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Development of novel small-size peptides as putative therapeutic drugs

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2010

**DEVELOPMENT OF NOVEL SMALL-SIZE PEPTIDES
AS PUTATIVE THERAPEUTIC DRUGS**

M. F. MASMAN



**rijksuniversiteit
 groningen**



The studies reported in this thesis were carried out partially at the Universidad Nacional de San Luis (UNSL), Argentina and the Rijksuniversiteit Groningen (RuG), The Netherlands as a cooperation fellowship between this two Universities. The printing out of this thesis was financially supported by the Faculty of Mathematics and Natural Sciences, RuG and the School of Behavioral and Cognitive Neurosciences (BCN). BCN have organized the educational program of the candidate during his stay in Groningen.

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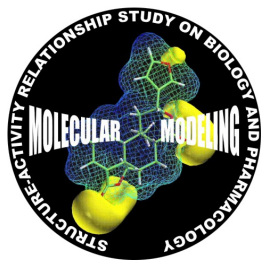
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*Se puede vivir una larga vida sin aprender nada.
Se puede durar sobre la tierra sin agregar ni cambiar una pincelada del paisaje.
Se puede simplemente no estar muerto sin estar tampoco vivo.
Basta con no amar nunca a nada, a nadie.
Es la única receta infalible para no sufrir.
Yo aposté mi vida a todo lo contrario y hacía mucho tiempo que había dejado de importarme si lo perdido era
más que lo ganado.
Creía que ya estábamos a mano el mundo y yo, ahora que ninguno de los dos respetaba demasiado al otro.
Pero un día comprendí que todavía podía hacer algo para estar completamente vivo antes de estar definitivamente
muerto.
Entonces... me puse en movimiento*

[Jose, Caballos Salvajes, Argentinean film directed by Marcelo Piñeyro – 1995]

a Kiko y a mi amada Alma

PREFACE

Computational medicinal chemistry is a rapidly growing field of modern science. Mathematics and computational sciences have long played a dominant role in our understanding of physics, chemistry, and other life sciences. However, the wholesale application of computational methods in medicine, more specifically in drug design, is relatively recent. Currently, the intriguing questions of molecular interactions, conformational molecular behavior, protein folding, cell signaling, cell movement, genomics, ecology, infectious diseases, and diseases development are being successfully tackled with and analyzed using mathematical and computational methods.

This thesis is based upon studies conducted during the period between March 2005 and August 2009 at the Molecular Modeling group (2005-2007), Universidad Nacional de San Luis, Argentina, and at the Molecular Neurobiology group (2007-2009), Rijksuniversiteit Groningen, The Netherlands. These studies have been funded by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina and by the Rijksuniversiteit Groningen, The Netherlands. The thesis consists of a total of eight chapters, five of which correspond to papers published in various international journals, and the material for yet another chapter is in preparation to be submitted for publication. These chapters cover various aspects of computational medicinal chemistry applied to peptide compounds with potentials to become a drug. The majority of these papers are written jointly with other scientists, some of whom are more theoretical chemists than biologists, while some are more biologists than theoretical chemists. In the first chapter, however, I have given a general introduction to peptides in medicinal chemistry and a survey of the new technological/scientific approaches. Thus, CHAPTER 1 has been written in such a way that it is relatively easy to read for any person who possesses a minimum scientific knowledge. This is also valid for CHAPTER 8, General discussion & future perspectives.

Besides my profound scientific background, I am deeply interested in several forms of art, among these however, visual art, especially painting is the form that allows me to express myself as an artist. My affinity for art and my scientific education give me a creative and analytical approach to life that I wanted to reflect in this thesis. Therefore, parallel to the hard scientific content presented in this thesis, I have decided on a more personal form of presentation, introducing each chapter with a painting. Thus, my relation to creative work can also be presented with the help of artistic suggestions in harmony with scientific content. The creation of these paintings, including the cover painting, has been based on selected key words, the inspirational words, related to the research topic of each chapter. Far from making a literal interpretation of the inspirational words, these paintings are a collection of life-experiences collected during my stay in Groningen. All these art works have been made "*alla prima*" (Italian for "*at once*"), which is a style of painting where, instead of building colors up with layers or glazing over an underpainting, the whole painting is completed while the paint is still wet. The charm of *alla prima* is that it retains the fresh and spontaneous feelings that come as one paints. It seems to me the most intuitive way to paint.

This thesis is my ultimate attempt to harmonically conjugate art and science into a personal project. Of course, no such project can be free from errors and incompleteness, which with time and more hard work can be improved in a near future. ■

M.F. Masman, 5th May 2010, Groningen.

“Every portrait that is painted with feeling is a portrait of the artist, not of the sitter”

O. Wilde

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*"Bitter-sweetly and paradoxically, the disappointment
of a left hand allows the right hand to come"*
(M.F. M.)



"My left hand"

oil on paper (320x450 mm)

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