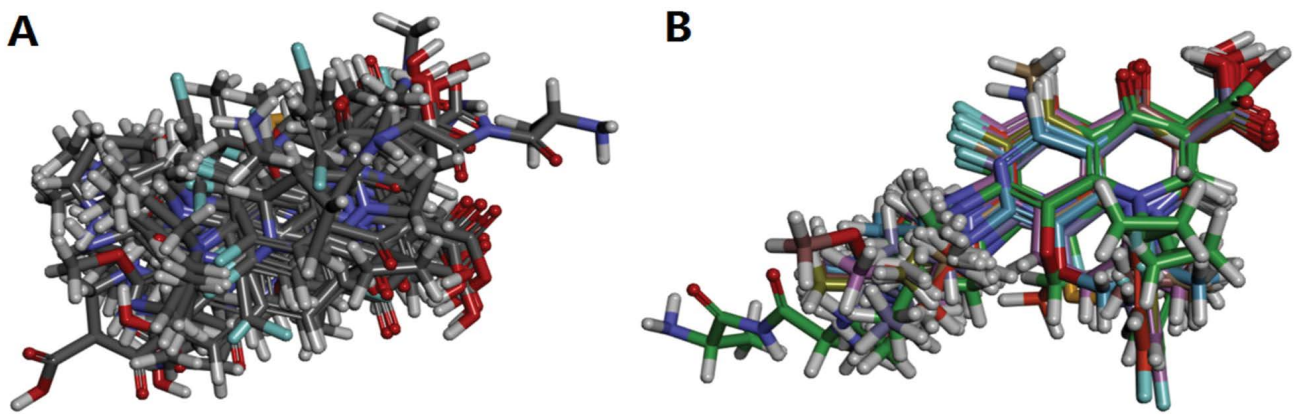

Figure 2: The structures of the studied xacins after energy minimization (A) and molecular overlay (B). Their steric conformations converged into a small volume after energy minimization in CHARMm force field. Overlapped with the quinolone core, their optimized structures indicated good consistency.

Table 1: The binding energy of the studied xacins into Human Topo I, II and III.

Topo I	-Energy (kcal/mol)	Topo II	-Energy (kcal/mol)	Topo III	-Energy (kcal/mol)
Grepafloxacin	36.0815	Alatrofloxacin	56.7101	Alatrofloxacin	56.9448
Moxifloxacin	35.8569	Grepafloxacin	55.1212	Temafloxacin	50.0223
Temafloxacin	35.7147	Gatifloxacin	53.571	Enoxacin	45.0582
Tosufloxacin	35.4954	Gemifloxacin	53.4783	Lomefloxacin	45.0336
Pipemidic acid	35.4817	Nadifloxacin	53.2681	Moxifloxacin	44.3815
Gemifloxacin	35.4202	Trovafloxacin	53.2223	Tosufloxacin	43.8647
Enoxacin	35.0297	Sparfloxacin	53.1397	Ciprofloxacin	43.0485
Trovafloxacin	34.7043	Moxifloxacin	53.1133	Gemifloxacin	42.6540
Sparfloxacin	32.8721	Ofloxacin	51.1086	Gatifloxacin	42.5980
Levofloxacin	31.2864	Temafloxacin	50.6039	Pipemidic acid	42.1612
Ofloxacin.cdx	30.6022	Tosufloxacin	50.5345	Nadifloxacin	41.5925
Pefloxacin.cdx	30.4232	Lomefloxacin	50.4750	Sparfloxacin	41.5637
Lomefloxacin	30.3799	Levofloxacin	49.7114	Fleroxacin	40.8749
Ciprofloxacin	30.3107	Norfloxacin	48.8138	Trovafloxacin	40.6068
Nalidixic acid	30.2423	Rufloxacin	48.5927	Rufloxacin	39.9158
Norfloxacin	29.9207	Fleroxacin	47.5199	Ofloxacin	39.2124
Fleroxacin	29.6700	Ciprofloxacin	47.3246	Levofloxacin	39.1278
Gatifloxacin	29.5761	Enoxacin	45.7953	Pefloxacin	38.9657
Nadifloxacin	29.2942	Pefloxacin	45.2658	Norfloxacin	37.9596
Rufloxacin	27.0945	Pipemidic acid	42.8552	Grepafloxacin	37.3532
Alatrofloxacin	Failed	Nalidixic acid	35.8082	Nalidixic acid	35.4947

Topo III > Topo I. This result had realistic meaning because topoisomerase-targeting anti-cancer agents were mainly focused on Human Topo II. Second, the binding situations were available for developing prodrugs for Topo II and Topo III from xacins. In convention, binding energy around 50 kcal/mol was fine for docking simulation. That means, several top ranked xacins could be potential inhibitors of the corresponding targets after a subsequent modification in druggability. Third, coincidently Alatrofloxacin was the top hit into Topo II and Topo III but failed when docked into Topo I. An optimistic opinion was that it could probably possess desirable selectivity as well.

One step further, we took Alatrofloxacin as representative to reveal the possible binding patterns of the studied xacins into Topo II and Topo III. For all the studied xacins, they could maintain several typical interactions via their similar cores. The possible hydrogen bonds with Arg98, Lys123, Thr215 of Topo II and the possible hydrogen bonds with Lys593 of Topo III all belonged to this kind of interactions. The *N*-substitute seemed more important for exploiting Topo III inhibitors with stronger interactions. The unique moieties of xacins distinguished their binding situations via the number and strength of key interactions. For Alatrofloxacin, it ranked the top

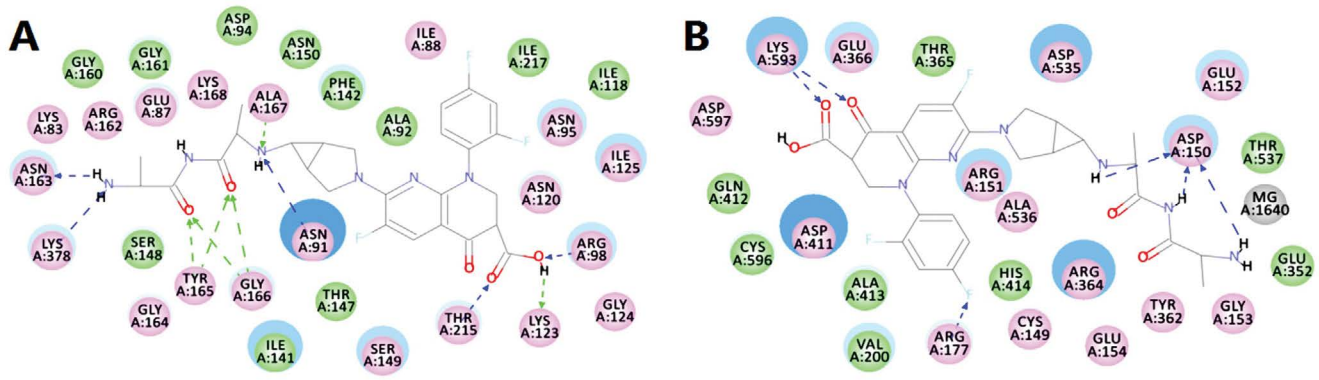

Figure 3: The 2D binding patterns of the representative Alatrofloxacin into the active sites of Human Topo II (A) and Topo III (B). The carboxyl group of the xacins indicated typical hydrogen bonds with Topo II and Topo III. Its N-substitute indicated key interactions with Topo III only. The unique moiety introduced more interactions, making Alatrofloxacin the top ranked one into both Topo II and Topo III.

because of the superb key interactions. Its unique moiety indicated seven possible hydrogen bonds with Topo II and three possible hydrogen bonds with Topo III, both being close to the ideal binding patterns. Thus, further modification could be performed by employing and refining the unique moiety of Alatrofloxacin on the re-designed quinolone cores to generate and seek for hit compounds against Human Topo II and Topo III (Figure 3).

To our knowledge, though antibiotics and carcinoma are both hot, rare researchers have successfully built the connection between these two fields. Since the xacins are commonly used drugs, their properties in pharmacology and toxicology have been studied. The findings in this work were unique and essential because the concept of recruiting anti-bacterial drugs to treat carcinoma has been investigated one step further. The results inferred the potential of the xacins in anti-tumor approaches. It was quite cheerful that the core backbone itself did have some significant interactions with both Topo II and Topo III. The unique moiety was important to bring more key interactions, which would be the requirement of future design. All the information here enhanced the confidence of eliminating drug resistance with available findings.

Conclusion

The traditional anti-bacterial xacins were potential hit compounds for developing Human Topo II and Topo III inhibitors. In this work, we collected the data of xacins, refined the steric conformations and performed the molecular docking simulation. It was an interesting finding that the xacins could interact with both Topo II and Topo III with its core structure. More key interactions could be introduced via modifying their unique moieties. Among the studied compounds, Alatrofloxacin indicated the most attractive binding pattern with key interactions via its unique moiety. Its unique character could be regarded as an important reference in future. The information raised in this work might lead to further investigation of developing quinolone-like anti-tumor agents and corresponding therapeutic approaches.

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