THE CORRELATION STUDIES OF ANTIMYCOBACTERIAL ACTIVITY FOR A NUMBER OF DERIVATIVES OF 4-CARBOXAMIDE

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ABSTRACT

In order to produce a desired physiological effect, substances have to cross cell membranes. The ability of a chemical compound to cross membranes is influenced primarily by the partition coefficient. This is a physical-chemical factor that directly influence the pharmacokinetic profile of the drug and indirect its pharmacodynamic profile. The paper is a QSAR study carried out on a class of substituted of carboxamide, having antimycobacterial activity against the atypical mycobacterial strains and that these compounds are inhibitors of the photosynthesis process. The purpose of such a study is to link the chemical structures of the compounds represented by a set of molecular descriptors with biological activity exhibited by them, expressed as IC_{50}. Identifying these descriptors leads to information of the changes induced by the presence and nature of different chemical groups in the molecule, which allows optimization of analyzed biological activity.

INTRODUCTION

Increasing resistance of tuberculosis to existing currently drugs prompted research antituberculosis into drug development /1-6/.

A study published in this context /7/ report the synthesis and biological activity for a series of carboxylic acid amide derivatives that have been shown to have anti-mycobacterial activity against the atypical mycobacterial strains. Furthermore, these compounds are inhibitors of the photosynthesis process /7/, which may initiate research towards achieving selective herbicides.

In terms of anti-mycobacterial activity, derivatives studied are interesting agents against Mycobacterium Tuberculosis, Mycobacterium Kansasii şi Mycobacterium Avium.

In connection with photosynthesis inhibitor activity, it was observed that the activity of some of these compounds inhibit the photosynthesis in chloroplasts.

MATERIALS AND METHODS

As mentioned study is more on chemical synthesis and biological activity experimentally determined, we plan below to perform an QSAR analysis (Quantitative Structure - Activity Relationship) for this class of substances.

The aim is to link the chemical structures of these compounds represented by a set of molecular descriptors with reported biological activity.

The chemical structures of the substances studied are shown in Figure 1.

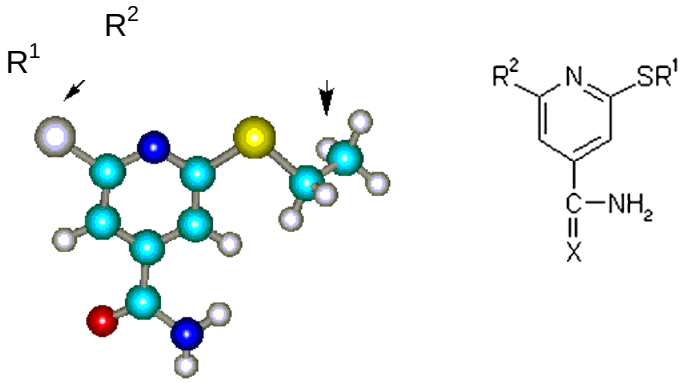

Figure 1. Carboxyamidate derivatives

In Table 1 are given the characteristics of these compounds and their biological activity as synthesis inhibitors of the activity studied in this paper. The biological activity is given under the form of IC_{50} representing 50% of concentration (in μmol / dm^3) to obtain a maximum biological response.

Table 1

Carboxyamidate derivatives and their biological activity /7/

Comp	R_1	R_2	X	IC_{50} (μmol/dm^3)	Comp	R_1	R_2	X	IC_{50} (μmol/dm^3)
1	C_2H_5	Cl	O	101.5	12	C_4H_{13}	SC_7H_{15}	O	543.6
2	C_3H_7	Cl	O	58.4	13	C_4H_{13}	SC_8H_{17}	O	258.8
3	C_4H_{13}	Cl	O	10.2	14	C_2H_5	Cl	S	104.8
4	CH_3	Br	O	76.7	15	C_3H_7	Cl	S	9.3
5	C_2H_5	Br	O	34.2	16	C_4H_{13}	Cl	S	29.8
6	C_4H_9	Br	O	10.6	17	CH_3	Br	S	187.7
7	C_7H_{15}	Br	O	5.9	18	C_2H_5	Br	S	19.6
9	C_4H_{13}	SC_2H_5	O	9.1	19	C_4H_9	Br	S	20.9
10	C_4H_{13}	SC_4H_9	O	203.5	20	C_7H_{15}	Br	S	61.0
11	C_4H_{13}	SC_5H_{11}	O	249.3	21	C_8H_{17}	Br	S	105.1

Modeling chemical structures was performed using the program HyperChem /8/, optimizing molecular geometries were performed in the first stage by molecular mechanics followed by optimization using cuantomolecular program MOPAC (Molecular Orbitals Package) (PM3) /9/; results contain a set of data such as molecular levels, electronic density on atoms or molecular levels, electric charges on atoms, the interaction energy between the atoms etc.

With this information it can be calculated a set of molecular descriptors with which can be represented every chemical structure. These descriptors can be: topological, geometrical, electrostatic, thermodynamic, informational or cuantomoleculari. In the literature there are currently few thousands of descriptors /10,11/ with which we attempt to correlate the chemical structures with their biological activities. The process is called QSAR (Quantitative Structure - Activity Relationship) and mean correlation Quantitative structure - biological activity. Correlation is achieved statistically through multilinear regression and is necessary because, in most cases, there is little information on how to interact chemical, called ligand, with the active sites of biological receptors (Figure 2).

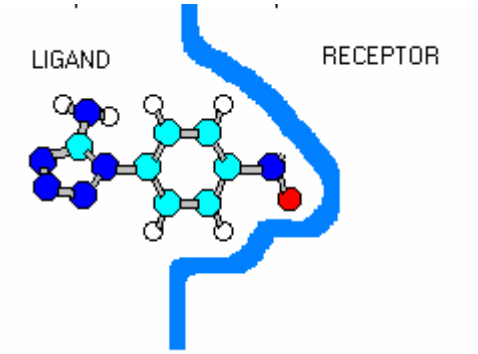

Figure 2. Ligand – receptor interaction

It is only known that this interaction is usually low, such as electrostatic, or hydrogen bonds, in which case the form of molecules (using the key-lock) plays an important role.

Linking structure - activity is, therefore, in full recognition of these interactions, but it is hoped that we select through this correlation those descriptors that are essential and also considered that the regression equation expressing biological activity as a function of these descriptors can predict biological activities for new chemical structures.

Research conducted on this class of substances have been targeted in a completely new direction in order to obtain information on the nature of molecular descriptors and how these descriptors are influenced by changes occurring in the chemical structures studied.

REZULTS AND DISCUTIONS

Results of regression correlations using output data performed with the MOPAC program are given in the following tables. In Table 2 is presented the multilinear correlation between biological activity and 6 or 5 molecular descriptors (Tables 2a şi 2b).

Table 2a

Multilinear regression equation

$$IC_{50} = a_0+a_1X_1+ a_2X_2+ a_3X_3 + a_4X_4 + a_5X_5 + a_6X_6$$

Regression correlation coefficient	***X_i = descriptors***
R2 = 98.44 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA X_4 - PPSA-3 Atomic charge weighted PPSA X_5 - Max electron-electron repulsion for a C-C bond X_6^I - FPSA-2 Fractional PPSA (PPSA-2/TMSA)
R2 = 98.43 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA X_4 - PPSA-3 Atomic charge weighted PPSA

	X_5 - Max electron-electron repulsion for a C-C bond X_6^{II} - Total molecular electrostatic interaction
R2 = 98.42 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA X_4 - PPSA-3 Atomic charge weighted PPSA X_5 - Max electron-electron repulsion for a C-C bond X_6^{III} - Principal moment of inertia B
R2 = 98.38 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA X_4 - PPSA-3 Atomic charge weighted PPSA X_5 - Max electron-electron repulsion for a C-C bond X_6^{IV} - FPSA-1 Fractional PPSA (PPSA-1/TMSA)
R2 = 98.34 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA X_4 - PPSA-3 Atomic charge weighted PPSA X_5 - Max electron-electron repulsion for a C-C bond X_6^{V} - DPSA-1 Difference in CPSAs (PPSA1-PNSA1)

Table 2b

Multilinear regression equation

$$IC_{50} = a_0+a_1X_1+ a_2X_2+ a_3X_3 + a_4X_4 + a_5X_5$$

Regression correlation coefficient	***X_i = descriptors***
R2 = 97.48 %	X_1^{I} - Max coulombic interaction for a C-H bond X_2^{I} - Min total interaction for a C-H bond X_3^{I} - Min net atomic charge for a C atom X_4 - PPSA-3 Atomic charge weighted PPSA X_5^{I} - PNSA-2 Total charge weighted PNSA

R2 = 97.28 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA (PNSA2*TMSA/1000) X_4^{II} - FPSA-3 Fractional PPSA (PPSA-3/TMSA) X_5^{II} - Principal moment of inertia A / # of atoms
R2 = 97.24 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond X_3 - WNSA-2 Weighted PNSA (PNSA2*TMSA/1000) X_4 - PPSA-3 Atomic charge weighted PPSA X_6^{IV} - FPSA-1 Fractional PPSA (PPSA-1/TMSA)

As it can be seen from this table, the correlation between the biological activity as photosynthesis inhibitors and 6, respective 5 molecular descriptors show that these descriptions can be classified /12/ in:

1 - "internal" descriptors directly linked to the structure and chemical bonds, such as Coulomb type interactions (X_1), the minimum resonance energy for C-H bonds (X_2) etc.

2 - "external"descriptors that are directly linked to the interaction ligand - receptor, such as shape descriptors (X_6 inertia moments) or the distribution of positive and negative electrical charges on the atoms in different ways (X_3, X_4, X_6^{III}, X_6^{IV}, X_6) or even the total electrostatic interaction (X_6^{I}).

This classification may help to a better understanding of how different substituents influence the ligand - receiver interactions. In other words, there is a clear interdependence between what we called "external" and "internal" descriptors that may be useful in modulating chemical structures /12/, to obtain better biological activities. It would be another way of QSAR research in which inside the class of the structures we not take into account the explicitly nature of the various substituents and that classified molecular descriptors into "internal" and "external" /12/.

By reducing the number of descriptors will be achieved gradually only "internal"molecular descriptors directly linked to the formation and characteristics of chemical bonds in molecules. Indeed, if the 6 or 5 descriptors have a lot of "internal" and "external" molecular descriptors for which the correlation coefficients are close to unity, for 4 or 3 descriptors (Tables 3a şi 3b),

Table 3a

Multilinear regression equation
$IC_{50} = a_0+a_1X_1+ a_2X_2+ a_3X_3 + a_4X_4$

Regression correlation coefficient	***X_i = descriptors***
R2 = 96.70 %	X_1^I - Max coulombic interaction for a C-H bond X_2^I - Min total interaction for a C-H bond X_3^I - Min electron-nuclear attraction for a C-S bond X_4^I - Max atomic nucleoph. react. index for a C atom
R2 = 96.32 %	X_1 - Min coulombic interaction for a C-C bond X_2^I - Min total interaction for a C-H bond X_3^I - Min coulombic interaction for a C-S bond X_4^I - Max atomic nucleoph. react. index for a C atom
R2 = 96.29 %	X_1 - Min coulombic interaction for a C-C bond X_2^I - Min total interaction for a C-H bond X_3^I - Min coulombic interaction for a C-S bond X_4^{II} - RNCS Relative negative charged SA
R2 = 96.26 %	X_1 - Min coulombic interaction for a C-C bond X_2^I - Min total interaction for a C-H bond X_3^I - Min coulombic interaction for a C-S bond X_4^{III} - Min total interaction for a C-S bond

Table 3b

Multilinear regression equation
$IC_{50} = a_0+a_1X_1+ a_2X_2+ a_3X_3$

Regression correlation coefficient	***X_i = descriptors***
R2 = 93.79 %	X_1^I - Max coulombic interaction for a C-H bond X_2^I - Min total interaction for a C-H bond X_3^I - Min electron-nuclear attraction for a C-S bond
R2 = 93.78 %	X_1^I - Max coulombic interaction for a C-H bond X_2^I - Min total interaction for a C-H bond X_3^{II} - Min net atomic charge for a C atom
	X_1 - Min coulombic interaction for a C-C

R2 = 93.11 %	bond X_2^I - Min total interaction for a C-H bond X_4^I - Max atomic nucleoph. react. index for a C atom

the number of "external" descriptors dependent on electric charge distribution on atoms decreases and for 2 or 1 descriptors (Tables 4a şi 4b),

Table 4a

Multilinear regression equation
$IC_{50} = a_0+a_1X_1+ a_2X_2$

Regression correlation coefficient	***X_i = descriptors***
R2 = 88.55 %	X_1 - Min coulombic interaction for a C-C bond X_2 - Min resonance energy for a C-H bond
R2 = 88.08 %	X_1 - Min coulombic interaction for a C-C bond X_2^I - Min total interaction for a C-H bond
R2 = 87.28 %	X_1^I - Max coulombic interaction for a C-H bond X_2^I - Min total interaction for a C-H bond

Table 4b

Multilinear regression equation
$IC_{50} = a_0+a_1X_1$

Regression correlation coefficient	***X_i = descriptors***
R2 = 73.42 %	X_1 - Min coulombic interaction for a C-C bond
R2 = 70.89 %	X_1^I - Max coulombic interaction for a C-H bond
R2 = 67.30 %	X_1 - Min nuclear-nuclear repulsion for a C-C bond

remain virtually only "internal" descriptors directly linked to the actual chemical structures.

CONCLUSIONS

Identifying these "internal" descriptors actually contain information on changes induced by the presence and nature of the different chemical groups in the molecule.

Thus we identify those atoms or those chemical bonds (C-C and C-H bonds) to which the "internal" descriptors refers to. In this way, one can understand the influence of chemical groups on these descriptors, and can optimize the biological activity, which allows obtaining new compounds of potential anti-mycobacterial activity.

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