REVIEW ON STRUCTURE-ACTIVITY RELATIONSHIP (SAR) USING ANTIMALARIAL DRUG DESIGN AS A CASE STUDY

S. Cosmas (Cos242@yahoo.com), D.E. Ekpo (ekpodaniele@gmail.com), R. O. Asomadu (rita.asomadu@unn.edu.ng), J.O. Assor (johnassor@gmail.com), V. I. Nnamani (vyando1000@gmail.com), *O. A Durojaye (lanre.durojaye@yahoo.com).

ABSTRACT

Structure-activity relationship (SAR) is a method used in the detection of the chemical and biological activity relationship of compounds. This concept therefore points to the link between the chemical structures and biological and the biological activities of compounds, which also includes the toxicity. Production of new drugs with a higher potency and limited side effects, but having structural similarity with the original drug is another application of SAR theory. The essence of the structure-activity relationships also cuts across the toxicological studies on a compound. The design of commercial chemicals with specific wanted properties for long has involved the use of SARs. The importance also includes the prediction of therapeutic activities and pharmacological properties in drug design processes. Where the biological activity is quantified, quantitative structure-activity relationship (QSAR) is defined. Chemical structures and biological activities take advantage of the QSAR to build a mathematical relationship where a reliable measure depends solely on chemicals descriptors and their activities. SAR aims to identify which functional groups are important for activity, thus, employs few methods to aid in its activity, including: alter, remove or mask a functional group and test the analogue for activity. There are numbers of chemical and biological molecules to which SAR is applicable, however, a common area of application is with the drugs. Understanding the mechanism of action of a particular drug is pertinent to effectively employing SAR. The known mechanism of drugs depends on their active sites. Drugs can act on enzymes either by activating or inhibiting them via competitive inhibition or by non-competitive inhibition. Artemisinins has been seen to be a good example for this process. Artemisinins are currently available as important antimalarial class of drugs, because of their effectiveness against resistant strains of the malarial parasites. Structure-activity relationship is therefore made obvious and practically applicable in this class of drug.

Keywords: Toxicity; Artemisinins; Antimalarial; SAR

INTRODUCTION

Medicinal chemistry is a chemistry-based discipline which covers a wide range of biological, medical and pharmaceutical sciences. Its connection with the discovery, design, identification and the art of preparing compounds which are biologically active cannot be separated [23]. Medicinal chemistry field also covers the study of metabolism of biologically active compounds, how they function at the molecular level and the prediction of their structure-activity relationship (SAR) i.e. the relationship between the biological activity and the three dimentional structure of a particular molecule [12]. Molecular modeling is a key factor in the derivation of (SAR). The use of structure-activity relationship encompasses the design and refinement of pharmaceutical agents. It also aids structural alerts at the sensing of toxicity and mutagenicity [7]. Structure-activity relationship ideally enables encoding and with chemical connectivity as well as 3D stereochemistry; including information from active and inactive compounds, and these requires no molecular superposition. It can as well express the resultant rules in a form readily understandable to chemists. The incorporation of this method was to build mathematical relationships between the chemical structure and biological activity of therapeutic agents. This is known as quantitative structure-activity relationships (QSAR) [14].

QSAR is a special case of structure activity relationships where the relationships become quantified thus integrated in the process of determination of the chemical groups responsible for evoking a target biological effect in the organism. The hypothetical assumption for all molecules is that similar molecules elicit similar effects. These similarities can be observed directly by the similarity in structures or by indirectly transforming a structure to its numerical representation (i.e. molecular descriptors, field descriptors) followed by the application of one of the similarity measures [28]. At the occurrence of conversion of the structures to a numerical representation, the assessment methods of similarity becomes quantitative. Reliability of this measure is depends

on the relationship between the numerical representation of chemicals and their activities, and this relationship should be known [4].

STRUCTURE-ACTIVITY RELATIONSHIP

Structure-activity relationship (SAR) explains the relationship between the three dimensional (3D) structure and its biological activity of a molecule of interest [26]. This in other words analyses the dependence of a chemical's biological effects on its molecular structure. The chemical structure includes molecular geometry, electronic structure, and crystal structure of a molecule. The description of the beneficial or adverse effects of a drug on a living matter explains the biological activity of the drug [6]. Given adequate information about both the molecular structures and the pharmacological activities of a relatively large group of congeners, it is possible to use computer analysis to identify the chemical properties (i.e. the pharmacophore) required for optimal action at the receptor site: size, shape, position, and orientation of charged groups or hydrogen bond donors, and so on. Advances in molecular modeling of organic compounds, methods for drug target (receptor) discovery and biochemical measurement of the primary actions of drugs at their receptors have enriched the quantification of structure-activity relationships and its use in drug design [7]. Structrue-activity relationship is also important in the identification of important functional groups that aids activity. Earlich's theory states that a drug will not work unless it's in a bound state. This explains the effect of chemical structure on pharmacological action and this goes further to explain that a drug should not be uniformly distributed in the body i.e it must be directed towards a particular target cellular molecule to elicit a pharmacological action. This in other words means that the drug molecule will be effective only when it binds to its target molecules and alter its activity [1].

METHODS OF STRUCTURE-ACTIVITY RELATIONSHIP

Structure activity relationship aims to identify which functional groups have important activity thus, employs few methods to aid in its activity. These methods include:

- Changing, masking or complete removal of the functional group.

- Testing the resulting analogue for desirable activities. The method of testing determines how conclusions can be inferred i.e *in vitro* and *in vivo* tests for binding interactions with targets and/or the pharmacokinetics properties.

The essence of these two methods is that, if a group is removed or modified and *in vitro* activity drops or diminishes, it implies that the group was important for binding, but if *in vivo* is unaffected, it implies that the group is not important [5].

STRUCTURE-ACTIVITY RELATIONSHIP CONSIDERATION IN DRUG DESIGN

There are numbers of chemical and biological molecule to which SAR is applicable, however, a common area of application is with drugs. A drug is a chemical substance used in the treatment, cure, or prevention of a disease state or to promote well-being [10]. Pharmaceutical drugs are often broadly classified into drug classes – groups of related drugs that have similar chemical structures, and those with the same mechanism of action (binding to same biological target). Route of administration of drug includes, parenteral routes, intramuscular injection, subcutaneous injection, oral, rectal, inhalation and transdermal routes etc [11].

MECHANISM OF DRUG ACTION

Understanding the mechanism of action of a particular drug is pertinent to effectively employing SAR. The known mechanism of drugs depends on their acting sites. Drugs can act on enzymes either by activating or inhibiting them via competitive inhibition or by non-competitive inhibition [9]. In competitive inhibition, drugs competes with the substrate for the same site of the enzyme and combines with it reversibly, while non-competitive is where the inhibitor binds itself to different sites on the enzymes and not on the active site [9]. Also, the chemical substances (allosteric inhibitors) that have no structural similarity with the substrate can also inhibit enzymes by competing directly with the activator for regulatory sites or by causing conformational changes which results in decreased affinity for substrate catalytic sites [21].

STRUCTURE-ACTIVITY RELATIONSHIP OF A KNOWN DRUG (ARTEMISININ)

ARTEMISININ (QINGHAOSU) & DERIVATIVES:

Artemisinin (ART), a natural product isolated from the plant *Artemisia annua*, was discovered in the early 1970s [22]. Artemisinin and its derivatives (either alone or as a combined therapy), are

the standards of care for any form of malaria [13]. Artemisinin-based anti-malarial drugs have proven to be harmless while demonstrating extraordinary anti-malarial activity [29]. Artemisinin is 3R-3α, 5αβ, 6β, 8αβ, 9α 12β. 12αR octahydro-3, 6, 9-trimethyl-3, 12- epoxy- 12H-pyrano [4, 3,-j]-1, 2-benzo-dioxepin-10 (3H)-one. It is soluble in organic solvents but almost insoluble in water, hence suitable derivatives such as arthemeter, arteether and sodium artesunate are effective and useful clinically [19]. Replacement or substitution in C-1, C-7, C-2 and C-3 leads to reduced or partial loss of activity. In C-4 and C-6, hydrogenationation of artemisinin produces deoxyartemisinin which is devoid of antimalarial activity. Ultimately, alteration or replacement in most carbon molecules may lead to a positive or negative result [8].

MECHANISM OF ACTION:

The drugs have high affinity for hemozoin, a storage form of hemin, which is retained by the parasite after digestion of haemoglobin, leading to a highly selective accumulation of the drug by the parasite. The drug then composes in the presence of iron, probably from and releases free radicals. This results in changes in membrane integrity and depression of protein synthesis resulting ultimately in cytotocity, phargocytosis and clearance by most leucocytes [20].

PHARMACOKINETIC PROPERTIES

Artemisinins can be administered by several routes. The water soluble derivative artesunate can be given by the oral, intramuscular, intravenous, and even intrarectal routes [18].The most clinically useful artemisinins are metabolized to dihydroartemisinin. The anti-malarial effect f artesunate metabolite compared to the parent compound is more important as it exhibits a longer elimination half-time which is 1 hour compared to the parent compound which has an elimination half-time of less than 10 minutes [21]. The relatively short half-time for elimination of dihydroartemisinin confers on it the theoretical advantage drug resistant malarial parasites. The disadvantage however is linked to a higher risk of recrudescence when these drugs are administered in mono therapeutic regimens.

Oral artesunate is absorbed in uncomplicated malaria at a very fast rate and this is accompanied with good bioavailability [3]. Absorption rate however may be changed by variables such as the artemisinin formulation, administration route and oil-solubility. An inference can be taken from cases of severe malaria where a slower absorption rate is experienced in the intramuscular route

administration of artemether when compared to the intramuscular route administration of artesunate [24].

PHARMACODYNAMIC PROPERTIES

The antimalarial activities of artemisinins are more rapid when compared to other types of antimalarial drugs. These activities include the killing of malarial parasites and inhibition of their major metabolic processes, such as glycolysis, nucleic acid and protein synthesis [30]. The activities of artemisinins also includes its specificity in attacking a broad range of parasites, from the tiniest rings that have recently invaded erythrocytes to more mature stages of parasites such as developing trophozoites and schizonts [2]. Their broad stage-specificity of action also extends to their ability to inhibit the development of gametocytes [27]. This property reduces circulating parasitaemia more rapidly than other anti malaria, sometimes by up to 2–3 log orders of magnitude [31]

STRUCTURE-ACTIVITY RELATIONSHIP FOR ARTESIMININ

Replacement of the methyl group at C-3 of artemisinin and 10-deoxodihydro-artemsinin by much larger groups, for example, phenylethyl, groups which are held to stabilize radicals, in artemisinin results in diminution in activity [4]. The C-4, C-5 or C-12 groups in artemisinin analogues which are also disposed on the same side as the peroxide markedly attenuate their activity. In artemisinin itself, inversion of the configuration at C-9 such that the methyl group is now on the same face of the molecule as the peroxide also attenuates its activity [25].

CONCLUSION:

While the bulk of (Q)SAR analyses are targeted at the interactions of a family of molecules with an enzyme or receptor binding site, (Q)SAR can also be useful in the study of the interactions between the structural domains of proteins [15]. Drug discovery has also been a major hallmark of (Q)SAR and it involves identifying the chemical structures that could have good inhibitory effects on specific targets and have low toxicity (non-specific activity) [16]. (Q)SAR models have been used for risk management and are suggested by regulatory authorities. A major watch-word in SAR is the “prediction” of the possible activity of a pharmacological molecule using the available pharmacological and pharmacokinetic parameters available to us. The assessment of

the reliability of (Q)SAR predictions remains a research topic however, (Q)SAR equations remain viable tools that can be used to predict or quantify biological activities of newer molecules before their synthesis [17].

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