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Tribute

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Professor Girolamo Cirrincione

A Tribute

This special issue of Arkivoc is dedicated to Professor Girolamo Cirrincione in recognition of his outstanding contributions in the research fields of Heterocyclic Chemistry and Bioactive Molecules

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Girolamo Cirrincione was born in Palermo in 1948. He studied chemistry at the University of Palermo, where he graduated in 1974 with honors. After completing one year of military service, he started his career as a laboratory technician in the Organic Chemistry Institute of the Faculty of Pharmacy in the University of Palermo. He was appointed Associate Professor of Medicinal Chemistry at the same institution in Nov 1981 and became full Professor of Medicinal Chemistry in 1994. After his retirement on Nov 1st 2018, he was appointed *Emeritus Professor of Medicinal Chemistry* by the Ministry of University and Scientific Research.

Girolamo Cirrincione was awarded CNR-NATO Fellowships (Sep. 1982–May 1983, Jul.–Aug. 1986, Jul.–Sep. 1989) and a British Council Fellowship (Aug. 1984), spent at the School of Chemical Sciences of the University of East Anglia (Norwich, UK).

His research has resulted in about 160 publications and 10 patents. He is author of the book "Biosynthesis of Heterocycles: from Isolation to Gene Cluster" (Editor J. Wiley) and also of several chapters in *Chemistry of Heterocyclic Compounds, Comprehensive Heterocyclic Chemistry* and *Advances in Heterocyclic Chemistry.* In addition, he was invited to lecture at numerous international conferences many as plenary speaker.

He has been involved in several interdisciplinary research initiatives and projects as attested by the award of the *Giordano Giacomello Medal* by the Medicinal Chemistry Division of the Italian Chemical Society (July 2018), *the Gold medal and Diploma by "International Foundation, "Scientific Partnership"* and *"InterBioScreen"* on the occasion of the centenary of the birth of Prof. A.N. Kost, "For Special Achievements in the Chemistry of Heterocycles and Biologically Active Compounds and for International Scientific Cooperation".

Throughout his career he undertook several institutional positions including, Director of the Istituto Farmacochimico (1995–1999), Head of the Dipartimento Farmacochimico Toss. Biol. (2000–2010); Vice Dean of the Faculty of Pharmacy (2004-2010); Dean of the Faculty of Pharmacy (2010–2013) and Pro-Rector for Research of the University of Palermo (2015-2018). He held the role of Vice President of the International Society of Heterocyclic Chemistry (2004 - 2005) and that of President of the Pharmaceutical Chemistry Division of the Italian Chemical Society (2013-2015). His other commitments include: Member of the Drug Discovery Committee of the Pharmacology and Molecular Mechanisms (PAMM) Group of the European Organization for Research and Treatment of Cancer (EORTC); Member of the European Academy of Sciences and Arts, Salzburg Austria; Member of the ChemPubSoc Europe Journal Board; Member of the International Advisory Board of the Journal ChemMedChem and Scientific Editor of the journal Arkivoc.

Since 1984 he has been a member of various Scientific Committees and Chairman of a large number of National and International Congresses including the 20th International Congress of Heterocyclic Chemistry, Palermo (Jul. 31- Aug. 5, 2005) and most recently the Italian-Spanish-Portuguese Joint Meeting in Medicinal Chemistry held in Palermo (17-20 July 2018).

Opening Ceremony of the 20th International Congress of Heterocyclic Chemistry *(from the left): Girolamo (Gilmo) Cirrincione, Chairperson of the Congress; Domenico (Mimmo) Spinelli, Honorary Chairperson of the Congress; Giuseppe Silvestri, Rector of the University of Palermo; David Black, IUPAC representative; Marco Ciufolini, President of the International Society of Heterocyclic Chemistry*.

Girolamo Cirrincione has always invested a great deal of effort into his didactic commitments. In addition to his expertise, his students appreciated his humanity and his passion for transmitting knowledge in the field of medicinal chemistry. To date, he continues to be a guide and a source of inspiration to his former co-workers.

Research Interests

Professor Cirrincione's research has been devoted to studies of the reactivity of the pyrrole, indole and isoindole systems and the design, synthesis, biological evaluation and SAR of heterocyclic compounds as anti-tumor and anti-infective agents.

One of his initial topics concerned nucleophilic substitution in pyrroles as a tool to functionalize the nitrogen nucleus to provide material for the synthesis of polycyclic systems. Studies of nucleophilic substitution were also performed on other electron-rich heterocycles such as indoles and isoindoles. At that time, he devoted attention to studies of diazopyrroles and diazoindoles as synthons for the synthesis of pharmacologically active systems. In this context, a series of pyrrolo-tetrazinones, deaza-analogues of the antitumor imidazo-tetrazinone "temozolomide", were synthesized and tested as antitumor agents against multidrug resistant cell lines. Studies within the PAMM Group of the European Organization of Research and Treatment of Cancer revealed that these antitumor agents act as antimitotic agents rather than alkylating agents.

Later, he developed a very fruitful collaboration with Professor Francesco Dall'Acqua and his group at the University of Padova, where the main lines of this collaborative research concerned photoactive chemotherapeutic agents and pyrrolo-fused heterocyclic systems with anti-tumor activity. Both topics led to several papers and patents. For instance, pyrrolo[3,2-h]quinoline derivatives showed potent photo-toxycity, high production of ROS and no significant DNA damage in modulating the long term side effects such as the risk of mutagenesis and skin cancers as shown by the drug 8-MOP. Another important series included isoindolo[2,1-

a]quinoxaline derivatives which exhibited potent antitumor activity with dual inhibition of tubulin polymerization and topoisomerase I. Both series of compounds were covered by international patents.

A further important field of his research was the development of marine alkaloid analogues. This topic was developed in collaboration with Dr. Nadia Zaffaroni and her group at the National Institute of Tumors (Istituto Nazionale dei Tumori) of Milan. Many nortopsentin analogues showed remarkable antiproliferative activity in human cancer cells. In particular, most thiazole derivatives showed strong CDK1 inhibition. These compounds, evaluated on STO cells xenotransplanted in mice, showed marked inhibition of tumor growth at well-tolerated doses without any appreciable sign of toxicity. Moreover, pre-treatment of the colon rectal cancer stem cells (CR-CSCs) with the most active compound, makes those cells more sensitive to standard chemotherapy thus enhancing the hypothesis that this compound may be useful in therapy.

A very recent research topic involves the discovery of new anti-infective drugs capable of offsetting antibiotic resistance and in particular anti-biofilm agents. Contrary to conventional antibiotics, anti-biofilm compounds act as anti-virulence agents, compounds able to target key virulence factors, thus disarming the pathogens, rather than killing them or inhibiting their growth. Within this topic, a series of imidazo[2,1-b][1,3,4]thiadiazole derivatives and analogues of the marine alkaloid topsentin showed potent staphylococcal biofilm inhibitory activity and some compounds targeted bacterial transpeptidase sortase A.

In honor and recognition of Professor Girolamo Cirrincione's outstanding career contributions to the fields of organic and medicinal chemistry, this special issue of Arkivoc welcomes the submission of original research manuscripts or reviews in these areas. We plan to receive submissions from now to 31st October 2021.

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Selected Publications

1. P. Diana, G. Cirrincione "*Biosynthesis of Heterocycles: from Isolation to Gene Cluster"*. J. Wiley & sons Inc. Publisher, **2015**, 784 pp.
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