Quantitative Structure–Activity Relationships of Antimicrobial Compounds

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38 Quantitative Structure–Activity Relationships of Antimicrobial Compounds

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Abstract: A thorough antimicrobial review of an increasing number of reports reveals a broad spectrum of research activity in the development practices that are used to treat a variety of diseases. The quantitative relationship between chemical structure and biological activity has received considerable attention in recent years because it allows one to predict theoretically bioactivity without an inordinate amount of experimental time and effort. In this chapter we collect and discuss critically published results concerning the QSAR research on antimicrobial compounds. Finally, we present an updated perspective about the future trends in this area.

Introduction

Antimicrobial drugs are drugs designed to kill, or prevent the growth of microorganisms (bacteria, fungi, and viruses). The development of antimicrobial agents for clinical use has brought unquestionable benefit to individuals and society. Infectious diseases that were formerly often fatal became curable (Lerner 1998). However, antibiotics ultimately have lost their original effectiveness as they have been used over time and resistant strains of bacteria have been developed and there is thus an urgent need to identify novel, active chemotypes as leads for better drug development (Cragg et al. 1997; Hall 2004; Mcdermott et al. 2003).

The versatility of bacterial populations to adapt to environmental toxicity and associated facilities for transferring genetic material show that the antibiotic resistance a biological phenomenon is inevitable and will continue to be a chronic medical condition. The appropriate employment of antimicrobials in use and the continued development of new ones are vital to protect the health of men and animals from pathogens (Mcdermott et al. 2003).

Natural products could play a crucial role in meeting this demand (Cragg and Newman 2001). The use of natural products for the treatment of human diseases is a practice that has been used for a long time. It is estimated that 40% of medicines available for the current treatment of diseases have been developed from natural sources (Cragg and Newman 2001; Shu 1998). The knowledge generated as a result of the use of natural product derivatives of the higher plants, microorganisms, and toxins animals was essential in the discovery of new drugs for modern medical treatment.

In medicine, natural products provide high number of drugs useful in case of complex chemical synthesis and can also serve as basic compound models of synthetic drugs or suitable modifications that reduce its toxicity (Demain 1999).

The quantitative relationship between chemical structure and biological activity has received considerable attention in recent years because it allows one to predict theoretically bioactivity without an inordinate amount of experimental time and demanding efforts.

Computational methods for predicting compounds with specific pharmacodynamic, pharmacokinetic, or toxicological properties are useful for facilitating drug discovery and drug safety evaluation. The quantitative structure-activity relationship (QSAR) and quantitative structure–property relationship (QSPR) methods are the most successfully used statistical learning methods for predicting compounds with specific properties.

More recently, other statistical learning methods such as neural networks and support vector machines have been explored for predicting compounds of higher structural diversity than those covered by QSAR and QSPR approaches. These methods have shown promising potential in a number of studies. Many attempts have been made to elucidate the QSAR of antimicrobials by using different physicochemical parameters.

This chapter is intended to review some of the strategies and current progresses in using statistical learning methods for predicting compounds with specific desired properties in antimicrobial activity.

General Overview of Methods Used in QSAR of Antimicrobial Compounds

Antimicrobial Activity Determination

As microbiological methods incorporate viable test microorganisms, predictability of the outcome is not always clear and subject to many environmental influences that may impact on a given response. Hence, it is of the utmost importance that parameters such as plant collection, validation of laboratory equipment, chemical analysis, and various intricacies of antimicrobial investigations be carefully defined.

Although several methods are used to assess antimicrobial activity, the two most common methods used are disk diffusion and minimum inhibitory concentration (MIC) assays. Generally disk diffusion studies are the method of choice due to their simplicity and capacity to analyze a large number of test samples. Even though disk diffusion methodology is a quick simple means of screening for antimicrobial activity, it is a qualitative assay because it shows if there is antimicrobial activity or not. The MIC measurement to determine antimicrobial activity is a quantitative method based on the principle of contact of a test organism to a series of dilutions of test substance. Assays involving MIC methodology are widely used and an accepted criterion for measuring the susceptibility of organisms to inhibitors (Lambert and Pearson 2000).

Quantitative Structure–Activity Relationship (QSAR)

Quantitative structure–activity relationship (QSAR) analysis is in constant development since the works of Hansch (Hansch and Fujita 1964) in early 1960s. The QSAR methodology focuses on finding a model, which allows one for correlating the activity to structure within a family of compounds. QSAR studies can reduce the costly failures of drug candidates in clinical trials by filtering the combinatorial libraries. Virtual filtering can eliminate compounds with predicted toxic of poor pharmacokinetic properties (Hodgson 2001; van de Waterbeemd and Gifford 2003) early in the pipeline.

Considering activity optimization, building target-specific structure-activity models based on identified hits can guide high throughput screening (HTS), a recent technological improvement in drug discovery pipeline, by rapidly screening the library for most promising candidates (Dudek et al. 2006). Such focused screening can reduce the number of experiments and allows for use of more complex and low throughput assays (Bajorath 2002). Interpretation of created models gives insight into the chemical space in proximity of the hit compound. Feedback loops of high-throughput and virtual screening, resulting in sequential screening approach (Lewis 2005), allow therefore for more rational progress toward high quality lead compounds. Later in the drug discovery pipeline, accurate QSAR models constructed on the basis of the lead series can assist in optimizing the lead (Prado-Prado et al. 2008).

Main stages of a QSAR study can be divided into three groups, i.e., extracting descriptors from molecular structure, choosing those informative in the context of the analyzed activity, and, finally, using the values of the descriptors as independent variables to define a mapping that correlates them with the activity in question (Dudek et al. 2006).

Generation of Molecular Descriptors from Structure

Compounds are defined by their structure, encoded as a set of atoms and covalent bonds between them. However, the structure cannot be directly used for creating structure-activity mappings because it does not usually contain in an explicit form the information that relates to activity. Molecular descriptors accentuate different chemical properties implicit in the structure of the molecule and so those properties may correlate more directly with the activity. Such properties range from physicochemical and quantum-chemical to geometrical and topological features.

On the other hand, most methods of statistical data analysis employed to predict the activity require as input numerical vectors of features of uniform length for all molecules. Chemical structures of compounds are diverse in size and nature and as such do not fit into this model directly. Molecular descriptors convert the structure to the form of well-defined sets of numerical values.

Selection of Relevant Molecular Descriptors

Although it is possible to generate hundreds or thousands of different molecular descriptors, only some of them are significantly correlated with the activity. Furthermore, many of the descriptors are intercorrelated. This has negative effects on several aspects of QSAR analysis. Some statistical methods require that the number of compounds is significantly greater than the number of descriptors and using large descriptor sets would require large datasets. Other methods, while capable of handling datasets with large descriptors to compounds ratios, nonetheless suffer from loss of accuracy. Large number of descriptors also affect interpretability of the final model. To tackle these problems, a wide range of methods for automated narrowing of the set of descriptors to the most informative ones is used in QSAR analysis.

Mapping the Descriptors to Activity

Once the relevant molecular descriptors are computed and selected, the final task of creating a function between their values and the analyzed activity can be carried out. The value quantifying the activity is expressed as a function of the values of the descriptors. The most accurate mapping function from some wide family of functions is usually fitted based on the information available in the training set, i.e., compounds for which the activity is known. A wide range of mapping function families can be used, including linear or nonlinear ones, and many methods for carrying out the training to obtain the optimal function can be employed.

Descriptors Used in Antimicrobial Activity Studies

The QSAR techniques involve correlating the logarithm of the reciprocal molar concentration of a bioactive compounds required for a specific biological response such as ED_{50} (dose of a drug that is pharmacologically effective for 50% of the population exposed to the drug or a 50% response in a biological system that is exposed to the drug) or LD_{50} (Lethal Dose 50%, dose that kills half population tested) values with linear free energy constants such as the Hammett constant σ, a measure of aromatic substituent electronic effects; Taft polar constant σ^*, a measure of substituent polar effects; the logarithm of the 1-octanol/water partition coefficient (log *P*), a measure of hydrophobic-hydrophilic effects; and the Taft steric constant *E*s, a measure of substituent steric effects, etc.

A very important role may be played by computer aided drug design techniques based on multi-target quantitative structure–activity relationships (mt-QSAR) studies. It means that they are models connecting the structure of drugs with the biological activity against different targets (microbial species in the case of antimicrobial drugs) (Prado-Prado et al. 2008, 2009). This kind of study may also help in a multi objective optimization (MOOP) of desired properties or activity of drugs against different targets; see for instance the recent works carried out by Cruz-Monteagudo in the topic (Cruz-Monteagudo et al. 2008a, b). In principle, up to date there are over 1,500 molecular descriptors that may be generalized and used to solve the former problem (González et al. 2004; Kubinyi 1990; Marrero-Ponce et al. 2005; Todeschini and Consonni 2002).

Many of these indices are known as topological indices (TIs) or simply invariants of a molecular graph, whose vertices are atoms weighed with physicochemical properties (mass, polarity, electro negativity, or charge) (Estrada and Molina 2001).

QSAR Studies of Antimicrobial Compounds

Coumarins

As a result of the continuously growing interest for antimicrobial activity of coumarins (Al-Haiza et al. 2003; Althaus et al. 1988; Galm et al. 2004; Hoult and Paya 1996; Kulkarni and Patil 1981, 1983; Laurin et al. 1999; Reusser and Dolak 1986; Rodighiero and Antonello 1958; Vieira et al. 2001), a few coumarin antibiotics became candidates for human and veterinary medicine applications. The most important representative is the 3-aminocoumarin derivative novobiocin, the antibiotic that has been relatively recently approved for medical use in the USA for SA infection treatment (Schmutz et al. 2003). Besides novobiocin, other coumarin derivatives like eskuletin, umbelliferon, and related compounds possess antibacterial properties as well (Heinrich et al. 2004). Antifungal activity has been attributed to some of the coumarin derivatives, including coumarin (1,2-benzopyranone) itself (Mares 1987). Antimicrobial activity of 3-nitrocoumarins and related compounds against *Caudida albicans* and *Staphyloccus aureus* has been shown recently (Tisi et al. 2001).

Debeljak et al. (2007) studied 3-nitrocoumarins and related compounds, in order to explore their activity and molecular properties that determine their antimicrobial effects. QSAR models involved most of the 64 descriptors extracted from semiempirical and density functional theory (DFT) founded calculations have been proposed. For the study, literature data containing results

of microbiological activity screening of 33 coumarin derivatives against selected clinical isolates of *Caudida albicans* and *Staphyloccus aureus* were selected. Candidate molecules were checked by cross-validated models, and selected derivatives were synthesized. Their antimicrobial activities were compared to antimicrobial activities of the representative derivatives from the original set in terms of minimal inhibitory concentration (MIC). High ranking of descriptors consistent with the degree of hydrolytic instability of selected compounds is common to models of antimicrobial activity against both microorganisms. However, descriptor ranking indicates different antimicrobial mechanisms of action of chosen coumarin derivatives against selected microbial species.

A set of 68 coumarins and coumarin derivatives with already reported antifungal activities was selected and eleven attributes were generated in order to represent a relationship between the physicochemical properties and their biological activities. The descriptors were used to perform artificial neural network (ANN) and to build a model for predicting effectiveness of the new ones. With good correlation between the experimental and the predicted MIC values pertaining to all the coumarins, the study paves the way for further researches about antifungal activity of coumarins, and offers a powerful tool in modeling and prediction of their bioactivities (Soltani et al. 2009).

A series of new coumarin derivatives has been synthesized and the in vitro antimicrobial activity against thirteen strains of bacteria and three fungal/yeast strains were screened. They were shown to possess a wide range of activities from almost completely inactive compounds to medium active ones (Dekić et al. 2010).

Benzamides

Benzamides are an important class of compounds that show various types of biological activities (Itaru et al. 1973; Mrozik et al. 1969). Oxyclozanide was reported as an antihelmintic agent effective against *Fasciola hepatica* for the treatment of liver fluke infection (Mrozik et al. 1969). The synthesis of some *N*-(ohydroxyphenyl) benzamides and phenylacetamides as possible metabolites of antimicrobial active benzoxazoles has been reported (Sener et al. 2000).

A series of substituted benzamides were synthesized by (Kumar et al. 2007). The synthesized compounds were evaluated for in vitro antibacterial activity against Gram-positive *Staphylococcus aureus*, *Bacillus subtilis* and Gram-negative *Escherichia coli*, and in vitro antifungal activity against *Aspergillus ficcum* and *Aspergillus parasiticus*. In antibacterial assay minimum inhibitory concentrations (MIC) were determined, and the antifungal activity against the fungal species was determined by serial dilution method. The structural characteristics governing antibacterial activities of substituted benzamides were studied using QSAR methodology. The results obtained indicate that the benzamides are effective against the microbial species tested, and that the *N*-(2-hydroxyphenyl)-3-methoxy-2-nitrobenzamide and *N*-(2-hydroxy-6-carbmethoxyphenyl)-2-benzyloxybenzamide are the most effective ones. A general trend showed that the presence of electron-withdrawing groups (NO_2, Cl) leads to an increase in the activity in comparison to the presence of electron releasing group. The results showed that the antimicrobial activity could be modeled using the topological descriptors, molecular connectivity indices ($^2\chi^v$ and $^2\chi$), and Kiers shape index ($\kappa\alpha_1$). The low residual activity and high cross-validated r^2 values (r^2_{cv}) observed indicated the predictive ability of the developed QSAR models.

Cinnamic Acid

Cinnamic acid plays an important role for the antimicrobial activity (Ahluwalia et al. 1986; Christine et al. 1984; Cremlyn et al. 1984, 1986). Derivatives of cinnamic acid, displaying a broad spectrum of biological activity and low toxicity, are of interest for the purposes of creating new effective drugs based on them (Simonyan 1993). There are several studies on cinnamic acid derivatives with antibacterial and antifungal activity (Ahmed et al. 1995; Lee and Ahn 1998; Ovale et al. 1996; Ramanan and Rao 1987; Srivastava et al. 1999; Tawata et al. 1996). Potential antimicrobial activity of sorbic, cinnamic, and ricinoleic acid derivatives was reported some time ago (Narasimhan et al. 2003). The synthesis and the correlation between physicochemical properties and biological activity were carried out. Later, the evaluation of the in vitro antimicrobial activity of over 30 compounds belonging to a series of esters, substituted derivatives, and amides of cinnamic acid was performed by Narasimhan et al. and the investigation of the relationship between their physicochemical properties and microbiological effects have been widely discussed (Narasimhan et al. 2004). Quantitative structure–activity relationship investigation with multiple linear regression analysis was applied to find a correlation between different calculated physicochemical parameters of the compounds and biological activity. All the compounds showed a good antibacterial activity against Gram-negative *Escherichia coli* than Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*. The chemical structure of each compound was described by three groups of parameters: steric, electronic and hydrophobic which were selected due to their encouraging effect in describing antimicrobial activity (Narasimhan et al. 2003). The quantitative models relating the structural features of cinnamic acid derivatives and their antimicrobial activity showed that Gram-negative *Escherichia coli* and *Candida albicans* (fungus) were the most sensitive microorganisms. The regression equations obtained for the bacterial species showed the importance of constitutional parameter unsaturation index (U_i), global topological charge index (JGT), and the lipophilic parameter log P in contribution to antibacterial activity.

Flavanones

Among the drugs approved between 1983 and 1994 by either the United States Food and Drug Administration (FDA) or comparable entities in other countries, drugs of natural origin predominated (78%) in the area of antibacterials (Cragg and Newman 2001). A large number of homoisoflavanones have been isolated from several hyacinthaceous genera including *Eucomis* L'Hér., *Merwilla* Speta, *Ledebouria* Roth, *Veltheimia* Gled. and *Drimiopsis* Lindl. and Paxton (Pohl et al. 2000). Homoisoflavanones belong to a small homogeneous group of naturally occurring oxygen heterocycles which, within the *Hyacinthaceae*, are largely but not exclusively restricted to the subfamily *Hyacinthoideae*. The few reports on the biological activity of homoisoflavanones describe anti-inflammatory, antibacterial, antihistaminic, antimutagenic, and angioprotective properties, and potent phosphodiesterase inhibition (Amschler et al. 1996; Della Loggia et al. 1989; Heller and Tamm 1981).

Du Toit et al. (2007) determinated the antibacterial activity of thirteen homoisoflavanones isolated from six Hyacinthaceae species against *Staphylococcus aureus*. They also developed a set of physicochemical parameters that would describe antibacterial activity for these and future compounds. Stepwise multiple linear regression analysis of the data yielded a statistically significant two-component model ($R^2 = 0.81$, $p < 0.003$).

Phenolic Compounds

Natural and synthetic phenolic compounds were evaluated against oral bacteria. Thus, many antimicrobial agents have been developed for the inhibition of halitosis bacteria and thus for the treatment of oral malodor (Giertsen 2004; Greenstein et al. 1997; Hayashi et al. 2007; Loesche 1979). Antibacterial compounds such as chlorhexidine, cetylpyridinium chloride, triclosan, and chlorine dioxide have been tested either alone or in different combinations. However, most compounds have been known to induce undesired side effects (Rule et al. 2005).

Greenberg et al. performed a systematic evaluation of various phenolic compounds to develop a quantitative structure-active relationship (QSAR) (Greenberg et al. 2007). They observed that a number of phenolic compounds in natural botanic extracts and flavors demonstrated antimicrobial activity. Among them, eugenol, magnolol, honokiol, thymol, and xanthorrhizol showed strong activity against oral bacteria. Magnolia bark extract, a traditional Chinese medicine isolated from the stem bark of *Magnolia officinalis*, consists primarily of magnolol and honokiol, the two phenolic isomers, and has a strong germ-kill activity against oral bacteria.

In the QSAR approach applied for a range of about 20 phenolic compounds the lipophilicity and steric effects were found to be two key factors in determining germ-kill activity (Greenberg et al. 2008). The optimum lipophilicity, measured by the logarithm of the octanol/water partition coefficient, or log *P*, was found to be 5.5 for *Fusobacterium nucleatum*, a Gram-negative type of oral bacteria that causes bad breath. The optimum log *P* was found to be 7.9 for *Streptococcus mutans*, a Gram-positive type of oral bacteria that causes tooth decay.

The steric effect of substituents ortho to the phenolic group was found to be critical in reducing antibacterial activity despite having increased lipid solubility approaching the optimum lipophilicity value. The antibacterial activity of phenolic compounds is likely exerted by multiple functions, primarily comes from its capability to act as a nonionic surface-active agent therefore disrupting the lipid–protein interface.

Furan Derivatives

Furan derivatives, both obtained from synthetic and natural sources, have much interest due to the wide range of pharmaceutical applications they have shown (Hofnung et al. 2002; Khan et al. 2005; Kupchan et al. 1971; Shevchenko 1999). A series of synthetic nitrofuranyl amides showed good in vitro inhibitory activity against *Mycobacterium tuberculosis* (Tangallapally et al. 2006; Tomlin 1994) especially 5-nitro-furan-2-carboxylic acid *N*-[4-(4-benzylpiperazin-1-yl)-benzyl]-5-nitrofuran-2-carboxamide and 2-methyl-*N*-phenylfuran-3-carboxamide.

Preparation of furan-3-carboxylic acid and derivatives and their assessment against a panel of microorganisms including yeast-like fungi, bacteria, and algae were reported (Zanatta et al. 2004). Because some of the furan-3-carboxamides exhibited significant in vitro antimicrobial activity, the synthesis and characterization of an extended and planned series of new furan-3-carboxamides was carried out (Zanatta et al. 2007). The obtained furan-3-carboxamides were assessed against a panel of microorganisms including yeast, filamentous fungi, bacteria, and algae. Preliminary antimicrobial activity assays of some of the furan-3-carboxamides exhibited significant in vitro antimicrobial activity. QSAR investigation was applied to find

a correlation between the different physicochemical parameters of the compounds studied and their biological activity. Yeasts showed a negative correlation with the indicator variables I_R, but *Saccharomyces cerevisiae* showed a better correlation with the steric and polarity descriptors, Gram-positive and Gram-negative bacteria correlate with the increase of the steric volume and the polarizability parameter and negatively correlated with hardness, and filamentous fungi correlate with the increase of the steric volume and the polarity of groups.

An interesting QSAR study of diacyl-hydrazine derivatives containing furan rings was conducted and compared with the DFT method and AM1-MOPAC method (Zhang et al. 2010). The DFT-optimized conformations and ESP-fitting charges of the target compounds were also used for 3D-QSAR analysis, including CoMFA and CoMSIA. The QSAR results were consistent with the 3D-QSAR results, indicating that the electrostatic and hydrophobic properties of the target compounds were significant to the biological activity.

mt-QSAR Studies

One limitation of almost QSAR models is that they predict the biological activity of drugs against only one species of fungi, virus, bacteria or parasite species. Consequently, the development of multitasking QSAR models (mt-QSAR) to predict drugs activity against different species of antimicrobial agents is of vital importance. These mt-QSARs offer also a good opportunity to construct drug–drug Complex Networks (CNs) that can be used to explore large and complex drug-viral species databases. In very large CNs it is possible to use the Giant Component (GC) as a representative sub-set of nodes (drugs) and but the drug–drug similarity function selected may strongly determines the final network obtained. Several mt-QSAR models were reported to predict the antimicrobial activity against different fungi (González-Díaz et al. 2006), bacteria (Prado-Prado et al. 2007), parasite (Prado-Prado et al. 2008), and virus species (Prado-Prado et al. 2009) and to calculate the parameters for RNAs of both parasites and hosts (González-Díaz et al. 2011).

For example, the most important limitation of antifungal QSAR models is that they predict the biological activity of drugs against only one fungal species due the fact that most of the up-to-date reported molecular descriptors encode only information about the molecular structure. Prado-Prado et al. calculated, within a unifying framework, the probabilities of antifungal action of drugs against many different species based on spectral moment's analysis (Prado-Prado et al. 2009). They calculated new multi-target spectral moments to fit a QSAR model that predicts the antifungal activity of more than 280 drugs against 90 fungi species. Linear discriminant analysis was used to classify drugs into two classes as active or non-active against the different tested fungal species. Moreover, it was developed one single unified equation explaining the antifungal activity of structurally heterogeneous series of compounds against as many fungus species as possible (González-Díaz and Prado-Prado 2008; González-Díaz et al. 2006).

In fact, other mt-QSAR approaches, with demonstrated usefulness, have been introduced recently in medicinal chemistry (González-Díaz et al. 2006; Marrero-Ponce et al. 2004; Molina et al. 2004). A Markov Model encoding molecular backbones information was introduced in the method named the MARCH-INSIDE, MARkovian CHemicals IN SIlico DEsign (González-Díaz et al.). This method allows one to introduce matrix invariants such as stochastic entropies,

potentials, and spectral moments for the study of molecular properties (González-Díaz et al. 2005; Ramos de Armas et al. 2004) and they have been largely used for small molecule mt-QSAR problems including the design of fluckicidal, anticancer, and antihypertensive drugs (Prado-Prado et al. 2007). Applications to macromolecules have been restricted to the field of RNA without applications to proteins (González-Díaz and Uriarte 2005; González-Díaz et al. 2003, 2007; Saiz-Urra et al. 2005).

The QSAR models based on different MARCH-INSIDE indices may be very useful to optimize important aspects such as activity, toxicity, or pharmacokinetics using one single model in many bioorganic and medicinal chemistry problems such as estimation of anticoccidial activity, modeling the interaction between drugs and HIV-packaging-region RNA, and predicting proteins and virus activity (González-Díaz et al. 2004, 2006). In recent studies, the MARCH-INSIDE method has been extended to encompass molecular environment, interesting information in addition to molecular structure data (Cruz-Monteagudo et al. 2007).

Multiple applications of MARCH-INSIDE to classic QSAR, macromolecular QSAR, and specially mt-QSAR were discussed (González-Díaz et al. 2007, 2008a, b; Mahiwal et al. 2010).

Finally, with the mt-QSAR methodology it is possible to predict the biological activity of drugs in more general situations than with the traditional QSAR models, whose greatest limitation is predicting the biological activity of drugs against only one microbial species. Then, this methodology improves models and allows one to predict biological activity of many organic compounds against a very large diversity of pathogens microorganisms.

Conclusions

During the last decade an increasing number of reports describe the antimicrobial activity of several compounds. A review of the literature reveals the existence of a broad-spectrum of research activity in the development practices that are used to treat a variety of diseases and significant current progresses in using statistical learning methods for predicting compounds of specific property in antimicrobial activity.

The quantitative relationship between chemical structure and biological activity allows one to predict theoretically bioactivity without resorting to an inordinate amount of time and effort making the experimental determinations. Many attempts have been performed to elucidate the QSAR of antimicrobials by using different physicochemical parameters.

In this review we have discussed published results concerning the QSAR research on antimicrobial properties of synthetic and natural compounds. Antifungal and antimicrobial activity of some coumarin derivatives, various types of biological activities of benzamides, several studies on cinnamic acid derivatives with antibacterial and antifungal activity, reports on the biological activity of homoisoflavanones and phenolic compounds, as well as pharmaceutical applications of furan derivatives have been shown.

The actual capabilities of multitasking QSAR methodology and mt-QSAR models to predict drugs activity against different species of antimicrobial agents have also been revised.

It was been demonstrated that with the mt-QSAR methodology it is possible to predict the biological activity of drugs in more general situations than with the traditional QSAR models, predicting biological activity of many organic compounds against a very large diversity of pathogens microorganisms.

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