ADVANCED STRATEGY FOR TEACHING PHARMACEUTICAL CHEMISTRY COURSES BY IMPLEMENTING PHARMACOPHORES STRATEGY INSTEAD OF SAR ONE

Mohamed Abdel Hamid Ismail
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt
Email: mhismaeel@yahoo.com

ABSTRACT

After studying pharmaceutical chemistry course, the students should learn exact relation between chemical structures of drugs (medicines) and their biological activity. This means that when students watch the chemical structure of any drug, they should predict their biological activity at a definite target. In this article a new method was implemented, for the first time, to predict the biological activity of any drug based on pharmacophores concept rather than the structure-activity-relationship (SAR) one. The pharmacophores are template that could represent the interactions exerted by the essential function groups that are carried by chemical nucleus of the drug. The nucleus of any drug acts only as a scaffold to carry the essential groups to the nearest point to the complementary function groups at the binding sites of the drug targets. If we change the chemical nucleus by bioisosteric one that have the same interactions pattern, it will exert the same activity. Implementing this technique in teaching pharmaceutical chemistry courses may be more beneficial and accurate for the students to predict the biological activity of any drugs. [AJCE 4(2), Special Issue, May 2014]
INTRODUCTION

It is well known that any drug should combine with its target to elicit its biological activity. For example, combination of lead drugs at beta receptors [1], Angiotensin Converting Enzyme (ACE)[2] or Angeotensin II (Ang II) Receptors [3], will result in decreasing elevated blood pressure. Similarly, combination of lead drugs at PPARγ receptors will decrease blood glucose and treat diabetes mellitus type-II disease [4]. Meanwhile, combination of lead drugs at Mutated Kinase enzyme in cancer cells [5] will defeat cancer. Also, combination of lead drugs at topoisomerase I or II enzymes of the human cancer cells will result in treating some kinds of cancers [6]. Combination of beta-lactame antibiotics at trans-peptidase enzyme of bacterial cells will result in treating bacterial infections [7]. The mode of interactions with the binding sites may be either irreversible (formation of covalent interactions) or reversible (formation of dipolar, H-bonding or Van Dear Wall interactions) [8].

There are four classes of drug targets; the receptors (at the surface of cell wall), the enzymes, proteins (at blood circulation), the DNA, RNA or genomes (at the cell nuclei) [9]. The 3D structures of most of these targets were unknown till the last few decades. Thus, the pharmaceutical chemists could predict the activity of drugs by virtue of their structures themselves and not through the interactions with the targets. This method is termed Structure Activity Relationship (SAR). For example, the topoisomerase-IV enzyme that is responsible for bacterial replications, is existed only in the bacterial cell and not existed in human cells, were found to be inhibited by quinolone molecules having general structures and corresponding structural activity relationship (SAR) represented in Figure 1 [10]:
Indeed, there are tens of quinolone molecules that are marketed as antibacterial agents and comply with the given SAR in Figure 1. Among these marketed molecules were Nalidixic acid (1), Norfloxacin (2), Sparfloxacin (3), Moxifloxacin (4), Gatifloxacin (5), levofloxacin (6), etc. (Figure 2) [10].

Actually, in this article, the new non-quinolone molecules (structure 7) (Figure 3), was introduced here, and was found to show 1.3 folds higher activity as topoisomerase-IV inhibitor
more than the reference quinolone drug; norfloxacin (2), inspite of, it is not comply and not match with the reported SARs of quinolones molecules mentioned in Figure 1.

Figure 3: (Structure 7: A non-quinolone molecule that have high topoisomerase inhibitor activity higher than the quinolone molecules)

The reasons of the persistent anti-microbial activity of structure (7) as topoisomerase IV inhibitor is attributed to its ability to interact with the binding site of its target by a similar interactions like the quinolones analogue (2~6), but through another bioisoteric groups. The tetrazole function at molecule 7 is bioisosteric to the COOH group in molecules 2~6. These two bioisoteric functions can make the same dipolar ionic interaction with binding site. Also, the terminal aminopropoxy function at position 8 in structure 7, is bioisosteric to the N₁ of the quinolone analogues 2~6. This raised the assumption that the SAR concept of the embedded heterocyclic nucleus may not be the reason for biological activities. Indeed, the biologically activity of any ligand is due to the interaction exerted by the attached function groups at the embedded hetero-cycle. If we change the heterocyclic system and/or the attached function groups by other bioisoteric ones that give the same interactions with the receptors, the biological activity will remain. The function groups which have the same mode of interactions with the binding sites are termed features and the collections of many features at certain binding site are termed pharmacophores [9].
In this subject, a new method was implemented here, at the first time, to predict the biological activity of any drug without referring to the SAR theory, but referring to pharmacophores concept.

DISCUSSIONS

After the great scientific progresses in all aspects, especially in the biological sciences, molecular modeling, and 3D X-ray crystal structures elucidations, the scientists could recognize the 3D structures of most of living cells targets. These targets became available at the websites (www.pdb.com) and could be used as a template to recognize their own ligands. Molecular modeling generation of the pharmacophores of the essential leads’ function groups (or their complementary function groups at the binding site), of any binding site, would facilitate the prediction of the biological activity of any test set molecules by running the compare/fit study between them.

Pharmacophores are a collection of function groups of certain Lead and their interactions with the binding site. The different features in any pharmacophore may be: Hydrogen bond acceptor features (Vector), Hydrogen bond donor features, Hydrophobic features, Hydrophobic – aromatic features (point or plane), Negative Ionizable features (point), Positive Ionizable features (point), Negative Charge features (atom), Positive Charge features (atom) and Ring-aromatic features (vector) [9]. Each target has its own pharmacophores, which are completely different from one target to the others in the kinds of these features, their numbers, the distances and angles between them. So, they are considered as finger-prints for each target [9]. Figures 4, 5 and 6 represent the features of the topoisomerase IV inhibitors pharmacophore, their distances and angles.
Generation of Pharmacophores

The pharmacophores of any binding site could be directly built from the complementary function groups of binding sites, by running special molecular modeling modules during docking protocols of Accelrys/DS modules. Also, the pharmacophores could be indirectly built from a group of biologically active leads (5-15 leads with similar activity), that are reported to combine with the same given binding site, then run Common Feature Pharmacophore Generation using Accelrys/Catalyst/DS module [11].

For example, the above mentioned topoisomerase IV inhibitors pharmacophore (figures 4, 5 and 6) were generated from the binding site of the 3D crystal structure of topoisomerse IV protein complexed with norfloxacin (2) ligand, by determining the protein aminoacids molecules
of the binding site that bind with this ligand, and then build the corresponding spherical meshes of each interaction at each bound aminoacid molecule to directly get the pharmacophores. Also, the same pharmacophore (figures 4, 5 & 6) could be indirectly constructed from the reported lead molecules (5-15); Nalidixic acid (1), Norfloxacin (2), Sparfloxacina (3), Moxifloxacin (4), Gatifloxacin (5) and levofloxacin (6) (Figure 2), by running Common Feature Pharmacophore generation protocol of Accelrys/Catalyst/DS module [11].

Uses of Pharmacophores in predicting biological activity of any agents

The pharmacophores of most of the binding sites are generated and validated by many authors and are now reported in the literature and could be collected as data bases. The data bases of the different pharmacophores could be used as templates to perform fitting studies with all the available ligand molecules. So, we should have data bases of different pharmacophores and data base of different lead molecules. There are millions of reported and synthesized ligands that have unknown biological activity and the compare fitting virtual screening studies between the different pharmacophores and these millions of ligands compounds by applying simulation compare/fit techniques, could predict the active molecules among these ligands. Molecules that give the highest fitting scores than the reference leads are predicted to have higher activity at this target.

In this study, the generated topoisomerase IV inhibitor pharmacophore (Figures 4, 5 and 6) was used as a template to run compare/fit virtual screening protocol with the non-quinolone molecule [structure 7 (figure 3)], where compound 7 gave higher fitting score (equal 4.95/5=99%) than that of the reference drug; norofloxacin (4.1/5=88%) (Figure 7).
Antimicrobial Evaluation

The antibacterial activity testing for this non-quinolone molecule (7) and the reference drug; norofloxacin, against various microorganisms was actually performed using zone inhibition and serial dilutions techniques. The results showed that molecule (7) gave 1.3 folds higher antimicrobial activity than the reference drug norofloxacin (2).

Conclusion of molecular modeling virtual screening and antimicrobial evaluation:

The high compare fit score between the topoisomerase IV inhibitors` pharmacophore and the non-quinolone structure (7) was found to be matched with its high antimicrobial activity testing in comparison to the reference drug norofloxacin (2). This result and other similar reported results indicated that the use of pharmacophores as a tool to predict the biological activity of any ligand toward any target is a successful and perfect method. Thus, we can use pharmacophores technique to predict the biological activity.
How to apply Pharmacophores in education of pharmaceutical chemistry courses to predict biological activity

The students or the pharmacists should have Lap-Tops, Tablet or, Mobile Telephone Devices in which the Molecular Modeling Modules were installed. Also, the data bases of the pharmacophores of the different targets and data bases of test set ligands molecules were downloaded to these devices.

Then the students could perform the compare/fitting virtual study between pharmacophores and the tested compounds. The compare/fit scores are criteria for biological activity.

Other Benefits of Pharmacophores

We can apply this concept in research, to perform drug design of new molecules. Also, we can apply this technique for predicting the biological activities of isolated molecules from natural products [12].

REFERENCES

2. Angiotensin-converting enzyme (ACE) inhibitors, ACE inhibitors treat a variety of conditions, such as high blood pressure, scleroderma and migraines. Find out more about this class of medication, By Mayo Clinic Staff.


11. INFORMATION TECHNOLOGY SECTOR, SOFTWARE INDUSTRY, ACCL, accelrys inc (ACCL:NASDAQ GS).

12. Feras Saeed Haj Taleb, Rasha Kasser Finyar, Hiba Omar Baba, Siba Moneer Barakat, Hussam Abd Alrizaq Al shihabi, Graduation project tittled: “Virtual Screening of Some 3D Structures from Natural Sources having Unknown Biological Activities” Presented For the fulfillment of The graduation project course of Bachelor of Pharmacy and Pharmaceutical Chemistry Degree, Faculty of pharmacy, Kalamoon University, Syria, Supervised by Prof. Mohamed Abdel Hamid Ismail and Prof. Galal Taha Maatooq.