

**MINISTRY OF NATIONAL EDUCATION
MINISTRY OF AGRICULTURE AND RURAL DEVELOPMENT
FACULTY OF AGRICULTURE AND HORTICULTURE
AGRICULTURAL AND FORESTRY
SCIENCES ACADEMY- CRAIOVA BRANCH
THE ROMANIAN HORTICULTURAL SOCIETY**



SCIENTIFIC CONFERENCES WITH INTERNATIONAL PARTICIPATION

PARTICULAR FOCUS OF THE CONFERENCE

**„SUSTAINABLE DEVELOPMENT IN AGRICULTURE AND
HORTICULTURE”
AND
„DURABLE AGRICULTURE – AGRICULTURE OF FUTURE”**

THE TENTH EDITION

VOL. XLIV/1/2014

**ISSN 1841-8317
ISSN CD-ROM 2066-950X**

**CRAIOVA
ROMANIA**

13th-14th NOVEMBER 2014

Editorial Board

Professor SOARE MARIN, PhD., Dean
Professor CĂLINA AUREL, PhD., Vice Dean
Professor asociate OLARU LIVIU AUREL, PhD., Vice Dean
Professor ALEXANDRU TUDOR, PhD.
Professor asociate NICULESCU MARIANA, PhD.,
Professor asociate PÂNZARU RADU LUCIAN, PhD.
Professor asociate MATEI GHEORGHE, PhD.

Editorial Review Board

Professor Dan Claudiu DĂNIȘOR, PhD., Rector University of Craiova
Professor Dan POPESCU, PhD., Vice-Rector University of Craiova
Professor SOARE MARIN, PhD. – Faculty of Agriculture and Horticulture Craiova, Dean
Professor CĂLINA AUREL, PhD., – Faculty of Agriculture and Horticulture Craiova, Vice Dean
Professor asociate OLARU LIVIU AUREL, PhD., – Faculty of Agriculture and Horticulture Craiova, Vice Dean
Professor asociate NICULESCU MARIANA, PhD – Faculty of Agriculture and Horticulture Craiova
Professor STEFANO GREGO, PhD. – Univerity Tusccia, Viterbo, President of the E.S.N.A., Italy
Professor VLADO LICINA, PhD. - University of Belgrad, Faculty of Agriculture, Vice-President of the E.S.N.A., Serbia
Professor MICHAEL PÖSCHL, PhD. – University of Agriculture and Forestry in Brno, Czech Republic
Professor IVAN ILIEV, PhD. – University of Forestry, Sofia, Bulgaria
Professor SAVIN LAZAR PhD. - University of Novi Sad, Faculty of Agriculture, Serbia
Dr. LASZLO FENYVESI - Director of Hungarien Institute of Agricultural Engineering Godolo, Hungary
Professor asociate LIDIA MISHEVA, PhD.- Institute of Soil Science, Sofia, Bulgaria
Professor NICOLESCU MIHAI, PhD. – Vice President of the A.S.A.S. "Gheorghe Ionescu Șișești"
Acad. Professor HERA CRISTIAN, PhD. - Romanian Academy, A.S.A.S "Gheorghe Ionescu Șișești"
Professor ROMAN VALENTIN GHEORGHE, PhD. –U.S.A.M.V. București, member of the A.S.A.S "Gheorghe Ionescu Șișești"
Professor Radu SESTRĂȘ, PhD. - University of Agronomic Sciences and Veterinary Medicine Cluj-Napoca, Romania
Professor ROTAR IOAN, PhD. – U.A.S.M.V. Cluj-Napoca, Faculty of Agriculture Cluj-Napoca
Professor CIONTU CONSTANTIN, PhD. – U.S.A.M.V. București, Faculty of Agriculture
Professor LEONTE CONSTANTIN, PhD. – U.S.A.M.V. Iași, Faculty of Agriculture
Professor MARIN DORU, PhD.- U.S.A.M.V. București, Faculty of Agriculture
Professor BĂBEANU CRISTINA, PhD.- University of Craiova, Faculty of exact Sciences
Professor BERCU RODICA , PhD.- „Ovidius„, University of Constanța, Faculty of Natural Sciences and Agricultural Sciences
Professor asociate CICHI DANIELA DOLORIS, PhD. - University of Craiova, Faculty of Agriculture and Horticulture
Professor asociate DUMITRU ILIE, PhD. - University of Craiova, Faculty of Mechanical Engineering
Professor asociate BORUZ SORIN PETRUȚ, PhD. - University of Craiova, Faculty of Agriculture and Horticulture
Professor asociate IMBREA FLORIN, PhD. - USAMVB Timisoara
Professor asociate PÂNZARU RADU LUCIAN, PhD. –Universitz of Craiova, Faculty of Agriculture and Horticulture
Professor asociate VLADU MARIUS, PhD. – University of Craiova, Faculty of Agriculture and Horticulture
Professor asociate FĂGĂRAȘ MARIUS, PhD. - „Ovidius„, University of Constanța, Faculty of Natural Sciences and Agricultural Sciences

Lecturer POPESCU GABRIELA, PhD. - USAMVB Timisoara

Dr. PIRNĂ ION - INMA București

Dr. VLĂDUȚ VALENTIN - INMA București

Secretary

Prof. assoc. Constantinescu Emilia, PhD., Faculty of Agriculture and Horticulture, University of Craiova

Lecturer MilutMarius, PhD., Faculty of Agriculture and Horticulture, University of Craiova

Lecturer Medelele Dragos, Pfd., Faculty of Agriculture and Horticulture, University of Craiova

Lecturer Croitoru Alin, PhD., Faculty of Agriculture and Horticulture, University of Craiova

Lecturer Cioboată Marius, PhD., Faculty of Agriculture and Horticulture, University of Craiova

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

**EMILIA AMZOIU¹, LARISA ELISABETH AVERIS¹, CORNELIA BEJENARU¹,
MANUEL OVIDIU AMZOIU², PAUL GABRIEL ANOAIKA³**

¹Faculty of Pharmacy, University of Medicine and Pharmacy, Craiova

² Technical college "I.G. Murgulescu", Craiova

³ Faculty of Medicine, University of Medicine and Pharmacy, Craiova

corresponding author: emanro2002@yahoo.com

Keywords: partition coefficient, anti-mycobacterial activity, internal descriptors, external descriptors, correlation regression

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 IC₅₀. 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* și *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.

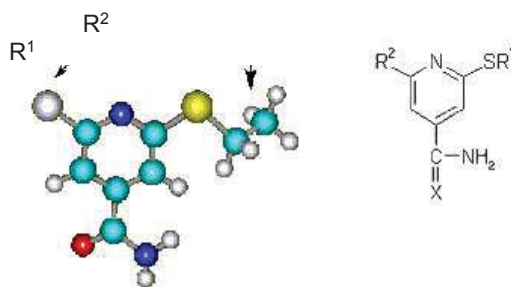


Figure 1. Carboxamidate derivatives

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 $\mu\text{mol} / \text{dm}^3$) to obtain a maximum biological response.

Table 1

Carboxamidate derivatives and their biological activity /7/

Comp	R ₁	R ₂	X	IC ₅₀ ($\mu\text{mol}/\text{dm}^3$)	Comp	R ₁	R ₂	X	IC ₅₀ ($\mu\text{mol}/\text{dm}^3$)
1	C ₂ H ₅	Cl	O	101.5	12	C ₆ H ₁₃	SC ₂ H ₅	O	343.6
2	C ₃ H ₇	Cl	O	58.4	13	C ₆ H ₁₃	SC ₂ H ₅	O	258.8
3	C ₆ H ₁₃	Cl	O	102.	14	C ₂ H ₅	Cl	S	104.8
4	CH ₃	Br	O	76.7	15	C ₂ H ₅	Cl	S	9.3
5	C ₂ H ₅	Br	O	34.2	16	C ₂ H ₁₃	Cl	S	29.8
6	C ₄ H ₉	Br	O	10.6	17	CH ₃	Br	S	187.7
7	C ₂ H ₅	Br	O	5.9	18	C ₂ H ₅	Br	S	19.6
9	C ₆ H ₁₃	SC ₂ H ₅	O	9.1	19	C ₄ H ₉	Br	S	20.9
10	C ₆ H ₁₃	SC ₄ H ₉	O	203.5	20	C ₂ H ₅	Br	S	61.0
11	C ₂ H ₅	SC ₂ H ₅	O	249.3	21	C ₂ H ₅	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).

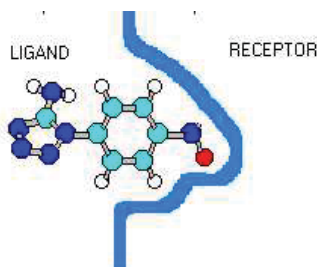


Figure 2. Ligand – receptor interaction

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.

RESULTS AND DISCUSSIONS

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 și 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 [†] - 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 %	<p>X₁ - Min coulombic interaction for a C-C bond X₂ - Min resonance energy for a C-H bond X₃ - WNSA-2 Weighted PNSA (PNSA2*TMSA/1000) X₄^{II} - FPSA-3 Fractional PPSA (PPSA-3/TMSA) X₅^{II} - Principal moment of inertia A / # of atoms</p>
R2 = 97.24 %	<p>X₁ - Min coulombic interaction for a C-C bond X₂ - Min resonance energy for a C-H bond X₃ - WNSA-2 Weighted PNSA (PNSA2*TMSA/1000) X₄ - PPSA-3 Atomic charge weighted PPSA X₆^{IV} - FPSA-1 Fractional PPSA (PPSA-1/TMSA)</p>

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 (X₁), the minimum resonance energy for C-H bonds (X₂) etc.

2 - "external" descriptors that are directly linked to the interaction ligand - receptor, such as shape descriptors (X₆ inertia moments) or the distribution of positive and negative electrical charges on the atoms in different ways (X₃, X₄, X₆^{III}, X₆^{IV}, X₆) or even the total electrostatic interaction (X₆^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 și 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