
BIOGRAPHICAL SKETCH

NAME: Giovanni Grazioso

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Catania	Chimica e tecnologia farmaceutiche (CTF)	07/2001	Medicinal Chemistry – Pharmacy
University of Milan	PhD in “Chimica del farmaco”	12/2004	Computational Drug design and synthesis of pharmacologically active compounds

A. Personal Statement

My research activity in medicinal chemistry started in 2000 with the master's degree thesis at the University of Catania, dealing with the synthesis of a set of putative immunoadjuvants, designed to fight the early stages of cancer. Then, during my experience at the University of Milan in the framework of the PhD in Medicinal Chemistry (2001-2004), I realized that “computer-aided drug design” would represent an ideal conjugation between my passion for medicinal chemistry and my deep interest in computer science. Indeed, in the last twenty years I have been studying different biochemical mechanisms through computational approaches, focusing on enzyme-substrate and drug-target interactions. The rational design of new molecular probes with intrinsic pharmaceutical value is currently assisted by the application of theoretical studies, a strategy that frequently permits to improve the pharmacological profile and/or to ameliorate the pharmacokinetic properties of leads compounds from natural sources or emerging from previous structure-activity relationships investigations. As an example, in 2011 I published the first paper reporting the optimization of the sequence of a natural conotoxin, which led to a meaningful gain in the selectivity profile for a specific heteromeric nicotinic acetylcholine receptor subtype. More recently, I applied the same approach to isolate lupin-related peptides as novel inhibitors of PCSK9, a new and promising target for the treatment of hypercholesterolemia. In the specific research field, with my colleagues at the University of Milan I published about ten highly cited articles, reporting on peptides, peptidomimetics, and small molecules as inhibitors of PCSK9. In addition, we have recently filed a national patent (n. 102020000012130) and a PCT application, covering a novel chemical scaffold characterized by a remarkably high PCSK9 inhibitory activity (WO2021234654A1). From 2016, thanks to a scientific collaboration with Dr. A. Cavalli and Dr. Uguccioni of the IRB of Bellinzona (CH), I performed more in-depth studies on inflammation, focusing on those diseases in which a treatment with inhibitors of the HMGB1 protein could be beneficial. This research activity led to the publication of two articles in the medicinal chemistry field in journals with high editorial impact. Worth mentioning, the identification of a nonapeptide endowed with the highest affinity on HMGB1 known so far.

The main results of my research activity have been the subject of posters and oral communications in international congresses/national meetings in the medicinal chemistry and drug-discovery scientific areas. In 2019 I have been member of the scientific and organizing committee of the Schrödinger workshop entitled: "New Approaches in Molecular Modeling", University of Milan, 13-09-2019. During my research activity I started and promoted a number of national and international scientific collaborations with scientists like: L. Scapozza, M. Parrinello, F. Clementi, C. Gotti, C. U. Madsen, H. Bräuner-Osborne, G. De Sarro, M. Gobbi, T. Mennini, L. Toma, A. Cavalli (Unibo - IIT), M. Recanatini, F. Prati, J. D. Docquier, A. Cavalli (IRB-Bellinzona), A. Magistrato, G. Colombo, J. Bosch, C. Lammi, and A. Silvani. These collaborations led to an international patent on novel PCSK9 inhibitors, 2 book chapters, and 75 original articles published in the most qualified international journals of medicinal chemistry and in multidisciplinary journals with high editorial impact (JACS, Sci. Rep., Pharmaceutics, J. Medicinal Chemistry, and Int. J. Mol. Sciences). My official h-index is 23, with 1383 citations (Scopus, data access 2025 September 29th). I am associate editor of Scientific Reports (Nature publishing group), Int. J. Mol. Sciences (MDPI), Annals of Microbiology (BMC), and I served as reviewer for numerous articles published in ACS, Elsevier, and MDPI journals.

My research activity has been financed by the University of Milan (Linea 2 funding), Ministero dell'Istruzione, dell'Università e della Ricerca in the framework of Research Projects of National Relevance (PRIN 2007 (20072BTSR2_003) and PRIN 2009 (2009R7WCZS_002), in which I participated as member of the Medicinal Chemistry Research Unit. These projects were focused on the structure and function of ionotropic receptors, and my contribution was centered on molecular modeling studies aimed to rationalize the behavior of various sets of small molecules as well as novel peptides mainly targeting nicotinic and glutamate receptors. I'm now responsible of the UNIMI research unit of the PRIN_2022 project entitled "Fine definition of systemic and mucosal response in SARS-CoV-2 vaccinated subjects", approved for granting in May 2023, for a total amount of 222.636 € (PRIN 2022 code 2022HRBE4E). In the financial resources included in the Italian PNRR program, I have attained a grant for the research on RNA-based drugs (call related to the creation of National Centers). This grant started in July 2022 and financed my research activity for an amount of 180.000€ (MUR code CN00000041).

Nevertheless, one of the advantages of the research in computational chemistry is that it does not require excessive costs for consumables. Funding acquisition is therefore primarily related to "computational grants" from the main supercomputer centers, such as CILEA (Milano), CASPUR (Roma) and, now CINECA (Bologna). All applications are screened by scientific and technical committees that ascertain the quality and the correctness of the predicted computational cost. Over the years, I received numerous grants for scientific calculations, i.e., more than 3 million CPU computing hours.

At present, I am member of the Scientific Committee of the INDACO Unitech, it provides high-performance computing resources to the users (and not only) of the University of Milan.

B. Positions, Scientific Appointments, and Honors

In 2003 and 2008 I was a visiting researcher at the ETHZ of Zurich (prof. L. Scapozza and prof. M. Parrinello) and from 2006 to 2017 I was a senior researcher at the University of Milan, Department of Pharmaceutical Sciences. In 2017 I was appointed as Associate Professor of Medicinal Chemistry and, at present, I teach "Analysis of Medicines I" (graduation in Pharmaceutical Chemistry and Technology), and Medicinal Chemistry I (graduation in Pharmacy).

In 2022, I have obtained the "national scientific qualification" (Abilitazione scientifica nazionale - ASN) to full professor.

I was a member of the scientific board of the PhD program in “Pharmaceutical Sciences” at the Department of Pharmaceutical Sciences of the University of Milan from 2013 to 2024 and, at present, I am supervising the scientific activity of two PhD students.

C. Contributions to Science

Successful applications of theoretical approaches to drug discovery and/or to investigate protein functions:

- Enrico M.A. Fassi, Edisa Pirani, Valentina Cecchinato, Andrea Cavalli, Gabriella Roda, Mariagrazia Uguccioni M, Jacopo Sgrignani, Giovanni Grazioso. *A potent nonapeptide inhibitor for the CXCL12/HMGB1 heterocomplex: A computational and experimental approach*. Comput Struct Biotechnol J. (2025) Apr 18;27:1677-1685. DOI: 10.1016/j.csbj.2025.04.023.

- Enrico M.A. Fassi, Roberta Manuela Moretti, Marina Montagnani Marelli, Mariangela Garofalo, Alessandro Gori, Cristiano Pesce, Marco Albani, Erica Ginevra Milano, Jacopo Sgrignani, Andrea Cavalli, Giovanni Grazioso. *FYCO1 Peptide Analogs: Design and Characterization of Autophagy Inhibitors as Co-Adjuvants in Taxane Chemotherapy of Prostate Cancer*. Int J Mol Sci. 26(11):5365. (2025) Jun 3. DOI:10.3390/ijms26115365.

- Marco Albani, Enrico M.A. Fassi, Roberta Manuela Moretti, Mariangela Garofalo, Marina Montagnani Marelli, Gabriella Roda, Jacopo Sgrignani, Andrea Cavalli, Giovanni Grazioso. *Computational Design of Novel Cyclic Peptides Endowed with Autophagy-Inhibiting Activity on Cancer Cell Lines*. (2024) Int J Mol Sci. 25(9):4622. DOI:10.3390/ijms25094622

- Jacopo Sgrignani, Valentina Cecchinato, Enrico M.A. Fassi, Gianluca D'Agostino, Maura Garofalo, Gabriela Danelon, Mattia Pedotti, Luca Simonelli, Luca Varani, Giovanni Grazioso, Mariagrazia Uguccioni, and Andrea Cavalli. *Systematic Development of Peptide Inhibitors Targeting the CXCL12/HMGB1 Interaction*. Journal of Medicinal Chemistry, (2021), 64, 18, 13439–13450. DOI: 10.1021/acs.jmedchem.1c00852.

- Carmen Lammi, Enrico M.A. Fassi, Jianqiang Li, Martina Bartolomei, Giulia Benigno, Gabriella Roda, Anna Arnoldi, and Giovanni Grazioso. *Computational Design and Biological Evaluation of Analogs of Lupin Peptide P5 Endowed with Dual PCSK9/HMG-CoAR Inhibiting Activity*. Pharmaceutics (2022), 14, 665. DOI: 10.3390/pharmaceutics14030665

- Lammi, C., Sgrignani, J., Arnoldi, A., Lesma, G., Spatti, C., Silvani, A., Grazioso, G. *Computationally Driven Structure Optimization, Synthesis, and Biological Evaluation of Imidazole-Based Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) Inhibitors*. (2019) Journal of Medicinal Chemistry, 62 (13), pp. 6163-6174. DOI: 10.1021/acs.jmedchem.9b00402

- Lammi, C., Zanoni, C., Aiello, G., Arnoldi, A., Grazioso, G. *Lupin peptides modulate the protein-protein interaction of PCSK9 with the low-density lipoprotein receptor in HepG2 cells*. (2016) Scientific Reports, 6, 29931, DOI: 10.1038/srep29931

- Mazzo, F., Pistillo, F., Grazioso, G., Clementi, F., Borgese, N., Gotti, C., Francesca Colombo, S. *Nicotine-modulated subunit stoichiometry affects stability and trafficking of $\alpha 3\beta 4$ nicotinic receptor*. (2013) Journal of Neuroscience, 33 (30), pp. 12316-12328. DOI: 10.1523/JNEUROSCI.2393-13.2013

- Pucci, L., Grazioso, G., Dallanocce, C., Rizzi, L., De Micheli, C., Clementi, F., Bertrand, S., Bertrand, D., Longhi, R., De Amici, M., Gotti, C. *Engineering of α -conotoxin MII-derived peptides with increased selectivity for native $\alpha 6\beta 2^*$ nicotinic acetylcholine receptors*. (2011) FASEB Journal, 25 (11), pp. 3775-3789. DOI: 10.1096/fj.10-179853

- Grazioso, G., Limongelli, V., Branduardi, D., Novellino, E., De Micheli, C., Cavalli, A., Parrinello, M. *Investigating the mechanism of substrate uptake and release in the glutamate transporter homologue GltPh through metadynamics simulations.* (2012) Journal of the American Chemical Society, 134 (1), pp. 453-463. DOI: 10.1021/ja208485w
- Stucchi, M., Grazioso, G., Lammi, C., Manara, S., Zanoni, C., Arnoldi, A., Lesma, G., Silvani, A. *Disrupting the PCSK9/LDLR protein-protein interaction by an imidazole-based minimalist peptidomimetic.* (2016) Organic and Biomolecular Chemistry, 14 (41), pp. 9736-9740. DOI: 10.1039/c6ob01642a
- Sgrignani, J., De Luca, F., Torosyan, H., Docquier, J.-D., Duan, D., Novati, B., Prati, F., Colombo, G., Grazioso, G. *Structure-based approach for identification of novel phenylboronic acids as serine- β -lactamase inhibitors.* (2016) Journal of Computer-Aided Molecular Design, 30 (10), pp. 851-861. DOI: 10.1007/s10822-016-9962-8
- Fassi, E.M.A., Sgrignani, J., D'Agostino, G., Cecchinato, V., Garofalo, M., Grazioso, G., Uguccioni, M., Cavalli, A. *Oxidation State Dependent Conformational Changes of HMGB1 Regulate the Formation of the CXCL12/HMGB1 Heterocomplex.* (2019) Computational and Structural Biotechnology Journal, 17, 886-894. DOI: 10.1016/j.csbj.2019.06.020

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